Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Panitumumab

Proprietary Product Name: Vectibix

Sponsor: Amgen Australia Pty Ltd

May 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	Major Variation (Extension of Indications)
Decision:	Approved
Date of decision:	21 December 2011
Active ingredient:	Panitumumab (PAN)

Product name:	Vectibix
Sponsor's name and address:	Amgen Australia Pty Ltd Level 7, 123 Epping Road North Sydney NSW 2113
Dose form:	Concentrated Solution for Injection
Strengths:	100 mg/5 mL, 200 mg/10 mL and 400 mg/20 mL
Container:	Vial
Approved therapeutic use:	Vectibix is indicated for the treatment of patients with wild-type KRAS metastatic colorectal cancer (mCRC) · As first line therapy in combination with FOLFOX. Efficacy is influenced by patient performance status (see Clinical Trials; Precautions). · As second line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). Efficacy may be influenced by patient performance status (see Clinical Trials). · As monotherapy in patients after the failure of standard chemotherapy.
Route of administration:	Intravenous (IV)
Dosage:	6 mg/kg
ARTG numbers:	128331, 128332 and 128270

Product background

Panitumumab (PAN) is a monoclonal antibody produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. It binds specifically to the human epidermal growth factor receptor (EGFR), resulting in inhibition of transmission of intracellular signals responsible for cell survival and proliferation.

This product was first registered in Australia in 2008 and the approved indication at the time of submission of the current application to amend the existing indication and extend the current indication reads as follows:

> *"… the treatment of EGFR-expressing metastatic colorectal carcinoma in patients with non-mutated (wild type) Kirsten rat sarcoma 2 viral oncogene homologue (KRAS) who have disease progression following treatment with fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy".*

The indication was revised in October 2011 following the submission of a Category 1 Application to amend the existing indication and extend the current indication (discussed below). The amended existing indication was approved on 11 October 2011:"*as monotherapy for the treatment of wild type KRAS metastatic colorectal cancer (mCRC) in patients who have disease progression following treatment with fluoropyrimidine, oxaliplatin- and irinotecan-based chemotherapy*" (Vectibix Australian Approved Product Information, 11 October 2011).

This AusPAR describes a new application for approval of this product for first (and later) line treatment of wild-type *KRAS* metastatic colorectal cancer, in combination with chemotherapy.

The currently approved dose for monotherapy is 6 mg/kg IV once every two weeks. The same dose is proposed for the new indication.

There is one other anti-EGFR monoclonal antibody product registered in Australia for the treatment of colon cancer (Cetuximab – Erbitux – Merck Serono). This product has already been granted a broad indication for use in combination with chemotherapy in the treatment of *KRAS* wild-type metastatic colorectal cancer following consideration by the Advisory Committee on Prescription Medicines (ACPM) at its December 2009 meeting.

Regulatory status

PAN is indicated in the US as a single agent for the treatment of EGFR expressing metastatic colorectal cancer (mCRC) with disease progression on or following Fluoropyrimidine, Oxaliplatin and Irinotecan containing chemotherapy regimens. In Europe, Canada, Switzerland, Australia and other regions where it is approved, PAN is indicated as a single agent for the treatment of patients with EGFR expressing mCRC with non-mutated (wild-type) *KRAS* after failure of Fluoropyrimidine, Oxaliplatin and Irinotecan containing chemotherapy regimens.

In Europe, the European Commission (EC) has approved the variation to the marketing authorization for Vectibix® (panitumumab) on 10 November 2010 to include indications for the treatment of patients with wild-type *KRAS* metastatic colorectal cancer (mCRC) in first-line in combination with FOLFOX and in second-line in combination with FOLFIRI in patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

The combination of Vectibix with chemotherapy has been approved in Japan, Israel and Russia. In Japan, Vectibix is indicated for *"unresectable, advanced or recurrent colorectal cancer with wild-type KRAS".* In Israel, Vectibix is indicated *"in combination with chemotherapy for the treatment of unresectable, advanced or recurrent colorectal cancer (mCRC) with wild-type KRAS ".* In Russia, Vectibix is indicated for the *"treatment of patients with wild-type KRAS metastatic colorectal cancer, in combination with chemotherapy, based on fluoropyrimidine and oxaliplatin as a first-line therapy;and in combination with chemotherapy, based on fluoropyrimidine and irinotecan as a second-line therapy".*

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

Amgen has been conducting a global clinical program to support the use of PAN in combination with chemotherapy as a potential new option for initial or second line treatment of mCRC. A pharmacokinetic drug to drug interaction study (Study 20062010) was undertaken to support the use of PAN in combination with chemotherapy for mCRC patients. This was a Phase I open label single arm PK study involving PAN and Irinotecan to determine the effect of concurrent administration of PAN on the pharmacokinetics of Irinotecan in subjects with unresectable mCRC with no prior exposure to EGFR inhibitors.

Efficacy data provided in this submission involve studies supporting the use of PAN in combination with either Oxaliplatin or Irinotecan based chemotherapy as initial or second line treatment for mCRC in patients with wild-type *KRAS* tumours from a total of five trials. These include the two pivotal Phase III studies, that is, 20050203 and 20050181. Study 203 was a Phase III open label randomised controlled study in previously untreated patients with mCRC to compare the efficacy of PAN in combination with FOLFOX to the efficacy of FOLFOX alone. Study 181 was a Phase III open label randomised controlled study in patients previously treated for mCRC to compare the efficacy of PAN in combination with FOLFIRI to the efficacy of FOLFIRI alone.

In addition, three Phase II studies (Studies 20060314, 20050184 and 20060277) were provided as supportive data for the use of PAN in combination with Irinotecan in patients with mCRC.

In the current Australian submission the clinical safety profile of PAN in combination with chemotherapy is based on results from 9 studies, involving a total of 1536 subjects including 585 patients who received PAN in combination with Oxaliplatin based chemotherapy and 951 subjects who received PAN in combination with Irinotecan based chemotherapy. The safety data includes the two large pivotal Phase III trials together with the three supportive Phase II studies. A further two studies, that is, Study 184[1], a safety study involving prevention of skin reactions is presented together with a Phase III study (20040249[2]) in which PAN is combined with Bevacizumab. There are also three ongoing Phase II trials in which adverse drug reaction reports are provided; Studies 20070509, 20060141 and 20070820.

All aspects of Good Clinical Practice (GCP) have been observed in these studies.

Pharmacodynamics

No new data were submitted under this heading.

Pharmacokinetics

In order to evaluate the potential for PAN to have a possible pharmacokinetic (PK) drug to drug interaction when combined with chemotherapy, a Phase I study combining PAN with Irinotecan in patients with mCRC was presented. Study 20062010 was a Phase I open label single arm PK study of PAN and Irinotecan in subjects with unresectable mCRC who have progressed on at least one prior 5-FU containing chemotherapy regimen. Subjects were to

[1] Sponsor comment: This was a supportive study.
[2] Sponsor comment: Study 20040249 is not related to the proposed indication.

have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2[3] and a life expectancy of at least three months documented by the investigator and no prior exposure to EGFR inhibitors.

The primary objective of the study was to determine if PAN affects the pharmacokinetic profile of Irinotecan. The secondary objective was to assess the safety of PAN in combination with Irinotecan. Exploratory objectives were also undertaken in this study to assess the overall response rate as reported by the investigator and to evaluate the PK of SN-38, the highly active metabolite of Irinotecan with and without concomitant PAN administration.

Irinotecan was to be administered by intravenous (IV) infusion on Day 1 of each cycle. During Cycle 1 Irinotecan was to be given on Day 1 followed on Day 4 by PAN. Cycle 2 Day 1 visit was to occur two weeks after Day 4 of Cycle 1. Irinotecan was to be administered after completion of the PAN infusion. For all subsequent cycles Irinotecan was to be given every two weeks after completion of PAN infusion. Cycle 1 served as a comparator arm to Cycle 2.

The primary objective of the study was to determine the effect of PAN on the pharmacokinetics of Irinotecan. The study was designed to analyse the PK of Irinotecan with and without PAN in a single arm design. This assumes that the PK of Irinotecan would not change from Cycle 1 to Cycle 2. The study was conducted at six sites in the US and Canada.

Based on the prescribing information for Irinotecan, the co efficient of variation (CV) for maximum observed concentration (C_{max}) and the area under the curve (AUC) after a 90 minute IV infusion at 125mg/m^2 is approximately 48% and 32%, respectively, indicating that Irinotecan is a highly variable medicinal agent (CV >30%). If a log normal distribution is assumed for the C_{max} and AUC values of Irinotecan, 22% of the treated subjects were experienced with C_{max} as there was more than 30% below the median C_{max} and 13% of the treated subjects AUCs would be at least 30% below the median AUC. This relatively high proportion of individuals suggests that 30% change in the C_{max} or AUC Irinotecan due to PAN co administration would not cause a clinically meaningful change in Irinotecan efficacy. Therefore, the 0.7-1.43 interval was prospectively pre specified as a criterion to assess the impact of PAN co administration on the PK of Irinotecan. It would be concluded that PAN did not have a clinically important effect on the PK of Irinotecan if 90% CIs of the ratio of geometric means for the C_{max} and AUC values for Irinotecan with and without concomitant PAN administration fell within the interval of 0.7 – 1.43.

The planned sample size for this study was 23 subjects, which were chosen in order to have 18 subjects evaluable for the primary endpoint. Assuming that the co administration with PAN would not alter the PK of Irinotecan, with 18 subjects there would be a >90% chance that 90% CI of the ratio of geometric means for C_{max} and AUC values for Irinotecan with or without concomitant PAN administration would both be contained in the interval 0.7 – 1.43.

[3] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

Blood samples for Irinotecan and SN-38 concentration measurements were collected. The PK analysis set included all subjects who received PAN 6 mg/kg every two weeks and Irinotecan 180 mg/m^2 every two weeks without dose reductions or delays and had completed the blood sample collection for a PK analysis during Cycle 1 and 2 (up to 72 hr after the end of Irinotecan infusion in each cycle).

Serum samples for anti PAN antibody analyses were collected before the first administration of PAN and the 30 day safety follow up visit.

A total of 28 subjects were enrolled in the study of and 27 of these received at least one dose of PAN or Irinotecan. The mean age of patients was 58 years with a range of 39 to 73 years. Most subjects were men (67%) and White (63%). Nineteen subjects met the criterion for inclusion in the PK analysis set.

The mean concentration/time profiles showed similar disposition characteristics of Irinotecan or SN-38 with and without PAN administration. This demonstrated that PAN had no clinically significantly effect on the Irinotecan or SN-38 exposure. The PK parameters for each cycle of Irinotecan and SN-38 are summarised in Table 2. The PK parameters for Irinotecan and SN-38 in the current study were similar to those that had been previously reported in the literature.

The statistical summary of the AUC and C_{max} values for Irinotecan and SN-38, with or without PAN administration, is given in Table 3. The ratio of geometric means, that is, Irinotecan with PAN versus Irinotecan alone or Irinotecan area under the plasma concentration time curve from time zero to infinity ($AUC_{0\text{-}inf}$) was 0.898. For Irinotecan the area under the plasma concentration time curve from time zero to the last measurable time point ($AUC_{0\text{-}last}$) was 0.897 and the C_{max} was 0.980. The 90% CI of the geometric mean ratios for the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} of Irinotecan were all inside the pre specified interval of 0.70-1.43%. This demonstrated that there was no clinically significant difference in Irinotecan PK with or without the presence of PAN. Similar results were also observed from the SN-38 data.

Evaluator's comment:

These data have therefore indicated that there is no evidence of a clinically significant interaction between PAN and Irinotecan to influence potential efficacy or safety aspects of combining PAN with chemotherapy.

Table 2. Summary of Irinotecan and SN-38 PK parameters after IV infusion of Irinotecan (Cycle 1) or Irinotecan with Panitumumab (Cycle 2).

Descriptive Statistics	t_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (hr·ng/mL)	$AUC_{0\text{-Inf}}$ (hr·ng/mL)	$t_{1/2,z}$ (hr)	CL (L/hr/m^2)
Irinotecan - cycle 1						
N	19	19	19	19	19	19
Mean	1.87	1570	11900	12000	13.4	17.0
SD	0.317	321	4290	4350	2.34	5.90
%CV	16.9	20.4	36.2	36.3	17.4	34.8
Irinotecan - cycle 2						
N	19	19	19	19	19	19
Mean	1.76	1570	10600	10700	13.7	18.8
SD	0.155	520	3870	3930	2.50	6.26
%CV	8.82	33.1	36.5	36.7	18.3	33.2
SN-38 - cycle 1						
N	19	19	19	17[a]	19	NC
Mean	2.29	27.6	309	350	24.6	NC
SD	0.712	10.6	122	135	8.86	NC
%CV	31.1	38.4	39.4	38.5	36.0	NC
SN-38 - cycle 2						
N	19	19	19	16[b]	16[b]	NC
Mean	2.50	24.0	273	311	21.9	NC
SD	0.862	13.8	111	122	4.48	NC
%CV	34.5	57.4	40.8	39.3	20.4	NC

[a] n=17, data excluded from summary statistics for AUC extrapolation > 20% (See Appendix Table 12.4.5 of the 20062010 Clinical Study Report)

[b] n=16, data excluded from summary statistics for R^2 of λ_z < 0.8 (See Appendix Table 12.4.2 of the 20062010 Clinical Study Report).

$AUC_{0\text{-Inf}}$ =Area under the plasma concentration-time curve from the time of dosing to infinity, $AUC_{0\text{-last}}$ =Area under the plasma concentration-time curve from the time of the last quantifiable concentration, C_{max} =Maximum observed concentration, NC=Not calculated, $t_{1/2,z}$ =Terminal half-life, t_{max}=Time of maximum observed concentration.

Table 3. Comparisons of AUC and Cmax of Irinotecan and SN-38 With and Without Panitumumab Administration (Pharmacokinetic Analysis Set)

Parameter (units)	Cycle 2 [a] N	Cycle 2 [a] LSM[b]	Cycle 1[a] N	Cycle 1[a] LSM[b]	Ratio of cycle 2/cycle 1	90% Confidence Interval[c]
Irinotecan						
C_{max} (ng/mL)	19	1508	19	1539	0.980	(0.894, 1.074)
$AUC_{0\text{-last}}$ (hr*ng/mL)	19	10000	19	11149	0.897	(0.818, 0.983)
$AUC_{0\text{-inf}}$ (hr*ng/mL)	19	10100	19	11248	0.898	(0.819, 0.985)
SN-38						
C_{max} (ng/mL)	19	21.3	19	25.9	0.823	(0.731, 0.926)
$AUC_{0\text{-last}}$ (hr*ng/mL)	19	252.3	19	287.7	0.877	(0.788, 0.976)
$AUC_{0\text{-inf}}$ (hr*ng/mL)	16	282.0	17	326.0	0.865	(0.773, 0.968)

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[a]Cycle 1 =irinotecan 180 mg/m^2, Cycle 2 = Panitumumab 6 mg/kg and irinotecan 180 mg/m^2
[b]Least Squares Mean: Least Squares Geometric Mean from the SAS PROC MIXED procedure.
[c]The ratio and confidence limits are based on nature log scale data converted back to the original scale.
N is the number of subjects with evaluable data. PK Cut-off date: 27March2009.
Pharmacokinetics Analysis Set = Subjects that complete the per protocol treatment during cycles 1 and 2 with panitumumab 6 mg/kg and irinotecan 180 mg/m^2 Q2W without dose reductions or delays and complete the blood sample collection for PK during cycles 1 and 2 (inclusive).
2 subjects from cycle 1 were excluded from $AUC_{0\text{-inf}}$ because their extrapolated portion of the AUC value was > 20%. And 3 subjects from cycle 2 were excluded from $AUC_{0\text{-inf}}$ because R^2 of lambda_z < 0.8.

Program: /stat/clinpharm/AMG954/20062010/analysis/final/tables/program/t_pk2_comp.sas
Output: /stat/clinpharm/AMG954/20062010/analysis/final/tables/output/t_09_002_pk2_comp.rtf (Date Generated: 15SEP09:15:34:43)
Source Data: /stat/clinpharm/AMG954/20062010/analysis/final/statdata/crt/pkparam.sas7bdat

Immunogenicity

The immunogenicity profile of PAN was evaluated to support the proposed indication for the treatment of patients with wild-type *KRAS* mCRC in combination with chemotherapy. The analysis included all Amgen sponsored studies related to the proposed indication or completed at the time of the data cut offs and which had antibody samples available for testing, that is, Studies 203, 181, 277 and 184. All samples confirmed to be positive for anti PAN antibodies by drug specificity testing in a screening immunoassay were further tested for neutralising antibodies in a cell based EGFR phosphorylation bioassay. For each of the assays the antibody incidence (number and percentage of positive subjects) was further categorised by subjects testing positive at any time point (total antibody incidence), subjects testing positive at baseline (pre existing antibody incidence) and subjects testing positive at the post baseline time point only (developing antibody incidence).

A total of 1325 subjects (558 treated with PAN plus Oxaliplatin and 767 treated with PAN plus Irinotecan) were tested for the presence (at baseline/screening) and/or development (post baseline) of anti PAN antibodies. Baseline samples were available for antibody testing from 1225 subjects (511 treated with PAN plus Oxaliplatin and 714 treated with PAN plus Irinotecan). Post-baseline samples were available for antibody testing from 1124 subjects (480 treated with PAN plus Oxaliplatin and 664 treated with PAN plus Irinotecan).

In the analysis of subjects treated with PAN plus Irinotecan based chemotherapy from Studies 181, 184 and 277, 29/767 subjects (3.8%) tested positive for binding anti PAN antibodies in the screening immunoassays at some time during study (total antibody incidence), 24/714 subjects (3.4%) tested positive at baseline and 6/644 subjects (0.9%) tested positive only at the post baseline time point (developing antibody incidence). Three (out of 767 or 0.4%) tested positive for neutralising anti PAN antibodies at baseline. No subject who tested negative for neutralising antibodies at baseline tested positive for neutralising antibodies at post baseline.

In the analysis of subjects treated with PAN plus FOLFOX-4 based chemotherapy from Study 203, 36/558 subjects (6.5%) tested positive for binding anti PAN antibodies some time during the study (total antibody incidence), 22/511 subjects (4.3%) tested positive at baseline and 14/480 subjects (2.9%) tested positive at a post baseline time point (developing antibody incidence). Four out of 558 subjects (0.7%) tested positive for neutralising anti PAN antibodies at some time point during the study, 2/511 (0.4%) subjects tested positive at baseline and 2/480 subjects (0.4%) tested positive only at the post-baseline time point.

In an analysis of subjects treated with chemotherapy alone, 61/1132 (5.4%) of subjects treated with chemotherapy alone tested positive in either immunoassay and eight subjects (0.7%) tested positive in the bioassay as indicated in Table 4.

Thirty four (3.3%) of these subjects tested positive at the baseline time point in either immunoassay and eight subjects (0.8%) tested positive at the baseline time point in the bioassay. Thirty subjects or 3.0% tested positive in the immunoassay post baseline time point only but no subjects tested positive in the bioassay post baseline. The rates of antibody positivity were similar to those observed in subjects treated with PAN. In subjects with the positive results who had not been treated with PAN this maybe due to the presence of pre existing cross reacting serum molecules capable of binding and/or neutralising PAN.

Table 4. Summary of Anti-panitumumab antibody incidences in subjects treated with chemotherapy alone.

		Chemotherapy Alone					
		KRAS Status: Wild Type		*KRAS* Status: Mutant		*KRAS* Status: All	
		Either Biacore or ELISA	Bioassay	Either Biacore or ELISA	Bioassay	Either Biacore or ELISA	Bioassay
Total Antibody Incidence - n2/n1 (%)	20050181	12/283 (4.2)	1/283 (0.4)	12/234 (5.1)	3/234 (1.3)	25/570 (4.4)	4/570 (0.7)
	20050203	21/316 (6.6)	4/316 (1.3)	12/209 (5.7)	0/209 (0.0)	36/562 (6.4)	4/562 (0.7)
	Irinotecan or Oxaliplatin	33/599 (5.5)	5/599 (0.8)	24/443 (5.4)	3/443 (0.7)	61/1132 (5.4)	8/1132 (0.7)
Pre-existing Antibody Incidence - n4/n3 (%)	20050181	9/263 (3.4)	1/263 (0.4)	6/202 (3.0)	3/202 (1.5)	16/511 (3.1)	4/511 (0.8)
	20050203	11/285 (3.9)	4/285 (1.4)	7/189 (3.7)	0/189 (0.0)	18/507 (3.6)	4/507 (0.8)
	Irinotecan or Oxaliplatin	20/548 (3.6)	5/548 (0.9)	13/391 (3.3)	3/391 (0.8)	34/1018 (3.3)	8/1018 (0.8)
Developing Antibody Incidence - n6/n5 (%)	20050181	5/253 (2.0)	0/253 (0.0)	6/208 (2.9)	0/208 (0.0)	11/507 (2.2)	0/507 (0.0)
	20050203	10/274 (3.6)	0/274 (0.0)	6/182 (3.3)	0/182 (0.0)	19/489 (3.9)	0/489 (0.0)
	Irinotecan or Oxaliplatin	15/527 (2.8)	0/527 (0.0)	12/390 (3.1)	0/390 (0.0)	30/996 (3.0)	0/996 (0.0)

n1=Number of subjects with at least one immunoassay result

n2=Number of subjects with a positive antibody result at any time point

n3=Number of subjects with a an immunoassay antibody result at or before baseline

n4=Number of subjects with a positive antibody result at or before baseline

n5=Number of subjects with at least one postbaseline immunoassay antibody result

n6=Number of subjects with negative or no antibody result at or before baseline and a positive antibody result at a postbaseline time point

In summary, 2457 subjects have been tested for anti PAN antibodies in the combination chemotherapy mCRC clinical trials. Pre existing antibodies were detected at baseline in 3.6% of subjects using the immunoassay and 0.6% of subjects using the bioassay. Out of the 1124 subjects treated with PAN, 20 subjects (1.8%) tested positive for the development of binding antibodies and two subjects (0.2%) tested positive for the development of neutralising antibodies. Antibody incidences were similar in subjects with tumours expressing wild-type versus mutant *KRAS* (2% versus 1.4% binding antibodies and 0.2% versus 0.2% neutralising antibodies, respectively). Developing antibody incidences were also similar in subjects treated with Oxaliplatin based chemotherapy (2.9% binding and 0.4% neutralising) when compared to subjects treated with Irinotecan based chemotherapy (0.9% binding and 0% neutralising). No evidence of an altered safety or PK profile was found in patients who tested positive for anti PAN antibodies.

Evaluator's comment:

The immunogenicity of PAN in the combination chemotherapy setting was similar to the immunogenicity observed in a monotherapy setting. This low rate of immunogenicity may well be attributed to the human nature of PAN.

Efficacy

Efficacy data supporting the use of PAN in combination with either Oxaliplatin or Irinotecan based chemotherapy as initial or second line treatment of mCRC in subjects with wild-type *KRAS* tumours were collected from five trials. These included two pivotal Phase III studies (20050203 or 203 and 20050181 or 181). Study 203 was a Phase III open labelled randomised controlled study in previously untreated patients with mCRC

comparing the efficacy of PAN in combination with FOLFOX to the efficacy of FOLFOX alone. Study 181 was a Phase III, open label randomised controlled study in patients previously treated for mCRC and it compared the efficacy of PAN in combination with FOLFIRI to the efficacy of FOLFIRI alone. Three supportive Phase II studies (Studies 20060314, 20050184 and 20060277) provided additional supportive efficacy data for the use of PAN in combination with chemotherapy in patients with mCRC.

The two large Phase III trials (Studies 203 and 181) in the mCRC setting provide safety and efficacy data for PAN in combination with FOLFOX and FOLFIRI, respectively. Both FOLFOX and FOLFIRI are recognised as appropriate chemotherapy regimens for the initial treatment of mCRC in patients with good performance status according to standard practice guidelines. In addition, after progression following initial therapy with a 5-FU containing chemotherapy regimen, the second line chemotherapy treatment choice is guided by the initial therapy received.

Studies 203 and 181 were generally similar in design and study population with the exception of two factors; previous and concomitant chemotherapy and the stratification factor. Both studies enrolled subjects 18 years of age or older with histologically or cytologically confirmed adenocarcinoma of the colon or rectum with at least one unidimensional measurable lesion of at least 2 cm according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria. They required an ECOG performance status of 0-2. Study 203 was designed to evaluate the treatment effect of PAN plus FOLFOX-4 as initial therapy. Randomisation was stratified by geographic region and ECOG performance status. Study 181 was designed to evaluate the treatment effect of PAN plus FOLFIRI as second line therapy in patients who had received only one prior chemotherapy regimen for mCRC consisting of a Fluoropyrimidine based chemotherapy. Randomisation was stratified by prior Oxaliplatin exposure to mCRC, prior Bevacizumab exposure for mCRC and ECOG performance status.

Both studies were open labelled, multicentre and randomised on a one to one basis trials of PAN (at 6 mg/kg every two weeks) plus chemotherapy versus chemotherapy alone.

It is to be noted that Studies 203 and 181 were underway when retrospective analyses from earlier trials indicated that the treatment effect of PAN was confined to patients with wild-type *KRAS* tumours. Accordingly the protocols for Studies 203 and 181 were revised prospectively to evaluate the treatment effect of PAN in combination with chemotherapy by *KRAS* status. These amendments occurred before any *KRAS* testing and before the plan to conduct a primary analysis of progression free survival (PFS) in the wild-type *KRAS* analysis set.

In Studies 203 and 181 subjects were permitted to receive chemotherapy with or without PAN until disease progression or until unacceptable toxicity occurred. Tumour response assessment was to be performed every eight weeks until disease progression occurred. If withdrawal from study treatment occurred prior to disease progression, tumour response assessments were to continue until disease progression occurred or to the end of the study. To assess overall survival (OS), all subjects were followed up at a clinic visit or via telephone contact every three months as well as the safety follow up visit until 30 months after the last subject was randomised.

Three supportive Phase II studies were submitted.

Study 314 was a single arm open labelled study evaluating the efficacy of PAN plus FOLFIRI as initial therapy for mCRC providing additional data on PAN in combination with chemotherapy in the first line setting.

Study 277 was an open label single arm study, which evaluated the efficacy of PAN plus FOLFIRI in patients who had previously received initial FOLFOX and Bevacizumab.

Study 409 [4]was a study PAN plus chemotherapy in the first line setting (first line study with IFL or FOLFIRI).

Like the Phase III studies, Studies 314 and 277 enrolled subjects unselected for *KRAS* status. After enrolment *KRAS* testing was performed at a central laboratory for the purpose of the study analysis and not for clinical decision making. Data from these studies were evaluated by tumour *KRAS* status as prospective primary analyses. Study 5409[4] was undertaken prior to knowledge of the influence of PAN in relation to *KRAS* status and therefore *KRAS* analyses were not undertaken.

The efficacy endpoints evaluated in the studies included standard assessments for oncology therapeutics for the initial and second line treatments of mCRC. PFS was the primary endpoint in both Studies 203 and 181. The primary analysis of PFS in these studies was based on blinded independent central radiological assessment of tumour scans as per modified RECIST criteria. Results based on investigator review every eight weeks using the modified RECIST also evaluated the secondary analysis. PFS was defined as the time from randomisation to disease progression as per modified RECIST criteria or death.

Overall survival was a secondary endpoint in Study 203 and an independently tested co primary endpoint in Study 181. In both studies OS was defined as the time from randomisation to the time of death. It should be noted that in both studies the evaluation of OS was complicated by the use of anti cancer therapies after the disease had progressed.

The objective response rate was a secondary endpoint in both studies and defined as the incidence of either a confirmed, complete or partial response by modified RECIST criteria as determined by a blinded independent central radiological review. An additional secondary endpoint, duration of the response, was calculated for those patients with a confirmed, complete or partial response as the time from the first (complete or partial) response to the first observed disease progression.

The time to response was a tertiary endpoint in both studies and defined as the time from randomisation to the first objective response. Other tertiary endpoints included patient reported outcome (PRO) as measured by EQ-5D health state index score[5] and their overall health rating.

All Phase II studies evaluated PFS and the objective response rate as prospectively defined efficacy endpoints. Overall survival was evaluated in Studies 277 and 409. Tumour assessments were based on modified RECIST criterion in all studies.

The treatment effectiveness analyses evaluated the efficacy of PAN in combination with chemotherapy compared to chemotherapy alone among subjects with wild-type *KRAS* tumours and mutant *KRAS* tumours by the above described endpoints. Analyses of the clinical utility of was *KRAS* was evaluated by an overall improvement in PFS, OS and objective response rate for PAN in combination with chemotherapy and whether it was significantly greater in patients with *KRAS* wild-type tumours compared to patients with *KRAS* mutant tumours in the Phase III studies.

In Study 203, the cut off date for the primary analysis of PFS was 30 September 2008, the date by which 380 central PFS events in the wild-type *KRAS* efficacy analysis set were projected to have occurred. In Study 181 the cut off date for the primary analysis of PFS was 8 April 2008 according to the same criteria.

[4] Sponsor comment: Study 409 is not related to the indication.
[5] EQ-5D™ is a standardised instrument for use as a measure of health outcome. It is applicable to a wide range of health conditions and treatments and it provides a simple descriptive profile and a single index value for health status.

In Study 203, the main analysis of OS included all events that had occurred by the cut off date of 28 August 2009, which ensured at least 50% of patients in each treatment arm in both the wild-type and mutant *KRAS* efficacy analyses sets had an event. In Study 181, the data cut off date of the primary OS analysis was the 30 April 2009, the date by which at least 380 OS events in the wild-type *KRAS* of the efficacy analysis set were projected to have occurred.

The data cut off dates for the Phase II studies were approximately 12 months after the last subject was enrolled in each study.

Kaplan-Meier methods were used to analyse the progression free survival in all five studies. For the primary analysis in Studies 203 and 181 log rank tests stratified by the randomisation factors were used to compare treatments with respect to PFS by *KRAS* status. PFS results based on both central investigator assessments were provided if available. Overall survival was also analysed using Kaplan-Meier methods. Similarly log rank tests for Studies 203 and 181 were used to compare treatments with respect to OS by *KRAS* status. Descriptive statistics were calculated for response rates, duration of response and time to response. PRO endpoints were assessed by a two sided significance level of 5% and were regarded as descriptive.

In the pivotal trial Study 203, PAN was administered at a dose of 6 mg/kg every two weeks while FOLFOX-4 involved administration of Oxaliplatin 85mg/m^2 IV and Leucovorin 200 mg/m^2 IV on day one, followed by 5-FU 400 mg/m^2 IV as a bolus and then 5-FU 600 mg/m^2 IV as an infusion over 22 hr. The doses of Leucovorin and 5-FU were repeated on Day 2. Courses were repeated every two weeks.

Inclusion criteria

- Histologically and cytologically concerned adenocarcinoma of the colorectum presenting with metastatic disease.
- A requirement for at least one uni dimensional measurable lesion.
- ECOG performance status was 0, 1 or 2.
- Paraffin embedded tumour tissue for EGFR and *KRAS* testing.
- Adequate renal hepatic and metabolic function was required.
- Patients who had had no prior chemotherapy or systemic therapy for treatment of metastatic disease.

Patients were randomly assigned on a 1:1 basis to receive PAN plus FOLFOX or FOLFOX alone.

Patients who received PAN plus FOLFOX and demonstrated objective response or had stable disease or became intolerant to chemotherapy or PAN, could continue PAN or chemotherapy, respectively, until disease progression or an intolerance to treatment.

Planned sample size was 1150 subjects.

A total of 1183 patients were randomised to the PAN plus FOLFOX arm (N=593) or the FOLFOX alone arm (N=590). Of the 1183 subjects, 1096 were evaluable for *KRAS* status (93%) and were included in the *KRAS* efficacy analysis set; 546 subjects (92%) in the PAN plus FOLFOX arm and 550 (93%) in the FOLFOX alone arm. Within each treatment arm approximately 55% of patients had wild-type *KRAS* tumours and 37% mutant *KRAS* tumours while 7% were not evaluable for *KRAS*. In relation to the wild-type *KRAS* efficacy analysis set, the mean actual follow up time was 78 weeks in the PAN plus FOLFOX arm and 71.3 weeks in the FOLFOX alone arm (as of the 20 August 2009). FOLFOX was discontinued in 307 subjects (94%) in the PAN plus FOLFOX arm and 321 subjects (97%)

in the FOLFOX alone arm, this was mostly due to disease progression (45% of the PAN plus FOLFOX arm compared to 51% of the FOLFOX alone arm). PAN was discontinued in 306 subjects (94%) with the most common reason being disease progression (in 49%).

The mean age was 60.6 years (range of 24-85 years). Most patients were men (64%) and White (92%). Some 94% of patients in each treatment arm had an ECOG performance status of 01. Similar percentage of patients in the PAN plus FOLFOX arm and FOLFOX arm alone had at least three sites of metastatic disease (44% in each treatment arm), carcinoembryonic antigen (CEA)[6] concentrations above the normal range (78% and 77%, respectively) and lactate dehydrogenase (LDH) >1.5 times upper limit of normal (28% and 29%, respectively).

In relation to the mutant *KRAS* efficacy analysis set, the mean actual follow up time was 64.3 weeks in the PAN plus FOLFOX arm and 70.4 weeks in the FOLFOX alone arm. FOLFOX was discontinued in 214 patients (97%) in the PAN plus FOLFOX arm and 213 patients (97%) in the FOLFOX alone arm. The most common reason for ending FOLFOX was disease progression (62% and 58%, respectively). PAN was discontinued in 97% of patients of whom 61% had disease progression. The mean age was 61.5 years (range 27 – 83 years) with 62% of patients being men and 89% White. Some 96% of patients in the PAN plus FOLFOX arm and 95% of patients in the FOLFOX alone arm had an ECOG performance status of 01. Some imbalances in baseline characteristics were noted between the treatment arms; in the PAN plus FOLFOX arm 50% of patients had at least three sites of metastatic disease which can be compared to 43% in the FOLFOX alone arm. CEA concentrations were above normal in 85% and 78% of patients, respectively, and LDH was at least 1.5 times the upper limit of normal in 33% and 27% of patients in the two groups, respectively.

Review of the wild-type *KRAS* efficacy analysis se and results of the key efficacy endpoints by central assessment is given in Table 5.

For PFS by central assessment, 157 subjects or 48% of the PAN plus FOLFOX arm and 172 subjects or 52% in the FOLFOX alone arm had progressed as of the data cut off point of 30 September 2008. Forty two patients (13%) of the PAN plus FOLFOX arm and 43 patients (13%) of the FOLFOX alone patients had died. Median PFS was 9.6 months with a 95% CI, 9.2, 11.1 in the PAN plus FOLFOX arm and 8 months or 95% CI, 7.5. 9.3 in the FOLFOX alone arm. This was an absolute difference of 1.6 months. PFS was significantly improved by log rank test with a P value of 0.023. The estimated hazard ratio was 0.798 favouring the PAN plus FOLFOX arm. Kaplan-Meier analysis of these PFS data is given in Figure 1 and shows that survival curves begin to separate after approximately six months and at the third quartile survival is 14.9 months for PAN plus FOLFOX versus 13 months for FOLFOX alone.

[6] A tumour marker.

Table 5. Study 20050203: Summary of efficacy endpoints (central assessment). (wild-type *KRAS* subjects).

	Panitumumab Plus FOLFOX		FOLFOX Alone
Progression-free survival (months)			
N	325		331
Subjects who progressed/died - n(%)	199 (61)		215 (65)
Median time (95% CI)	9.6 (9.2,11.1)		8.0 (7.5,9.3)
Log-rank test stratified by Region and ECOG score			
Normal score[a]		-2.27	
P-value		0.0234	
Hazard ratio (95% CI) stratified by Region and ECOG score		0.798 (0.656,0.971)	
Overall survival (months)			
N	325		331
Subjects who died - n(%)	165 (51)		190 (57)
Median time (95% CI)	23.9 (20.3,28.3)		19.7 (17.6,22.6)
Log-rank test stratified by Region and ECOG score			
Normal score[a]		-1.80	
P-value		0.0723	
Hazard ratio (95% CI) stratified by Region and ECOG score		0.825 (0.669,1.018)	

	Panitumumab Plus FOLFOX		FOLFOX Alone
Objective tumor response			
N	317		323
Subject responding -n(%)	175 (55)		154 (48)
Rate (95% CI) - %	55.21 (49.55,60.77)		47.68 (42.12,53.28)
Difference in rates (95% CI)		7.53 (-0.43,15.36)	
Odds ratio (95% CI) stratified by Region and ECOG score		1.35 (0.98,1.87)	

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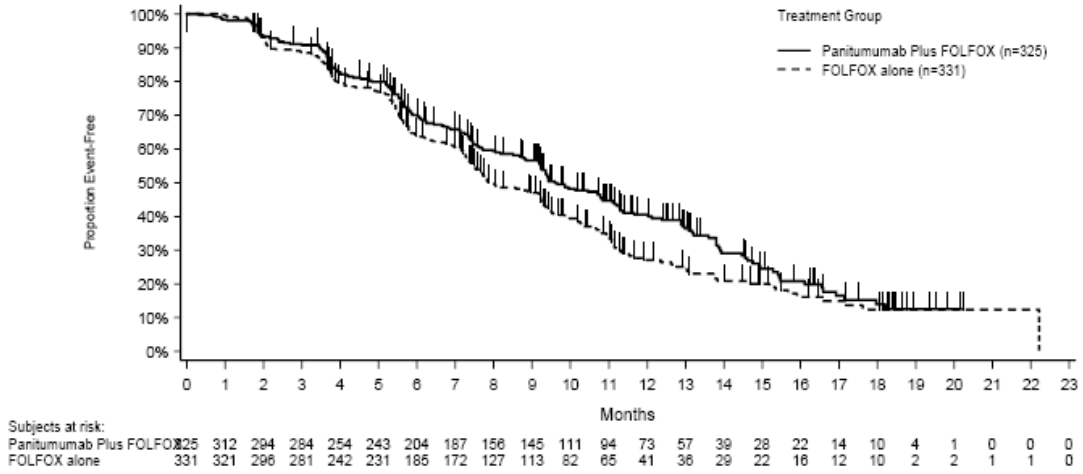
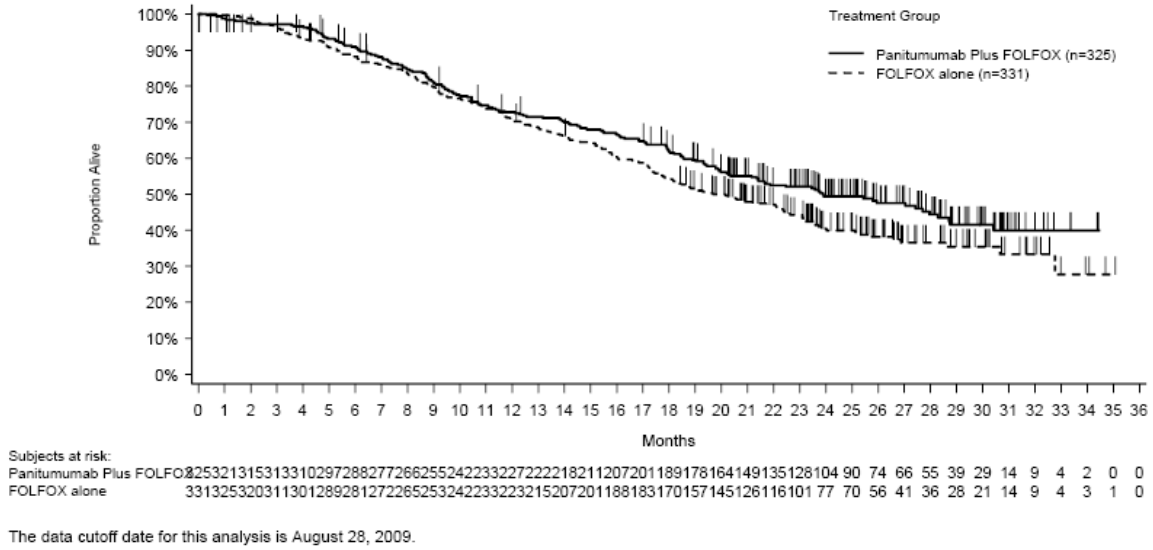
Disease assessment is based on a blinded central review of scans using modified-RECIST criteria.
Months are derived as days x 12/365.25.
The analyses of progression-free survival, overall survival, and time to disease progression are conducted on the Wild-type *KRAS* Efficacy Analysis Set. The analyses of objective tumor response and duration of response are conducted on the Wild-type *KRAS* Central Tumor Response Analysis Set.
[a] A normal score < 0 favors panitumumab..
[b]Number of subjects with confirmed response.
The data cutoff date for this analysis is 30 September 2008 (PFS and objective response) and 28 August 2009 (OS).

Figure 1. Kaplan-Meier plot of Progression Free Survival Time (central assessment) (wild-type *KRAS* Efficacy Analysis set).



In the primary analysis of OS, 165 patients (51%) in the PAN plus FOLFOX arm and 190 patients (57%) in the FOLFOX alone arm had died as of the data cut off point of 28 August 2009. Median OS was 23.9 months with 95% CI 20.3 – 28.3 in the PAN plus FOLFOX arm and 19.7 months with 95% CI 17.6, 22.6 in the FOLFOX alone arm. The stratified log rank test was P=0.072 with an absolute difference of 4.2 months. This is illustrated in Figure 2.

Figure 2. Study 20050203: Kaplan-Meier plot of survival time (wild-type *KRAS* efficacy analysis set).



The data cutoff date for this analysis is August 28, 2009.

The estimated hazard ratio was 0.825 favouring the PAN plus FOLFOX arm. Subsequent anti-EGFR therapy was reported in 8% of patients in the PAN plus FOLFOX arm and 17.8% of patients in the FOLFOX alone arm. Subsequent chemotherapy was reported for 53.2% and 61.9% of randomised patients, respectively. A best objective response rate, that is, complete or partial response by central radiological assessment, was achieved in 175 patients (55%) in the PAN plus FOLFOX arm with a 95% CI 50% and 61% and 154 patients (48%) in the FOLFOX alone arm with a 95% CI of 42%, 53% with the hazard ratio of 1.35 favouring the PAN arm.

The time to disease progression by central assessment was longer in the PAN plus FOLFOX arm (10.8 months) compared to the FOLFOX alone arm (median of 9.2 months). Results for the mutant *KRAS* efficacy analysis set are listed in Table 6.

Table 6. Study 20050203: Summary of efficacy endpoints (central assessment). (Mutant *KRAS* subjects).

	Panitumumab Plus FOLFOX		FOLFOX Alone
Progression-free survival (months)			
N	221		219
Subjects who progressed/died - n(%)	167 (76)		157 (72)
Median time (95% CI)	7.3 (6.3,8.0)		8.8 (7.7,9.4)
Log-rank test stratified by Region and ECOG score			
Normal score[a]		2.28	
P-value		0.0227	
Hazard ratio (95% CI) stratified by Region and ECOG score		1.294 (1.036,1.616)	
Overall survival (months)			
N	221		219
Subjects who died - n(%)	152 (69)		142 (65)
Median (95% CI)[a]	15.5 (13.1, 17.6)		19.3 (16.5, 21.8)
Log-rank test stratified by Region and ECOG score			
Normal score[a]		1.83	
P-value		0.0678	
Hazard ratio (95% CI) stratified by Region and ECOG score		1.241 (0.984,1.566)	

	Panitumumab Plus FOLFOX		FOLFOX Alone
Objective tumor response			
N	215		211
Subject responding -n(%)	85 (40)		85 (40)
Rate (95% CI) - %	39.53 (32.95,46.41)		40.28 (33.61,47.24)
Difference in rates (95% CI)		-0.75 (-10.30,8.81)	
Odds ratio (95% CI) stratified by Region and ECOG score		0.98 (0.65,1.47)	

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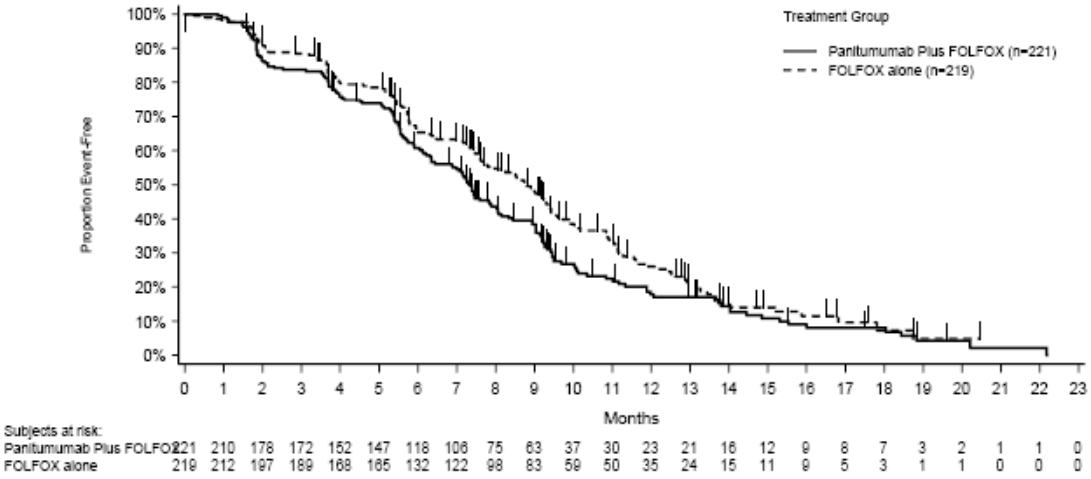
Disease assessment is based on a blinded central review of scans using modified-RECIST criteria.
Months are derived as days x 12/365.25.
The analyses of progression-free survival, overall survival, and time to disease progression are conducted on the Mutant *KRAS* Efficacy Analysis Set. The analyses of objective tumor response and duration of response are conducted on the Mutant *KRAS* Central Tumor Response Analysis Set.
[a] A normal score < 0 favors panitumumab..
[b] Number of subjects with confirmed response.
The data cutoff date for this analysis is 30 September 2008 (PFS and objective response) and 28 August 2009 (OS).

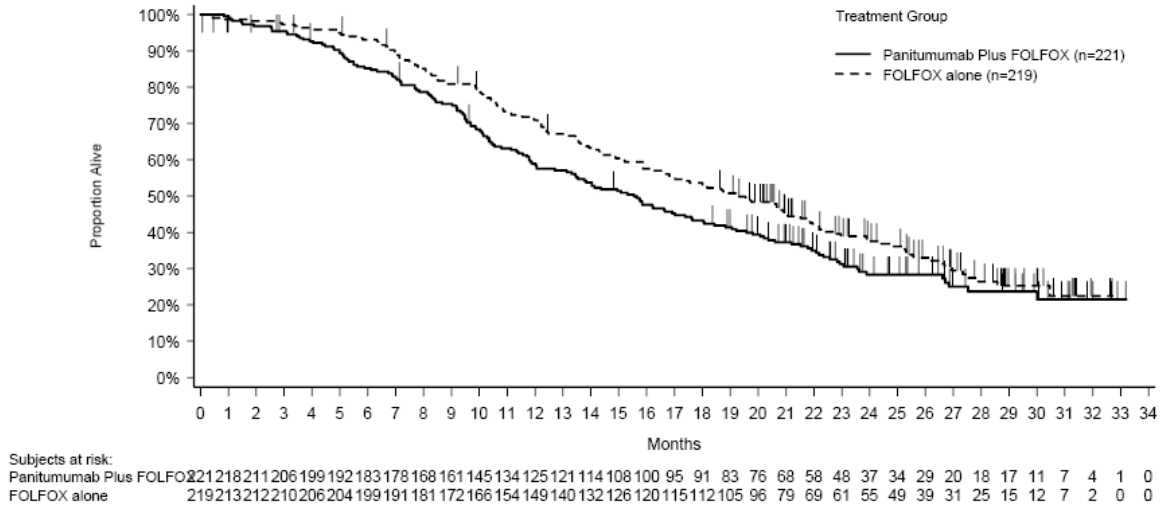
For PFS by central assessment, 125 (57%) of patients in the PAN plus FOLFOX arm and 129 (59%) of patients in the FOLFOX alone arm had progressed as of the data cut off point of 30 September 2008. Forty two patients (19%) on the PAN plus FOLFOX arm and 28 (13%) on the FOLFOX alone arm had died. The median PFS time was 7.3 months in the PAN plus FOLFOX arm and 8.8 months in the FOLFOX alone arm with an absolute difference of 1.5 months and a P value = 0.023. The estimated hazard ratio was 1.294 favouring the FOLFOX alone arm., Figure 3 indicates the Kaplan-Meier plot of PFS for this mutant *KRAS* efficacy analysis set.

Figure 3. Study 20050203: Kaplan-Meier plot of Progression Free Survival Time (Mutant *KRAS* Efficacy Analysis set).



A total of 152 patients (69%) in the PAN plus FOLFOX arm and 142 patients (65%) in the FOLFOX alone arm had died as of the data cut off point of 28 August 2009. The median OS was 15.5 months in the PAN plus FOLFOX arm and 19.3 months in the FOLFOX alone arm with absolute difference of 3.8 months and log rank P value 0.068. The estimated hazard ratio was 1.241 favouring the FOLFOX alone arm. This is illustrated by Kaplan-Meier plot in Figure 4.

Figure 4. Study 20050203: Kaplan-Meier plot of Survival Time (Mutant *KRAS* Efficacy Analysis set).



The data cutoff date for this analysis is August 28, 2009.

The number of responders were the same in both treatment arms (85 or 40% in the PAN plus FOLFOX arm and 85 or 40% in the FOLFOX alone arm with an odds ratio of 0.98). The median time to disease progression was 7.5 months for PAN plus FOLFOX and 9.0 months for FOLFOX alone, respectively.

Evaluator's comment:

The data from this study involving patients with previously untreated metastatic colorectal carcinoma has demonstrated that the addition of PAN to FOLFOX for chemotherapy is associated with a significant improvement in PFS. Nevertheless, OS did not reach a significantly different outcome. It is also worth commenting that the difference

in the extent of PFS, despite the statistical significance, is still relatively small being <three months. Nevertheless, in view of the relatively large patient population involved this did reach significant levels. It is clear that in patients with *KRAS* mutant tumours that the addition of PAN has no beneficial effect and may in fact have a detrimental effect on both PFS and OS.

It is also worth commenting on the Quality of Life analyses. The two questionnaires involved in determining PRO outcomes were the EQ-5D questionnaire[7] and also the EQ-5DO overall health rating. These were assessed at baseline and every eight weeks until study withdrawal. Overall, 67% of patients in both treatment arms complied with these evaluations. In relation to the wild-type *KRAS* subjects, there was evidence of benefit from the PAN treatment at two of the four time points but there was no overall significant benefit between treatment arms using the EQ-5D health state index score. Among the mutant *KRAS* analysis set there was no significant overall differences in health scores between the two treatment arms.

Study 181

This was considered to be the second pivotal trial; a randomised multicentre Phase III study which compared the efficacy of PAN in combination with (FOLFIRI) chemotherapy to the efficacy of chemotherapy alone in patients with previously treated metastatic colorectal cancer (mCRC).

The primary objective of the study was to evaluate the treatment effect of PAN plus FOLFIRI on both OS and PFS compared with FOLFIRI alone among patients with wild-type *KRAS* tumours and mutant *KRAS* tumours. The secondary objectives were to evaluate the overall objective response rate, time to progression, duration of response and safety.

The study was conducted in 190 centres across the USA, Australia, Western Europe, Eastern Europe and Japan. Study was conducted between the 30 June 2006 and the 30 April 2009.

Inclusion criteria for the trial included histologically or cytologically confirmed adenocarcinoma of the colorectum in patients presenting with metastatic disease. One and only one prior chemotherapy regimen for mCRC consisting of first line FU based chemotherapy (prior adjuvant FU based chemotherapy was allowed). Evidence of disease progression, either while receiving treatment or <six months after last dose of prior first line FU based chemotherapy was required. At least one uni dimensional measurable lesion was required as well as ECOG status of 0, 1 or 2. Paraffin embedded tumour tissue were prepared for central analysis of EGFR and biomarker testing. Patients required adequate haemalogic renal hepatic and metabolic function. Exclusion criteria included prior Irinotecan therapy or anti-EGFR antibody therapy.

Patients were randomised on a 1:1 basis to PAN plus FOLFIRI or to FOLFIRI alone. PAN was administered at a dose of 6 mg/kg every two weeks, while FOLFIRI involved administration of Irinotecan 180 mg/m^2 together with Leucovorin 400 mg/m^2 and a FU bolus of 400 mg/m^2 followed by a FU infusion 2400 mg/m^2 over 46 hr on Day 1. Cycles were repeated every 14 days.

A total of 1186 subjects were enrolled and randomised into the PAN plus FOLFIRI arm (N=591) or the FOLFIRI alone arm (N=595). Of the 1186 subjects 1083 (91%) were evaluable for *KRAS* and were included in the *KRAS* efficacy analysis set; 541 patients (92%) on the PAN plus FOLFIRI arm and 542 patients (91%) on the FOLFIRI alone arm. A similar percentage of patients in the PAN plus FOLFIRI arm and FOLFIRI alone arm had

[7] A five item scale utilising mobility, self care, usual activities, pain and discomfort and anxiety depression.

wild-type *KRAS* tumours (51% and 49%, respectively) and mutant tumours (40% and 42%, respectively).

Reviewing the data from the wild-type *KRAS* efficacy analysis set as of the data cut off date, the mean actual follow up time was 56.1 weeks in the PAN plus FOLFIRI arm and 51.1 weeks in the FOLFIRI alone arm. A total of 295 subjects (97%) in the PAN plus FOLFIRI arm and 290 subjects (99%) of the FOLFIRI alone arm discontinued therapy and 296 subjects (98%) discontinued PAN. The most common reason for ending PAN or chemotherapy treatment was disease progression.

Most patients in the PAN plus FOLFIRI and FOLFIRI alone arms were men (62% and 65%, respectively) and White (97% and 95%, respectively). The mean age was 60 years (range 28 - 84 years) in the PAN FOLFIRI arm and 61 years (range 29 – 86 years) in the FOLFIRI alone arm. Ninety-five percent of patients in PAN plus FOLFIRI arm and 93% of patients in the FOLFIRI alone arm had an ECOG performance status of 0 or 1. Ninety-nine percent of patients in the PAN plus FOLFIRI and FOLFIRI alone arms had received previous chemotherapy for mCRC with similar percentage of patients in each arm receiving prior FU (74% versus 71%), folinic acid (55% versus 50%), Oxaliplatin (67% versus 65%) and/or Bevacizumab (18% versus 20%).

Among the mutant *KRAS* efficacy analysis set the mean follow up time was 49.4 weeks in PAN plus FOLFIRI arm and 46 weeks in the FOLFIRI alone arm. This was a shorter duration than that recorded for the wild-type *KRAS* efficacy analysis set. A total of 237 patients (100%) in the PAN plus FOLFIRI arm and 245 patients (99%) of the FOLFIRI alone arm had discontinued chemotherapy with 236 subjects (99%) discontinuing PAN. The most common reason for ending PAN or chemotherapy treatment was disease progression.

Fifty-six percent of patients in the PAN plus FOLFIRI arm and 60% of patients in the FOLFIRI alone arm were men. Most patients were White (95% of PAN plus FOLFIRI arm and 96% of FOLFIRI alone arm). The median age was 61 years with a range of 29 to 83 years in the PAN plus FOLFIRI arm and 64 years (range of 29 to 86 years) in the FOLFIRI alone arm. Ninety-five percent of patients in the PAN plus FOLFIRI arm and 93% of patients in the FOLFIRI alone arm had an ECOG performance status was 0 or 1. Ninety-nine percent of patients in the PAN plus FOLFIRI arm and 98% in the FOLFIRI alone arm had received previous chemotherapy for mCRC. A higher percentage of patients in the PAN plus FOLFIRI arm relative to the FOLFIRI alone arm had received prior FU (73% versus 64%, respectively), folinic acid (54% versus 46%), prior Oxaliplatin (69% versus 68%) and/or Bevacizumab (19% versus 17%, respectively).

A summary of the results of the key efficacy endpoints for the wild-type *KRAS* efficacy analysis set as determined by central assessment is given in Table 7 below. At the time of the primary PFS analysis, 59% of patients in the PAN plus FOLFIRI arm and 69% of patients in the FOLFIRI alone arm had disease that had progressed or they died. There was a statistically significant difference in PFS in favour of PAN demonstrated with a P = 0.0036 by stratified log rank test. Median PFS times were 5.9 months in the PAN plus FOLFIRI arm and 3.9 months in the FOLFIRI alone arm with an absolute difference of two months as shown in the Kaplan-Meier plot Figure 5. The hazard ratio from a stratified Cox model was 0.732 favouring the PAN plus FOLFIRI arm. Secondary and sensitivity analyses were consistent with the findings in the primary analysis.

Table 7. Study 20050181. Summary of the Efficacy Endpoints (Central Assessment). wild-type *KRAS* subjects.

	Panitumumab Plus FOLFIRI		FOLFIRI Alone
Progression-free survival (months)			
N	303		294
Subjects who progressed/died - n(%)	178 (59)		203 (69)
Median time (95% CI)	5.9 (5.5,6.7)		3.9 (3.7,5.3)
Log-rank test stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure			
Normal score[a]		-2.91	
P-value		0.0036	
Hazard ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure		0.732 (0.593,0.903)	
Overall survival (months)			
N	303		294
Subjects who died - n(%)	200 (66)		207 (70)
Median time (95% CI)	14.5 (13.0,16.0)		12.5 (11.2,14.2)
Log-rank test stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure			
Normal score[a]		-1.57	
P-value		0.1154	
Hazard ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure		0.854 (0.702,1.039)	

	Panitumumab Plus FOLFIRI		FOLFIRI Alone
Objective tumor response			
N	297		285
Subject responding -n(%)	105 (35)		28 (10)
Rate (95% CI) - %	35.35 (29.92,41.08)		9.82 (6.63,13.89)
Difference in rates (95% CI)		25.53 (18.70,32.07)	
Odds ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure		5.33 (3.21,8.60)	

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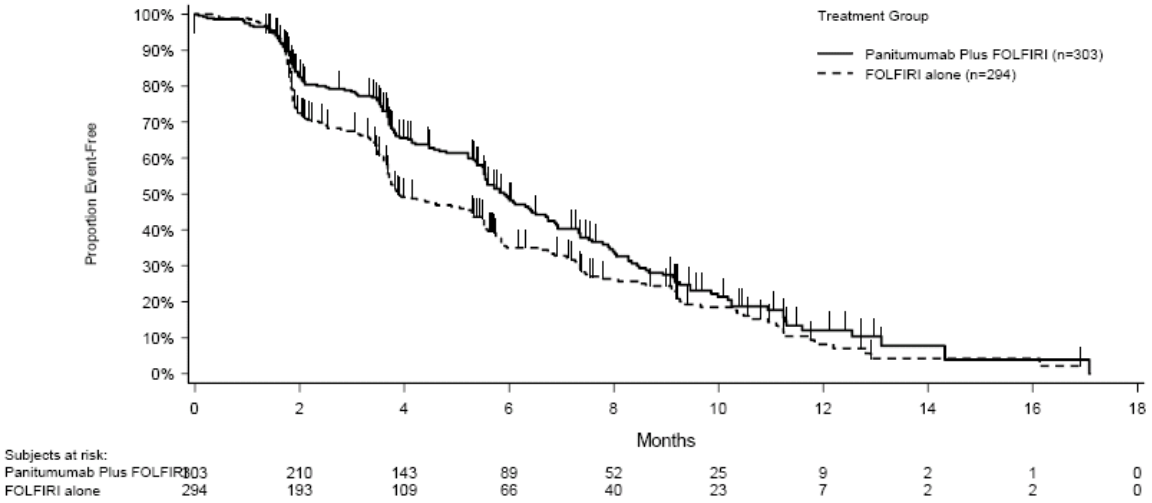
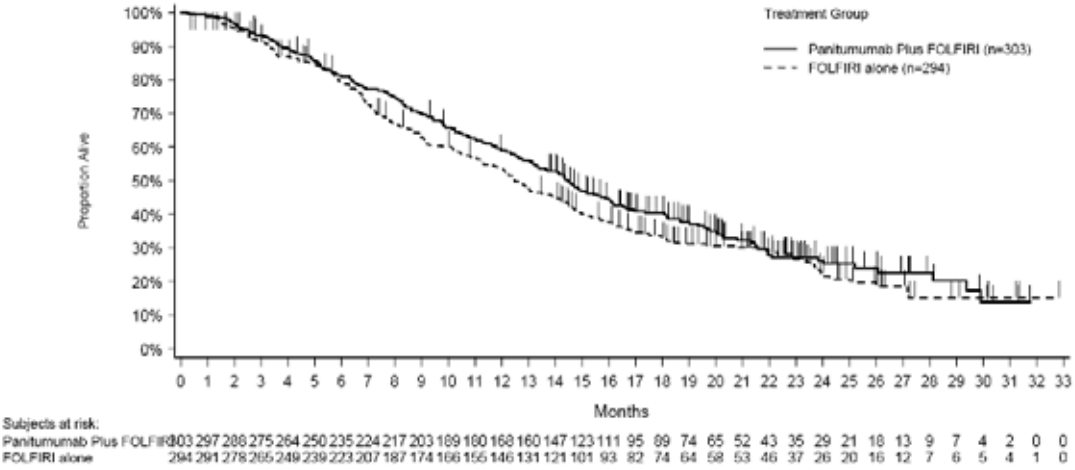
Disease assessment is based on a blinded central review of scans using modified-RECIST criteria.
Months are derived as days x 12/365.25
The analyses of progression-free survival, overall survival, and time to disease progression are conducted on the Wild-type *KRAS* Efficacy Analysis Set. The analyses of objective tumor response and duration of response are conducted on the Wild-type *KRAS* Central Tumor Response Analysis Set.
[a]A normal score < 0 indicates fewer than expected events for the panitumumab plus FOLFIRI arm and therefore a longer time to event.
The data cutoff dates for these analyses are 08 April 2008 (PFS) and 30APR2009 (OS and response)

Figure 5. Kaplan-Meier Plot of PFS Time (Central Assessment). wild-type *KRAS* Efficacy Analysis Set.



A total of 66% of patients in the PAN plus FOLFIRI arm and 70% of patients in the FOLFIRI alone arm died during treatment or the long term follow up. The estimated median overall survival was 14.5 months in the PAN plus FOLFIRI arm and 12.5 months in the FOLFIRI alone arm with an absolute difference of two months as graphically indicated in Figure 6. The P value for the stratified log rank test for OS did not achieve statistical significance (P=0.1154). It is of note that there was an imbalance in the incidence of subsequent anti-EGFR monoclonal antibody therapy between the PAN plus FOLFIRI arm (10.2%) and the FOLFIRI alone arm (30.6%), which may have had some confusing effect on the assessment of survival. The rate of subsequent chemotherapy was similar between the treatment arms, being 46.9% for the PAN plus FOLFIRI arm and 48.3% for the FOLFIRI alone arm.

Figure 6. Study 20050181. Kaplan-Meier Plot of Overall Survival. wild-type *KRAS* Efficacy Analysis Set.



The objective response rate (all were partial responses) was 35% for patients receiving PAN plus FOLFIRI and 10% for the subjects receiving FOLFIRI alone with the odds ratio for objective response being 5.33 favouring the PAN plus FOLFIRI arm.

When reviewing the data from the mutant *KRAS* efficacy analysis set (summarised in Table 8) it is evident that at the time of the primary PFS analysis, 68% of patients in the PAN plus FOLFIRI arm and 65% in the FOLFIRI alone arm had progressed or died. No statistically significant difference in PFS was observed between the treatment arms (P=0.1448 by stratified log rank test). The median PFS times were 5.0 months in the PAN

plus FOLFIRI arm and 4.9 months in the FOLFIRI alone arm with an absolute difference of 0.1 months. This is graphically illustrated in Figure 7. The hazard ratio from a stratified Cox model was 0.846 favouring the PAN plus FOLFIRI arm.

Table 8. Study 20050181. Summary of the Efficacy Endpoints (Central Assessment). Mutant *KRAS* subjects.

	Panitumumab Plus FOLFIRI		FOLFIRI Alone
Progression-free survival (months)			
N	238		248
Subjects who progressed/died - n(%)	162 (68)		161 (65)
Median time (95% CI)	5.0 (3.8,5.6)		4.9 (3.6,5.6)
Log-rank test stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure			
Normal score[a]		-1.46	
P-value		0.1448	
Hazard ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure		0.846 (0.677,1.059)	
Overall survival (months)			
N	238		248
Subjects who died - n(%)	181 (76)		193 (78)
Median time (95% CI)	11.8 (10.4,13.3)		11.1 (10.3,12.4)
Log-rank test stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure			
Normal score[a]		-0.60	
P-value		0.5503	
Hazard ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure		0.939 (0.764,1.154)	

	Panitumumab Plus FOLFIRI		FOLFIRI Alone
Objective tumor response			
N	232		237
Subject responding -n(%)	31 (13)		33 (14)
Rate (95% CI) - %	13.36 (9.26,18.43)		13.92 (9.78,19.00)
Difference in rates (95% CI)		-0.56 (-7.12,6.02)	
Odds ratio (95% CI) stratified by ECOG score, prior bevacizumab exposure, and prior oxaliplatin exposure		1.00 (0.56,1.76)	

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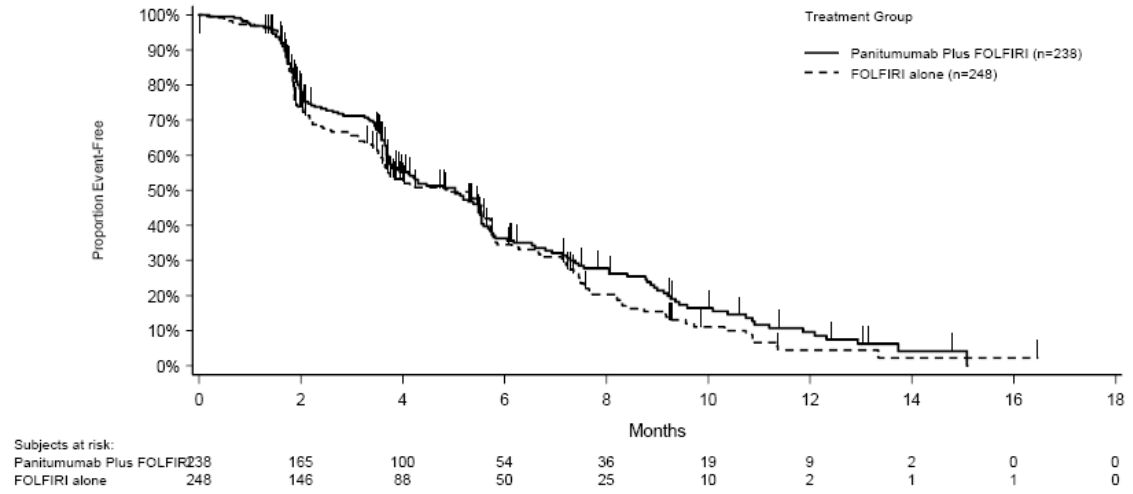
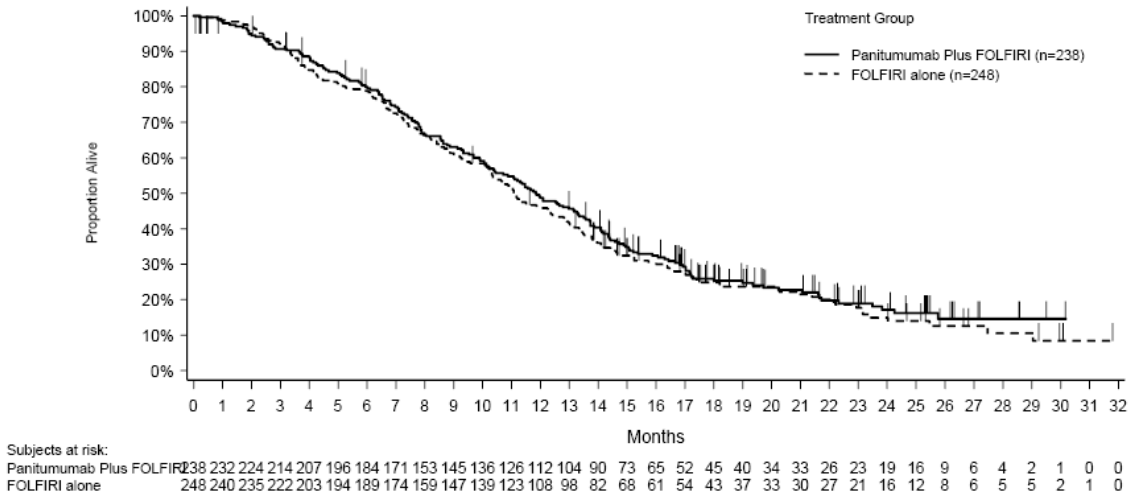
Disease assessment is based on a blinded central review of scans using modified-RECIST criteria.
Months are derived as days x 12/365.25
The analyses of progression-free survival, overall survival, and time to disease progression are conducted on the Mutant *KRAS* Efficacy Analysis Set. The analyses of objective tumor response and duration of response are conducted on the Mutant *KRAS* Central Tumor Response Analysis Set.
[a]A normal score < 0 indicates fewer than expected events for the panitumumab plus FOLFIRI arm and therefore a longer time to event.
The data cutoff dates for these analyses are 08 April 2008 (PFS) and 30APR2009 (OS and response)

Figure 7. Kaplan-Meier Plot of PFS Time (Central Assessment). Mutant *KRAS* Efficacy Analysis Set.



The formal test of the treatment difference for OS at the 4% level was not conducted as a significant difference was not demonstrated for the OS in the wild-type *KRAS* efficacy analysis set. A similar proportion of patients in each treatment arm had died (76% in the PAN plus FOLFIRI arm and the 78% in the FOLFIRI alone arm). The median OS times were 11.8 months in the PAN plus FOLFIRI arm and 11.1 months in the FOLFIRI alone arm for an absolute difference 0.7 months as illustrated Figure 8 below. The hazard ratio for OS was 0.939 favouring the PAN plus FOLFIRI arm.

Figure 8. Kaplan-Meier Plot of Survival Time. Mutant *KRAS* Efficacy Analysis Set.



Objective responses (all were partial responses) were observed in 13% and 14% of the patients in the PAN plus FOLFIRI and FOLFIRI alone arms, respectively. The odds ratio for objective response was 1.00.

Evaluation of PRO was also undertaken in the study utilising the EQ-5D scale. When reviewing the PRO endpoints according to the wild-type and mutant *KRAS* PRO analysis sets it was noted that in the wild-type *KRAS* PRO analysis set compliance was 65% in the PAN plus FOLFIRI arm and 62% in the FOLFIRI alone arm. Similar results were observed in the mutant *KRAS* PRO analysis set with overall compliance ranging from 61 to 66%.

Significant differences favouring the PAN plus FOLFIRI arm in some of the scores from the EQ-5D0 overall health rating were noted. These were however not consistent across all scales. Overall, there was no significant difference observed between the PAN plus

FOLFIRI arm and the FOLFIRI alone arm. There was a similar outcome for the mutant *KRAS* PRO analysis sets.

Evaluator's comment:

These data have once again demonstrated a benefit in relation to PFS for PAN in conjunction with FOLFIRI chemotherapy in patients who have received at least one prior chemotherapy for mCRC. Accordingly, it would certainly appear that there is evidence that the addition of PAN to chemotherapy is of benefit in patients who received either no prior chemotherapy or only one type of prior chemotherapy. As previously stated the level of improvement in PFS remains relatively small but nevertheless, in the context of a large study, significant. It is again noted that there is no apparent added benefit with respect to OS from including PAN in the treatment.

With respect to supportive studies, three have been provided in this Australian submission and design and methodology of these studies have been outlined above.

Study 314 was a single arm multicentre Phase II study of PAN in combination with FOLFIRI as first line therapy in patients with mCRC. The study was conducted across 36 sites in Austria, Belgium, France, Germany and Sweden from the 9 May 2007 through to the 18 June 2009. The primary objective of the study was to estimate the effect of *KRAS* mutation status (wild-type versus mutant) on objective response rate and other measures of efficacy for subjects treated with PAN in combination with FOLFIRI as first line therapy for mCRC. Secondary objectives included assessment of safety profile of the combination therapy in the first line setting and also to explore measures regarding PRO. PAN and FOLFIRI were administered in the same dosage schedules as in Study 181 and given every 14 days until patients were diagnosed with disease progression. When this occurred, patients were withdrawn from the treatment phase. Tumour response assessments were performed by the investigator per a modified RECIST every eight weeks through to Week 48 and every three months thereafter until evidence of disease progression. If patients withdrew from FOLFIRI due to toxicity they were allowed to continue with PAN monotherapy until disease progression at which time they were to end the treatment phase.

Inclusion criteria included:

- Histologic or cytologic confirmed and radiologically measurable metastatic colorectal cancer.
- No prior chemotherapy or anti-EGFR antibody therapy to be administered in the metastatic setting.
- ECOG performance status was 0, 1 or 2 and adequate haematologic renal hepatic and metabolic function.

A total of 154 patients were enrolled in the study and formed the full analysis set. Some 145 patients were evaluable for *KRAS* status. As of the data cut off date, 150 patients (97%) in the full analysis set had ended treatment with either PAN or FOLFIRI (97% with Wild type KRAS and 100% with mutant KRAS). A total of 147 patients or 95% had discontinued PAN (94% Wild type KRAS and 98% mutant KRAS). The most common reason for discontinuing PAN treatment was disease progression (a total of 36%; 31% with Wild type and 45% with mutant KRAS).

Most patients with wild-type and mutant *KRAS* status were men (78% and 54%, respectively) and White (97% and 98%, respectively). The median age was 63.5 years (range of 21 to 84 years) for patients with wild-type *KRAS* status and 65 years (range of 37 to 80 years) for patients with mutant *KRAS* status. ECOG performance status for the majority of the patients was 0 (58%) or 1 (36%).

In the full analysis set, 76 subjects (49%) had either a complete or partial tumour response. The median duration of response was 9.2 months with 95% CI 7.3, 13 months. The median PFS time was 7.6 months with a 95% CI 7.3, 8.9. The median time to disease progression was 7.8 months (95% CI 7.3, 9.2).

In the primary analysis set a higher percentage of patients with wild-type *KRAS* compared with mutant *KRAS* had either complete or partial tumour response. The objective response rates were 56.5% and 37.9% for patients in the wild-type *KRAS* and mutant *KRAS* groups, respectively. The difference in rates between the two *KRAS* groups was 18.5. The odds ratio for objective response rate was 2.12 favouring the wild-type *KRAS* group. The median duration of response was longer for patients with wild-type *KRAS* compared with patients in the mutant *KRAS* group (13 months and 7.4 months, respectively). The median PFS times were 8.9 months in the wild-type *KRAS* group and 7.2 months in the mutant *KRAS* group. The median time to disease progression also favoured the wild-type *KRAS* group (11.2 months compared to 7.3 months for the mutant *KRAS* group).

Study 277 was a multicentre open label single arm trial evaluating PAN in combination with FOLFIRI therapy following first line FOLFOX and Bevacizumab treatment of metastatic colorectal cancer. The study was conducted in the US from the 30 November 2006 through to the 2 January 2009.

The primary objective of the study was to estimate the effect of *KRAS* mutation status on efficacy endpoints in subjects with mCRC receiving second line FOLFIRIwith PAN after failing first line treatment containing FU and Oxaliplatin based chemotherapy with Bevacizumab. The safety profile of this drug combination was also assessed.

Patients received both PAN and FOLFIRI in the same regimen as described in Study 181. Treatment was continued until evidence of disease progression or intolerance to therapy, death or study withdrawal at request of the patient. Following disease progression patients were followed for survival every 12 weeks until the end of study.

Inclusion criteria included:

- Diagnosis of metastatic adenocarcinoma of the colorectum that had failed due to disease progression or toxicity with first line treatment containing FU and Oxaliplatin based chemotherapy with Bevacizumab.
- Measurable disease
- ECOG performance status of 0 or 1.

A total of 116 patients were enrolled in the study, 65 patients with wild-type *KRAS*, 45 patients with mutant *KRAS* and six patients in which the *KRAS* tumour status could not be evaluated. Some 115 of the enrolled patients received at least one dose of study treatment. The primary analysis set excluded the six patients without *KRAS* tumour status and thus consisted of 109 patients; that is 59% with wild-type *KRAS* (64 patients) and 41% (45 patients) with mutant *KRAS*. All patients in the primary analysis set had received prior Oxaliplatin and 98% had received prior Bevacizumab as part of first line therapy. Sixty-one (95%) patients with wild-type *KRAS* and 45 (100%) patients with mutant *KRAS* ended treatment in study. The most common reason was disease progression. However, the proportion of patients who ended study treatment for disease progression was lower in patients with wild-type *KRAS* (35 patients or 55%) than in patients with mutant *KRAS* (32 patients or 71%). Eighty-one (74%) of patients ended the study. A lower proportion of patients with wild-type *KRAS* (42 or 66%) ended study than patients with mutant *KRAS* (39 or 87%). The most common reasons for ending the study was death (34 patients or 53% with wild-type *KRAS* and 36 patients or 80% with mutant *KRAS*) or withdrawal of consent (five patients or 8% and three patients or 7%, respectively).

Most patients enrolled were men and the proportion of men versus women was higher in the wild-type *KRAS* stratum (73% men and 27% women) compared to the mutant *KRAS* stratum (58% men and 42% women). The median age was 59.5 years with a range of 33 to 85 years in the wild-type *KRAS* stratum and 60 years with a range of 29 to 80 years in the mutant *KRAS* stratum.

Overall, the results of the efficacy endpoints were in favour of patients with wild-type *KRAS*. The best response rate during study treatment was 23% for patients in the wild-type *KRAS* stratum and 16% for patients in the mutant *KRAS* stratum. The rate difference was 7%. For patients with a response, median duration of response was longer in the wild-type *KRAS* stratum (6.6 months) than the mutant *KRAS* stratum (5.4 months). The median time to response was 2.1 months in each of the two strata. Median PFS time was longer for patients in the wild-type *KRAS* stratum than patients in the mutant *KRAS* stratum (5.9 months versus 4.5 months, respectively). Compared with patients who had mutant *KRAS* tumours status, the rate of disease progression or death was reduced by approximately 20% in patients who had wild-type *KRAS* tumour status with a hazard ratio of 0.8. The median overall survival time was longer in the patients with wild-type *KRAS* tumours compared with patients with mutant *KRAS* tumours (11.4 months versus 7.2 months, respectively) with a HR 0.6. The median time to treatment failure was longer in the wild-type *KRAS* stratum compared with the mutant *KRAS* stratum (4.4 months versus 3.4 months, respectively). The median time to disease progression was also longer in patients with wild-type *KRAS* tumour status (6.0 months versus 3.9 months, respectively).

Study 409[8]. This study was initially involved a different chemotherapy regimen of Irinotecan with 5-FU in combination with PAN. Unfortunately, after a small number of had patients enrolled, a high incidence of diarrhoea toxicity was noted and the treatment was suspended. The study was redesigned and the original Irinotecan regimen was replaced by the FOLFIRI regimen. This became Part II of the trial.

The primary objective of this trial was to assess the efficacy and safety of PAN when given in combination with the FOLFIRI regimen as a first line treatment for patients with mCRC.

Study 409 was one of the first trials using PAN in combination with standard chemotherapy and accordingly evaluation of the trial in relation to *KRAS* status was not undertaken. Patients received both PAN and FOLFIRI according to standard schedules as previously indicated in Study 181. Treatment was continued until disease progression or other reason for discontinuation.

Inclusion criteria included:

- Metastatic adenocarcinoma of the colorectum with no prior treatment for disease other than surgery and 5-FU based adjuvant chemotherapy.
- Immunohistochemical proof of EGFR expression on tumour cells by relevant biopsy.

A total of 15 study centres within the US were involved in this trial. The study was initiated on the 9 July 2002 with patient enrolment completed on the 30 April 2004. The ultimate data cut off date was 30 March 2007.

A total of 24 patients went on to receive at least one dose of PAN plus chemotherapy. A total of eight patients (33%) ended treatment due to disease progression and four patients (17%) ceased therapy because of an adverse event. Median follow up time from the first dose of PAN to the last available contact was 10 months. Fifty-eight percent of the patients were men and 75% were White. The median age was 63 years with a range from 22 to 86 years. Four patients had received prior chemotherapy but none had received chemotherapy for advanced disease. Most patients entered onto study had an ECOG score of 0.

[8] Sponsor comment: Study 409 was not a supportive study for the current extension of indications application.

The overall objective response rate achieved was 8 patients (33%) which included no complete responses and eight partial responses. Eleven patients (46%) had stable disease as best response and three patients (13%) had progressive disease. The median time to response was nine weeks and median duration of response for the eight patients was estimated by the Kaplan-Meier method at 43 weeks.

Median progression free survival for all patients was 41 weeks. Time to disease progression was 47 weeks. Time to treatment failure was 22 weeks due to the number of patients who went off treatment for adverse events. The median overall survival estimated by Kaplan-Meier method was 22.5 months.

The sponsor's own summary of Phase II Study 184 (20050184) can be found under *Response from Sponsor* below.

Evaluator's comment:

These three supportive trials (two of which were conducted in patients who had received no prior chemotherapy for metastatic disease and one study with one prior line of chemotherapy for metastatic disease) essentially confirmed the data from the pivotal Studies 203 and 181; namely that the addition of PAN to FOLFIRI chemotherapy is associated with comparable objective responses which generally appear superior to that observed with chemotherapy alone. The data with regards to time to disease progression and survival are difficult to assess with confidence due to the relatively small numbers of patients in the three supportive studies. The data nevertheless do suggest comparable times to that seen from the pivotal trial. Overall this data is generally supportive of the efficacy of PAN in combination with FOLFIRI with a modest improvement in response rates compared to chemotherapy alone.

Safety

A total of 9 studies (see Figure 9) were provided with the current Australian submission to assess the clinical safety profile of PAN in combination with chemotherapy. Nine of the clinical studies involve the assessment of combination PAN with chemotherapy while one, Study 20040249[2], evaluates the combination of PAN in conjunction with Bevacizumab. This study will be dealt with separately.

For the nine clinical trials involving PAN plus chemotherapy, there is a total of data from 1536 subjects including 585 patients who received PAN in combination with Oxaliplatin based chemotherapy (the Oxaliplatin safety analysis set) and 951 patients who received PAN in combination with Irinotecan based chemotherapy (the Irinotecan safety analysis set). These data particularly emphasise the safety results from the two large Phase III open label randomised studies of PAN plus FOLFOX versus FOLFOX alone (Study 203) and PAN plus FOLFIRI versus FOLFIRI alone (Study 181).

It is noteworthy that in assessing the safety profile of PAN in combination with chemotherapy, the safety profile of PAN plus chemotherapy in both the wild-type and mutant *KRAS* groups was generally similar. Exceptions to this were patients with mutant *KRAS* receiving FOLFOX and this will be discussed below. Accordingly the safety analyses will focus on the overall PAN treated population in comparison to chemotherapy alone for patients receiving either Oxaliplatin or Irinotecan based chemotherapy.

Nine clinical studies of PAN in combination with Oxaliplatin and Irinotecan based chemotherapy in patients with mCRC (see Figure 9) provide data for the assessment of the safety of PAN in the proposed indication; for the treatment of patients with wild-type *KRAS* mCRC in combination with chemotherapy. Most of these studies have completed enrolment and <5% were still receiving PAN at the time of data cut off as indicated in

Table 9. These studies provide safety data from 1563 patients who have received at least one dose of PAN.

Figure 9. Studies with Panitumumab in combination with chemotherapy that support the proposed indications.

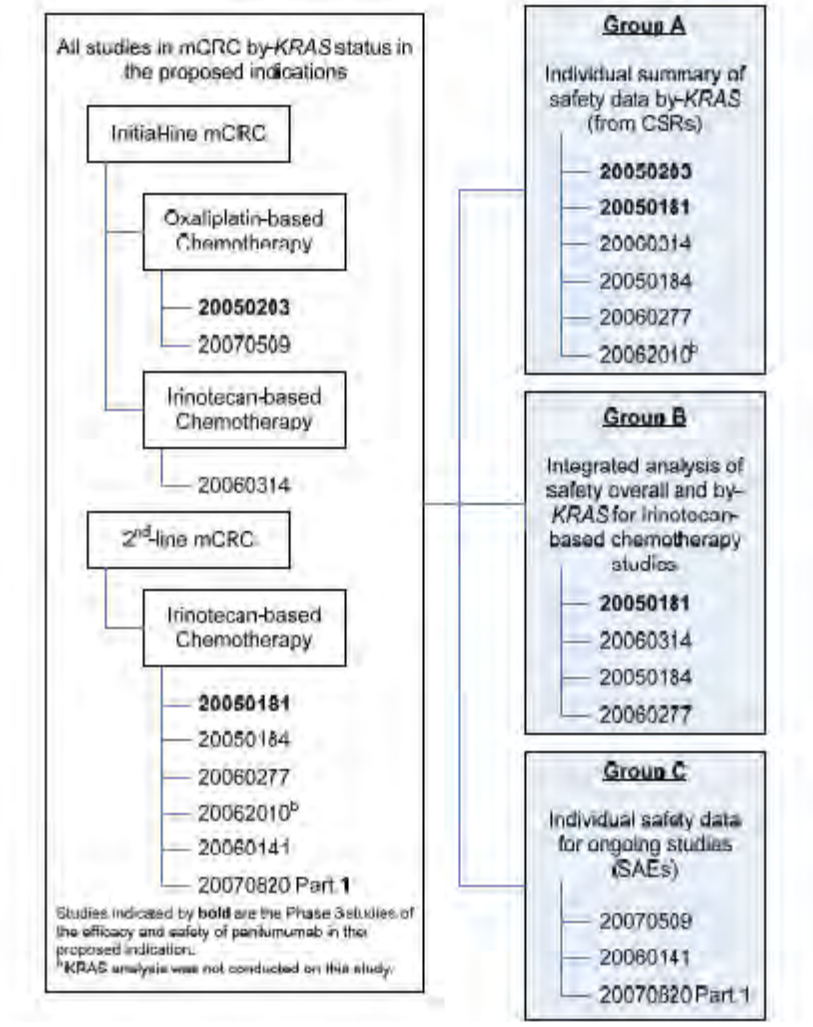


Table 9. Numbers of treated subjects included in the current Australian application.

	Panitumumab-treated Subjects Reported in CSRs	SAE Reports[a]
Combination Studies Supporting the Proposed Indication		
20050203	585	
20050181	587	
20060314	154	
20050184	95	
20060277	115	
20062010	27	
20070509		5
20060141		69
20070820 Part 1		2
Total	1563	76
Combination Studies Not Related to the Proposed Indication or *KRAS* Data Not Available		
20025409 Part 2	24	
20040249	518	
20040153	24	
20040206	41	
20060332		27
20060447		10
20050251		306
20050236		42
20040235		8
20062080		55
20062079		44
20080008		0
20060134		0
20060542		2
20040205		29
Total	607	523
Monotherapy Studies Not Related to the Proposed Indication		
20020408	229	
20030194	176	
20030250	203	
20030167	182	
20062088		17
20050236		42
20050252		5
Total	790	64

[a]Serious adverse event (SAE) report data from randomized studies with Data Monitoring Committee or Data Review Team reviews are not separated by treatment arm, but shown in aggregate. Therefore, the SAE numbers include subjects from both panitumumab-treated and control groups.

The primary safety analysis sets include all patients regardless of *KRAS* status and consist of the Oxaliplatin safety analysis set and the Irinotecan safety analysis set. The relevant cut off dates and the number of patients for these two primary analysis sets are given in Table 10. The secondary safety analysis sets were defined as the Oxaliplatin wild-type *KRAS* safety analysis set and the Irinotecan wild-type *KRAS* safety analysis set and these are summarised in Table 11.

Standard criteria, including National Cancer Institute (NCI) toxicity criteria[9], were used for description of adverse events for grading these adverse events.

Certain adverse events were prospectively identified for specific safety surveillance evaluation and these included assessment of cardiac toxicity; diarrhoea a common adverse effect associated with Irinotecan; hypomagnesemia; hypocalcaemia; impaired or delayed wound healing; infusion related reactions; disorders of skin, nail, hair; pulmonary toxicity; stomatitis/oral mucositis and vascular toxicities.

[9] Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

Table 10. Data cut off dates and number of subjects treated with study therapy in the primary analysis set.

Study Number	Data Cutoff Date	Accrual Status at Data Cutoff	Date Last Subject Enrolled	Subjects Treated at the time of the data cutoff	Subjects with Treatment Ongoing at the time of the data cutoff
Panitumumab in combination with oxaliplatin-based chemotherapy					
20050203 [a]	28 Aug 2009[d]	Closed	1 Feb 2008	1169 (585 [panitumumab arm]; 584 [no-panitumumab arm])	30
Panitumumab in combination with irinotecan-based chemotherapy					
20050181 [a]	30 Apr 2009[c]	Closed	13 Mar 2008	1181 (587 [panitumumab arm]; 594 [no-panitumumab arm])	16
20060314	18 June 2009[c]	Closed	18 Jun 2008	154	8
20050184	23 Sep 2008[b]	Closed	28 Sep 2007	95	0
20060277	02 Jan 2009[c]	Closed	4 Jan 2008	115	3
Total				1545	

[a] randomized phase 3 studies
[b] data cutoff for final CSR
[c] data cutoff for primary analysis
[d] data cutoff for primary OS CSR

Table 11. All Analysis Set.

	Panitumumab (N = 1536)	No Panitumumab (N = 1178)	All Subjects (N = 2714)
Oxaliplatin Safety Analysis Set[a]	585 (38)	584 (50)	1169 (43)
Irinotecan Safety Analysis Set[a]	951 (62)	594 (50)	1545 (57)
Oxaliplatin Wild-type KRAS Safety Analysis Set[a]	322 (21)	327 (28)	649 (24)
Irinotecan Wild-type KRAS Safety Analysis Set[a]	501 (33)	294 (25)	795 (29)

Page 1 of 1

[a] Subjects received at least one dose of study therapy are included in the safety analysis set and will be analyzed according to treatment received

Review of the extent of drug exposure indicated that for the 585 patients who received PAN plus FOLFOX chemotherapy in the Oxaliplatin safety analysis set, the median average dose of PAN delivered was 6 mg/kg. The median cumulative dose delivered was 59.8 mg/kg over a median of 10 infusions per subject. This dosage regimens are illustrated Table 12. The median average dose of PAN delivered was 6 mg/kg in both the wild-type and mutant type *KRAS* groups. Consistent with the longer PFS observed in the wild-type *KRAS* group, these patients had a longer duration of treatment and received more PAN than patients in the mutant *KRAS* groups. The median cumulative dose of PAN delivered was 62.3 mg/kg in the wild-type and 56.8 mg/kg in the mutant *KRAS* groups.

Table 12. Dosage of Panitumumab and chemotherapy (Oxaliplatin Safety Analysis Set). Table continued across two pages.

All Subjects	Panitumumab						No Panitumumab				
	Panitumumab (N = 585)	Oxaliplatin (N = 585)	l-Leucovorin (N = 585)	racemic Leucovorin (N = 585)	5-FU bolus (N = 585)	5-FU continuous infusion (N = 585)	Oxaliplatin (N = 584)	l-Leucovorin (N = 584)	racemic Leucovorin (N = 584)	5-FU bolus (N = 584)	5-FU continuous infusion (N = 584)
Duration of Treatment (weeks)											
n	585	583	171	423	583	583	584	130	458	584	584
Mean	32.4	27.7	30.8	32.7	32.5	32.6	27.9	26.5	32.1	31.0	31.1
SD	25.9	17.9	22.6	24.8	23.9	24.1	16.6	18.5	20.7	20.3	20.3
Median	26.0	25.9	26.1	27.3	27.0	27.0	25.9	24.4	26.9	26.4	26.6
Q1, Q3	15.0, 42.0	16.1, 34.0	17.1, 39.0	15.3, 42.0	16.9, 42.0	17.0, 42.0	18.0, 33.9	14.7, 33.0	19.0, 40.9	18.1, 39.7	18.1, 39.7
Min, Max	2, 135	2, 124	2, 135	2, 135	2, 135	2, 135	2, 111	2, 104	2, 137	2, 139	2, 139
Number of infusions per subject											
n	585	583	171	423	583	583	584	130	458	584	584
Mean	13.1	11.5	12.5	13.6	13.5	13.5	11.8	10.9	13.6	13.1	13.1
SD	10.6	7.1	9.1	10.1	9.8	9.9	6.7	7.2	8.6	8.4	8.4
Median	10.0	11.0	11.0	12.0	12.0	12.0	11.0	10.0	12.0	12.0	12.0
Q1, Q3	6.0, 18.0	7.0, 14.0	7.0, 16.0	7.0, 18.0	7.0, 17.0	7.0, 17.0	8.0, 14.0	6.0, 13.0	8.0, 17.0	8.0, 16.0	8.0, 16.0
Min, Max	1, 60	1, 47	1, 58	1, 55	1, 60	1, 60	1, 49	1, 42	1, 61	1, 62	1, 62

All Subjects	Panitumumab						No Panitumumab				
	Panitumumab (N = 585)	Oxaliplatin (N = 585)	l-Leucovorin (N = 585)	racemic Leucovorin (N = 585)	5-FU bolus (N = 585)	5-FU continuous infusion (N = 585)	Oxaliplatin (N = 584)	l-Leucovorin (N = 584)	racemic Leucovorin (N = 584)	5-FU bolus (N = 584)	5-FU continuous infusion (N = 584)
Cumulative dose delivered (adjusted for weight or BSA) [a]											
n	585	583	171	423	583	583	583	130	457	583	583
Mean	74.2	861.7	2468.5	5380.6	9578.0	14720.6	881.2	2140.9	5330.5	9452.7	14435.6
SD	58.8	485.6	1797.0	3984.9	6595.8	10199.2	448.5	1409.0	3313.6	5836.2	8868.6
Median	59.8	847.9	2251.8	4715.1	8543.8	13084.3	855.6	1990.6	4738.6	8641.5	13160.6
Q1, Q3	34.4, 96.7	512.4, 1080.1	1400.5, 3173.7	2449.5, 6901.1	4919.6, 12550.7	7840.0, 19198.7	598.8, 1086.2	1182.5, 2600.0	3240.7, 6632.6	5879.9, 11868.5	9089.7, 18188.5
Min, Max	0, 354	81, 3197	193, 11478	190, 21139	379, 47511	569, 71243	77, 2893	188, 8400	391, 22265	752, 39932	1128, 59771
Average dose delivered [b]											
n	585	583	171	423	583	583	583	130	457	583	583
Mean	5.8	77.1	199.7	393.9	729.5	1110.6	77.0	198.4	391.9	734.6	1117.0
SD	0.6	8.4	28.0	28.2	81.9	109.2	8.7	23.0	16.9	77.4	97.3
Median	6.0	79.8	198.0	397.6	760.7	1145.6	80.3	197.2	394.9	771.9	1157.9
Q1, Q3	5.7, 6.1	71.0, 84.0	193.6, 201.1	391.3, 402.7	676.5, 793.6	1044.1, 1190.2	71.3, 83.9	193.0, 200.0	387.9, 400.0	681.8, 793.6	1053.6, 1190.0
Min, Max	0, 7	52, 89	150, 406	190, 620	379, 931	569, 1920	46, 94	156, 388	272, 474	408, 839	791, 1487

All Subjects	Panitumumab						No Panitumumab				
	Panitumumab (N = 585)	Oxaliplatin (N = 585)	l-Leucovorin (N = 585)	racemic Leucovorin (N = 585)	5-FU bolus (N = 585)	5-FU continuous infusion (N = 585)	Oxaliplatin (N = 584)	l-Leucovorin (N = 584)	racemic Leucovorin (N = 584)	5-FU bolus (N = 584)	5-FU continuous infusion (N = 584)
Relative dose intensity [c] (%)											
n	585	583	171	423	583	583	583	130	457	583	583
Mean	80.2	77.8	84.3	84.3	77.7	79.0	78.6	85.5	84.9	79.7	80.6
SD	15.8	14.7	20.1	12.2	14.6	14.1	14.9	18.0	10.6	14.7	13.5
Median	82.2	78.5	83.4	85.8	78.4	79.6	79.7	85.0	86.1	80.7	81.4
Q1, Q3	69.8, 92.2	67.8, 89.5	75.1, 91.6	76.3, 92.7	66.8, 89.7	68.6, 90.2	68.4, 91.0	77.0, 94.5	78.2, 92.9	69.7, 91.5	71.6, 91.9
Min, Max	4, 109	26, 108	13, 203	40, 142	35, 108	35, 149	35, 110	37, 194	45, 105	37, 105	37, 103

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[a] Weight or BSA is most recent measure before infusion.
[b] Average dose delivered is weight or BSA adjusted cumulative dose divided by number of cycles delivered.
[c] Relative dose intensity is the ratio of the actual weight or BSA adjusted cumulative dose of drug to the protocol specified.

The PAN and no PAN arms of treatment received similar amounts of chemotherapy. The median number of Oxaliplatin cycles received was similar in the two treatment arms as was the median duration of treatment.

Exposure to Oxaliplatin in each treatment arm is shown for patients in the wild-type and mutant *KRAS* groups in Table 13. The median number of infusions per subject, median duration of treatment, median relative dose intensity and median average dose were all similar between the two treatment groups. However the median cumulative dose of Oxaliplatin was lower in the PAN arm in the mutant *KRAS* group.

Table 13. Exposure to Oxaliplatin in Study 20050203 Subjects in the wild-type and Mutant *KRAS* groups.

	Wild-type *KRAS*		Mutant *KRAS*	
	Panitumumab	No Panitumumab	Panitumumab	No Panitumumab
Median duration of treatment	26.0 weeks	25.7 weeks	25.1 weeks	26.0 weeks
Median relative dose intensity	77.1%	78.9%	79.6%	80.0%
Median average dose delivered	78.8 mg/m^2	80.7 mg/m^2	81.4 mg/m^2	78.9 mg/m^2
Median cumulative dose delivered	858.6 mg/m^2	871.8 mg/m^2	823.6 mg/m^2	860.2 mg/m^2
Median number of infusions per subject	11.0	11.0	11.0	11.0

For patients randomised to receive PAN plus FOLFIRI (587 patients in the PAN arm of Study 181), the median average dose of PAN delivered was 6 mg/kg and the median cumulative dose was 49.1 mg/kg over a median nine infusions per patient as indicated Table 14. This was the same for the 951 patients in the all PAN group of the Irinotecan safety analysis set. The median average dose of Irinotecan delivered was 176.6 mg/m^2 in the PAN arm and 176.5.mg/m^2 in the no PAN arm.

Exposure to Irinotecan in both treatment arms for the wild-type and mutant *KRAS* groups is shown in Table 15. The median average dose was similar for both treatment arms in both *KRAS* groups.

In relation to the disposition of patients in the Oxaliplatin safety analysis set, the median actual follow time was 79 weeks for both arms (including the 585 patients in the PAN arm and the 584 patients in the no PAN arm). However, in the wild-type *KRAS* group the actual follow up time was longer in the PAN arm (88 weeks) compared to the no PAN arm (81 weeks). The reverse was true in the mutant *KRAS* group (63 weeks for the PAN arm and 81 weeks for the no PAN arm).

For the Irinotecan safety analysis set in Study 181, the median actual follow up time in the PAN and no PAN arms were 55 and 49 weeks respectively. The median actual follow up time in the all PAN group was slightly shorter at 45 weeks. Patients in the wild-type *KRAS* group had longer median follow up in both treatment arms (60 and 52 weeks) compared to the patients in the mutant *KRAS* group (50 and 48 weeks) of Study 181. In the all PAN group, the actual follow up was longer for patients in the wild-type *KRAS* group (49 weeks) than the mutant *KRAS* group (42 weeks).

Table 14. Dosage of Panitumumab and chemotherapy (Irinotecan Safety Analysis Set). Study 20050181.

All Subjects	Panitumumab						No Panitumumab				
	Panitumumab (N = 587)	Irinotecan (N = 587)	l-Leucovorin (N = 587)	racemic Leucovorin (N = 587)	5-FU bolus (N = 587)	5-FU continuous infusion (N = 587)	Irinotecan (N = 594)	l-Leucovorin (N = 594)	racemic Leucovorin (N = 594)	5-FU bolus (N = 594)	5-FU continuous infusion (N = 594)
Duration of Treatment (weeks)											
n	587	587	163	444	586	587	594	134	471	593	594
Mean	25.6	26.0	20.5	26.6	25.6	25.7	21.6	19.0	21.7	21.4	21.5
SD	20.5	20.4	18.4	20.3	20.2	20.1	15.8	15.6	15.9	15.8	15.8
Median	21.1	22.7	17.0	23.0	22.0	22.1	18.0	15.9	18.0	18.0	18.0
Q1, Q3	9.9, 35.3	10.0, 34.7	7.9, 26.3	10.9, 36.2	9.9, 34.1	10.0, 34.1	8.9, 29.0	8.0, 26.0	9.0, 30.0	8.9, 28.1	8.9, 28.1
Min, Max	2, 115	2, 116	2, 116	2, 109	2, 116	2, 116	2, 105	2, 99	2, 105	2, 105	2, 105
Number of infusions per subject											
n	587	587	163	444	586	587	594	134	471	593	594
Mean	10.8	11.4	8.9	11.6	11.2	11.3	9.8	8.6	9.8	9.7	9.7
SD	8.5	8.8	7.8	8.9	8.8	8.7	7.2	7.1	7.3	7.3	7.3
Median	9.0	9.0	7.0	9.0	9.0	9.0	8.0	7.0	8.0	8.0	8.0
Q1, Q3	4.0, 15.0	4.0, 15.0	3.0, 12.0	5.0, 16.0	4.0, 15.0	4.0, 15.0	4.0, 13.0	4.0, 12.0	4.0, 13.0	4.0, 13.0	4.0, 13.0
Min, Max	1, 52	1, 52	1, 52	1, 47	1, 52	1, 52	1, 50	1, 46	1, 50	1, 50	1, 50

All Subjects	Panitumumab						No Panitumumab				
	Panitumumab (N = 587)	Irinotecan (N = 587)	l-Leucovorin (N = 587)	racemic Leucovorin (N = 587)	5-FU bolus (N = 587)	5-FU continuous infusion (N = 587)	Irinotecan (N = 594)	l-Leucovorin (N = 594)	racemic Leucovorin (N = 594)	5-FU bolus (N = 594)	5-FU continuous infusion (N = 594)
Cumulative dose delivered (adjusted for weight or BSA) [a]											
n	587	583	162	441	582	583	594	134	471	593	594
Mean	62.7	1915.2	1737.5	4509.3	4008.5	24508.2	1654.3	1689.0	3799.1	3555.2	21596.7
SD	49.4	1489.2	1547.3	3467.4	3120.7	18839.6	1224.6	1387.0	2853.9	2677.4	16206.9
Median	49.1	1589.3	1392.0	3619.0	3249.6	20723.2	1434.2	1381.0	3193.7	3130.9	18958.9
Q1, Q3	24.2, 85.5	725.0, 2554.9	598.3, 2382.3	1661.2, 6174.9	1598.5, 5250.7	9653.5, 32636.9	711.0, 2173.4	778.6, 2376.6	1584.6, 5092.0	1575.5, 4773.5	9489.8, 28755.0
Min, Max	6, 313	136, 9309	103, 10353	194, 19337	302, 20706	1828, 124236	134, 8784	191, 9208	185, 19798	298, 19840	1085, 113405
Average dose delivered [b]											
n	587	583	162	441	582	583	594	134	471	593	594
Mean	5.9	170.4	195.0	387.2	365.9	2223.9	170.2	197.7	387.5	371.6	2242.5
SD	0.4	14.6	22.0	39.4	42.7	256.8	14.4	20.9	34.3	40.8	223.2
Median	6.0	176.6	198.3	397.2	387.4	2329.2	176.5	197.4	396.2	390.3	2337.8
Q1, Q3	5.8, 6.1	164.8, 179.6	194.2, 200.0	390.2, 401.2	338.0, 398.3	2064.9, 2391.4	165.1, 179.5	193.7, 200.0	389.2, 400.4	350.5, 398.8	2128.4, 2391.8
Min, Max	4, 7	83, 192	102, 396	182, 549	193, 429	1074, 4308	107, 201	162, 405	181, 423	168, 591	543, 2905

All Subjects	Panitumumab						No Panitumumab				
	Panitumumab (N = 587)	Irinotecan (N = 587)	l-Leucovorin (N = 587)	racemic Leucovorin (N = 587)	5-FU bolus (N = 587)	5-FU continuous infusion (N = 587)	Irinotecan (N = 594)	l-Leucovorin (N = 594)	racemic Leucovorin (N = 594)	5-FU bolus (N = 594)	5-FU continuous infusion (N = 594)
Relative dose intensity [c] (%)											
n	587	583	162	441	582	583	594	134	471	593	594
Mean	84.9	84.4	87.4	86.0	81.6	82.7	86.2	91.0	87.9	84.9	85.2
SD	14.5	13.5	14.4	13.8	15.2	15.2	12.9	14.4	12.3	14.6	13.8
Median	87.2	86.6	88.1	88.7	83.7	84.2	90.0	91.3	91.2	89.2	89.0
Q1, Q3	75.3, 98.5	75.9, 96.5	80.0, 97.0	78.3, 97.3	70.6, 95.8	71.7, 95.9	77.0, 97.2	84.5, 97.8	82.2, 97.3	74.7, 96.8	74.8, 96.8
Min, Max	24, 108	40, 106	46, 198	32, 137	40, 107	39, 169	45, 112	55, 202	10, 104	39, 145	17, 121

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[a] Weight or BSA is most recent measure before infusion.
[b] Average dose delivered is weight or BSA adjusted cumulative dose divided by number of cycles delivered.
[c] Relative dose intensity is the ratio of the actual weight or BSA adjusted cumulative dose of drug to the protocol specified.

Table 15. Exposure to Irinotecan in Study 2005-181 Subjects in the wild-type and Mutant *KRAS* groups.

	Wild-type *KRAS*		Mutant *KRAS*	
	Panitumumab (n = 302)	No Panitumumab (n = 294)	Panitumumab	No Panitumumab
Median duration of treatment (weeks)	24.0 weeks	18.0 weeks	20.1 weeks	18.1 weeks
Median relative dose intensity	86.6%	89.9%	86.6%	90.0%
Median average dose delivered	176.4 mg/m^2	176.5 mg/m^2	176.6 mg/m^2	175.7 mg/m^2
Median cumulative dose delivered	1746.1 mg/m^2	1437.7 mg/m^2	1486.4 mg/m^2	1432.7 mg/m^2
Median number of infusions per subject	10.0	8.0	9.0	8.0

An overall summary of the adverse events experienced in the Oxaliplatin safety analysis set is indicated in Table 16.

Table 16. Summary of Adverse Events (Oxaliplatin Safety Analysis Set).

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Subjects with any adverse event - n(%)	322 (100)	323 (99)	215 (99)	217 (100)	583 (100)	579 (99)
Worst grade of 3[a]	181 (56)	161 (49)	127 (59)	115 (53)	325 (56)	296 (51)
Worst grade of 4[a]	90 (28)	66 (20)	46 (21)	45 (21)	149 (25)	120 (21)
Worst grade of 5[a]	16 (5)	20 (6)	17 (8)	7 (3)	39 (7)	28 (5)
Any Serious	135 (42)	118 (36)	103 (47)	65 (30)	262 (45)	198 (34)
Leading to permanent discontinuation of any study drug	81 (25)	49 (15)	47 (22)	29 (13)	136 (23)	84 (14)
Not serious	63 (20)	33 (10)	38 (18)	20 (9)	106 (18)	57 (10)
Serious	25 (8)	19 (6)	16 (7)	10 (5)	45 (8)	31 (5)

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Subjects with any treatment-related adverse event[b] - n(%)	321 (100)	315 (96)	214 (99)	211 (97)	581 (99)	565 (97)
Worst grade of 3[a]	190 (59)	159 (49)	134 (62)	117 (54)	344 (59)	292 (50)
Worst grade of 4[a]	74 (23)	48 (15)	38 (18)	35 (16)	123 (21)	90 (15)
Worst grade of 5[a]	4 (1)	4 (1)	2 (1)	1 (0)	8 (1)	5 (1)
Any Serious	83 (26)	52 (16)	64 (29)	28 (13)	162 (28)	89 (15)
Leading to permanent discontinuation of any study drug	72 (22)	35 (11)	38 (18)	24 (11)	117 (20)	63 (11)
Not serious	60 (19)	29 (9)	32 (15)	20 (9)	96 (16)	53 (9)
Serious	16 (5)	9 (3)	9 (4)	5 (2)	28 (5)	14 (2)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.
[b] The investigator considered there to be a reasonable possibility that the event may have been caused by study drug.

Nearly all patients in both treatment arms of Study 203 experienced adverse events including treatment related adverse events (99% and 97%, respectively). Serious adverse events occurred in 45% and 34% of patients in the PAN and no PAN arms, respectively, and serious adverse events were deemed to be treatment related in 28% and 15% of patients, respectively. Adverse events causing permanent discontinuation of any study drug occurred in 23% and 14% of patients in the PAN and no PAN arm, respectively. Fatal adverse events occurred in 7% and 5% of patients in the two arms, respectively. There were few treatment related fatal adverse events (eight patients in the PAN arm and five in the no PAN arm). The number of high level adverse events, that is, Grade III or greater was generally similar in each *KRAS* group of the overall Oxaliplatin safety analyses set. One exception was a greater difference between treatment arms in the number of serious adverse events in the mutant *KRAS* group (47% for PAN and 30% for no PAN) compared with the wild-type *KRAS* group (42% and 36%, respectively). In addition, the incidence of

fatal adverse events was higher in the PAN arm than in the no PAN arm among patients in the mutant *KRAS* group (8% and 3%, respectively) compared to the wild-type *KRAS* group (5% and 6%, respectively).

A summary of the adverse events in the Irinotecan safety analysis set for subjects in the wild-type and mutant *KRAS* groups is given Table 17.

Table 17. Summary of Adverse Events (Irinotecan Safety Analysis Set).

	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Subjects with any adverse event - n(%)	500 (100)	301 (100)	289 (98)	377 (99)	235 (99)	237 (96)	948 (100)	584 (99)	573 (96)
Worst grade of 3[a]	275 (55)	161 (53)	102 (35)	181 (48)	113 (48)	89 (36)	492 (52)	300 (51)	209 (35)
Worst grade of 4[a]	92 (18)	58 (19)	50 (17)	66 (17)	38 (16)	34 (14)	171 (18)	104 (18)	90 (15)
Worst grade of 5[a]	27 (5)	12 (4)	18 (6)	28 (7)	17 (7)	13 (5)	62 (7)	34 (6)	32 (5)
Any Serious	214 (43)	124 (41)	91 (31)	152 (40)	88 (37)	74 (30)	398 (42)	232 (40)	175 (29)
Leading to permanent discontinuation of any study drug	121 (24)	64 (21)	37 (13)	85 (22)	46 (19)	25 (10)	223 (23)	123 (21)	64 (11)
Not serious	81 (16)	40 (13)	26 (9)	58 (15)	33 (14)	8 (3)	151 (16)	83 (14)	36 (6)
Serious	47 (9)	28 (9)	14 (5)	35 (9)	16 (7)	17 (7)	89 (9)	49 (8)	32 (5)
Missing	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Subjects with any treatment-related adverse event[b] - n(%)	497 (99)	299 (99)	277 (94)	370 (98)	231 (97)	222 (90)	936 (98)	577 (98)	542 (91)
Worst grade of 3[a]	274 (55)	162 (54)	92 (31)	197 (52)	121 (51)	76 (31)	509 (54)	310 (53)	181 (30)
Worst grade of 4[a]	66 (13)	42 (14)	34 (12)	43 (11)	25 (11)	23 (9)	119 (13)	73 (12)	61 (10)
Worst grade of 5[a]	5 (1)	2 (1)	4 (1)	2 (1)	1 (0)	1 (0)	9 (1)	5 (1)	6 (1)
Any Serious	113 (23)	66 (22)	46 (16)	84 (22)	48 (20)	39 (16)	215 (23)	124 (21)	90 (15)
Leading to permanent discontinuation of any study drug	94 (19)	48 (16)	23 (8)	69 (18)	39 (16)	11 (4)	177 (19)	97 (17)	34 (6)
Not serious	72 (14)	35 (12)	16 (5)	54 (14)	32 (14)	4 (2)	137 (14)	76 (13)	20 (3)
Serious	24 (5)	15 (5)	7 (2)	18 (5)	8 (3)	7 (3)	46 (5)	25 (4)	14 (2)
Missing	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.
[b] The investigator considered there to be a reasonable possibility that the event may have been caused by study drug.

In Study 181 nearly all patients in both treatment arms experienced adverse events including treatment related adverse events. Serious adverse events occurred in 40% and 29% of patients in the PAN and no PAN arms, respectively, and were deemed treatment related in 21% and 15% of patients, respectively. Adverse events causing permanent discontinuation of any study drug was noted in 21% and 11% of patients in the PAN and no PAN arms, respectively. Fatal adverse events and treatment related fatal adverse events occurred at similar rates in the PAN and no PAN arms. The number of high level adverse events, being Grade III or greater, were similar in the overall Irinotecan safety analysis set and in each *KRAS* group. In the all PAN group, serious adverse events occurred in similar proportion of patients in the wild-type (43%) and mutant (40%) *KRAS* groups. In Study 181, the subject incidences for serious adverse events was similar between *KRAS* groups; 41% for the PAN arm and 31% for the no PAN arm in the wild-type *KRAS* group and 37% in the PAN arm and 30% in the no PAN arm in the mutant *KRAS* group.

It is worth noting that the overall adverse event pattern in both the Oxaliplatin safety analysis set and the Irinotecan safety analysis set did not change over the various time periods including three months, six months and the entire duration of study evaluation.

A review of common adverse events occurring in at least 20% of patients in the Oxaliplatin safety analysis set is shown in Table 18.

Table 18. Subject Incidences of Adverse Events in Descending order of Preferred term (for events with ≥20% incidence in the Panitumumab group of All Subjects Set). Oxaliplatin Safety Analysis Set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	322 (100)	323 (99)	215 (99)	217 (100)	583 (100)	579 (99)
Diarrhoea	201 (62)	169 (52)	131 (60)	102 (47)	356 (61)	286 (49)
Neutropenia	192 (60)	201 (61)	108 (50)	136 (62)	320 (55)	357 (61)
Rash	179 (56)	24 (7)	105 (48)	10 (5)	308 (53)	40 (7)
Nausea	144 (45)	165 (50)	100 (46)	101 (46)	263 (45)	288 (49)
Fatigue	119 (37)	112 (34)	75 (35)	78 (36)	202 (35)	198 (34)
Anorexia	116 (36)	85 (26)	72 (33)	38 (17)	202 (35)	134 (23)
Paraesthesia	106 (33)	110 (34)	60 (28)	84 (39)	180 (31)	204 (35)
Dermatitis acneiform	104 (32)	0 (0)	70 (32)	2 (<1)	188 (32)	2 (<1)
Pyrexia	100 (31)	94 (29)	66 (30)	56 (26)	181 (31)	158 (27)
Vomiting	97 (30)	105 (32)	67 (31)	69 (32)	180 (31)	190 (33)
Hypomagnesaemia	96 (30)	26 (8)	67 (31)	12 (6)	176 (30)	39 (7)
Constipation	92 (29)	91 (28)	52 (24)	56 (26)	154 (26)	155 (27)
Abdominal pain	90 (28)	76 (23)	58 (27)	50 (23)	158 (27)	136 (23)
Stomatitis	87 (27)	42 (13)	42 (19)	30 (14)	139 (24)	77 (13)

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Mucosal inflammation	82 (25)	53 (16)	52 (24)	30 (14)	146 (25)	88 (15)
Asthenia	79 (25)	62 (19)	44 (20)	49 (22)	135 (23)	119 (20)
Pruritus	75 (23)	14 (4)	44 (20)	8 (4)	128 (22)	26 (4)
Dry skin	68 (21)	13 (4)	39 (18)	5 (2)	120 (21)	20 (3)
Hypokalaemia	68 (21)	42 (13)	43 (20)	27 (12)	118 (20)	73 (13)
Paronychia	68 (21)	0 (0)	40 (18)	0 (0)	120 (21)	0 (0)
Thrombocytopenia	61 (19)	88 (27)	43 (20)	62 (28)	117 (20)	158 (27)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

The most frequent adverse events were diarrhoea, neutropenia, nausea, fatigue and anorexia. These events are well recognised in relation to Oxaliplatin based combination chemotherapy. Other frequent adverse events consistent with the known safety profile for PAN included rash, dermatitis, acneiform and hypomagnesemia. It is worth noting that certain adverse events occurred with a higher incidence in the no PAN arm; nausea, paresthesia and vomiting. This indicates that the addition of PAN had no apparent exacerbating effect on these common toxicities of FOLFOX. The incidence of some haematologic toxicities was either similar or higher in the no PAN arm; neutropenia, thrombocytopenia and anaemia. The pattern of common adverse events was generally similar in the wild-type and mutant *KRAS* groups except for neutropenia. The latter occurred with a similar incidence rate in the two treatment arms in of the wild-type *KRAS* group (60% in the PAN arm and 61% in the no PAN arm) but had a lower incidence in the PAN arm of the mutant *KRAS* group (50% in the PAN arm and 62% in the no PAN arm).

A review of the incidences of adverse events with at least a 5% difference between the treatment arms (Oxaliplatin safety analysis set) are given in Table 19.

Table 19. Subject Incidences of Adverse Events with at least 5% difference in rates between the treatment arms in Phase III studies in descending order of Preferred term. Oxaliplatin Safety Analysis Set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	320 (99)	298 (91)	211 (97)	202 (93)	575 (98)	527 (90)
Diarrhoea	201 (62)	169 (52)	131 (60)	102 (47)	356 (61)	286 (49)
Rash	179 (56)	24 (7)	105 (48)	10 (5)	308 (53)	40 (7)
Nausea	144 (45)	165 (50)	0 (0)	0 (0)	0 (0)	0 (0)
Anorexia	116 (36)	85 (26)	72 (33)	38 (17)	202 (35)	134 (23)
Dermatitis acneiform	104 (32)	0 (0)	70 (32)	2 (<1)	188 (32)	2 (<1)
Hypomagnesaemia	96 (30)	26 (8)	67 (31)	12 (6)	176 (30)	39 (7)
Stomatitis	87 (27)	42 (13)	42 (19)	30 (14)	139 (24)	77 (13)
Mucosal inflammation	82 (25)	53 (16)	52 (24)	30 (14)	146 (25)	88 (15)
Asthenia	79 (25)	62 (19)	0 (0)	0 (0)	0 (0)	0 (0)
Pruritus	75 (23)	14 (4)	44 (20)	8 (4)	128 (22)	26 (4)
Dry skin	68 (21)	13 (4)	39 (18)	5 (2)	120 (21)	20 (3)
Hypokalaemia	68 (21)	42 (13)	43 (20)	27 (12)	118 (20)	73 (13)

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Paronychia	68 (21)	0 (0)	40 (18)	0 (0)	120 (21)	0 (0)
Neuropathy peripheral	61 (19)	80 (24)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	61 (19)	88 (27)	43 (20)	62 (28)	117 (20)	158 (27)
Conjunctivitis	58 (18)	10 (3)	40 (18)	8 (4)	103 (18)	20 (3)
Weight decreased	58 (18)	22 (7)	36 (17)	12 (6)	98 (17)	39 (7)
Erythema	50 (16)	14 (4)	34 (16)	6 (3)	94 (16)	22 (4)
Skin fissures	50 (16)	1 (<1)	35 (16)	1 (<1)	89 (15)	2 (<1)
Alopecia	47 (15)	30 (9)	0 (0)	0 (0)	0 (0)	0 (0)
Epistaxis	46 (14)	30 (9)	0 (0)	0 (0)	0 (0)	0 (0)
Acne	44 (14)	1 (<1)	27 (12)	1 (<1)	74 (13)	2 (<1)
Nail disorder	32 (10)	4 (1)	0 (0)	0 (0)	49 (8)	11 (2)
Cough	31 (10)	57 (17)	0 (0)	0 (0)	54 (9)	84 (14)
Palmar-plantar erythrodysaesthesia syndrome	30 (9)	9 (3)	22 (10)	11 (5)	55 (9)	21 (4)
Dehydration	26 (8)	10 (3)	24 (11)	1 (<1)	52 (9)	13 (2)

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

Headache	19 (6)	42 (13)	15 (7)	29 (13)	37 (6)	72 (12)
Dyspnoea	0 (0)	0 (0)	21 (10)	8 (4)	0 (0)	0 (0)
Hypertension	0 (0)	0 (0)	2 (<1)	14 (6)	0 (0)	0 (0)
Neutropenia	0 (0)	0 (0)	108 (50)	136 (62)	320 (55)	357 (61)
Paraesthesia	0 (0)	0 (0)	60 (28)	84 (39)	0 (0)	0 (0)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.
Zeroes (0 (0)) will be displayed for treatment groups that have differences less than 5% in rows where other treatment groups have a 5% or greater difference.

Most of the events documented were consistent with the known safety profile of PAN. Adverse events reported with the highest subject incidence in the no PAN arm compared with the PAN arm were cough, neutropenia, headache and thrombocytopenia. The events of asthenia, dyspnoea, epistaxis and nausea were reported with a >5% difference between the PAN arm and no PAN arm in either of the wild-type or mutant *KRAS* groups but not in the Overall Safety Analysis set. Adverse events with at least a 5% difference between the treatment arms, that were not listed in the core reference safety document for PAN or considered separate adverse events of interest, included the hand/foot syndrome (PPE) anorexia and decreased weight. As summarised in Table 20, these events were rarely reported as serious and rarely led to treatment or study discontinuation.

Table 20. Summary of adverse events with a 5% higher incidence in the Panitumumab arm (Newly Identified Risks). Oxaliplatin Safety Analysis Set.

	Percent of Subjects Panitumumab, No-Panitumumab Arms of Study 20050203		
	Grade Distribution	Serious	Led to Discontinuation
Anorexia	Any: 35%, 23% 1: 18%, 14% 2: 12%, 7% 3: 4%, 2% 4: <1%, <1%	2%, < 1%	< 1%, < 1%
Palmar-plantar erythrodys-esthesia syndrome	Any: 9%, 4% 1: 4%, 2% 2: 4%, 1% 3: 2%, 1%	None reported	< 1%, 0%
Decreased weight	Any: 17%, 7% 1: 6%, 3% 2: 10%, 4% 3: 1%, <1%	< 1%, 0%	< 1%, < 1%

It was also noted that the rate of hypokalemia tended to be more pronounced in patients receiving PAN in combination with Oxaliplatin chemotherapy (20% versus 13%) as illustrated in Table 19. It is also noteworthy that one patient had sudden death attributed to possible hypokalemia. It was noted that there was no obvious differences between the wild-type and mutant *KRAS* groups.

Review of the incidence of adverse events occurring in at least 20% in the Irinotecan Safety Analysis set revealed that the most common events included diarrhoea, nausea, fatigue, neutropenia and vomiting. All of these except diarrhoea (64% in the PAN group and 55% in the no PAN group) occurred with similar incidences in the two arms of Study 181 relative to the overall PAN group.

The pattern of common adverse events in the wild-type and mutant *KRAS* groups in Study 181 and the all PAN group were generally similar to the overall population as described above. However, it is noted that dermatitis acneiform occurred in 35% of patients in the wild-type *KRAS* group and 29% in the mutant *KRAS* group, while pruritus was noted in 26% in the wild-type and 21% in the mutant group; and hypomagnesemia 25% in the wild-type and 16% in the mutant *KRAS* groups.

Table 21. Subject Incidences of Adverse Events in Descending order of preferred term (for events with ≥20% incidence in the Panitumumab group of All Subjects set). Irinotecan Analysis set.

	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	500 (100)	301 (100)	289 (98)	377 (99)	235 (99)	237 (96)	948 (100)	584 (99)	573 (96)
Diarrhoea	353 (70)	200 (66)	167 (57)	251 (66)	147 (62)	138 (56)	650 (68)	377 (64)	329 (55)
Nausea	267 (53)	154 (51)	141 (48)	191 (50)	110 (46)	111 (45)	488 (51)	281 (48)	271 (46)
Rash	231 (46)	158 (52)	23 (8)	189 (50)	138 (58)	12 (5)	464 (49)	331 (56)	38 (6)
Fatigue	198 (40)	105 (35)	93 (32)	154 (41)	87 (37)	87 (35)	373 (39)	203 (35)	189 (32)
Dermatitis acneiform	173 (35)	83 (27)	2 (<1)	111 (29)	53 (22)	1 (<1)	295 (31)	141 (24)	3 (<1)
Neutropenia	166 (33)	112 (37)	118 (40)	128 (34)	73 (31)	80 (33)	325 (34)	210 (36)	216 (36)
Vomiting	146 (29)	82 (27)	84 (29)	116 (31)	67 (28)	75 (30)	282 (30)	162 (28)	170 (29)
Pruritus	130 (26)	58 (19)	12 (4)	79 (21)	39 (16)	6 (2)	224 (24)	108 (18)	18 (3)
Dry skin	128 (26)	62 (21)	14 (5)	99 (26)	59 (25)	8 (3)	239 (25)	129 (22)	23 (4)
Alopecia	127 (25)	68 (23)	65 (22)	95 (25)	47 (20)	66 (27)	236 (25)	124 (21)	136 (23)
Anorexia	127 (25)	75 (25)	47 (16)	96 (25)	58 (24)	40 (16)	245 (26)	148 (25)	95 (16)
Hypomagnesaemia	124 (25)	78 (26)	8 (3)	59 (16)	36 (15)	5 (2)	194 (20)	122 (21)	15 (3)
Stomatitis	123 (25)	68 (23)	36 (12)	93 (25)	56 (24)	34 (14)	228 (24)	131 (22)	76 (13)
Abdominal pain	117 (23)	72 (24)	55 (19)	80 (21)	40 (17)	50 (20)	217 (23)	126 (21)	113 (19)
Constipation	115 (23)	71 (24)	61 (21)	106 (28)	61 (26)	54 (22)	239 (25)	139 (24)	126 (21)
Mucosal inflammation	111 (22)	60 (20)	40 (14)	100 (26)	55 (23)	29 (12)	226 (24)	123 (21)	72 (12)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

Table 22 shows the incidence of adverse events with at least a 5% difference between treatment arms in the Irinotecan Safety Analysis set.

Once again, adverse events with a >5% incidence in the PAN treated arm and which had not been previously recognised included anorexia, PPE and decreased weight. These appear to be newly identified risks for PAN.

Again , hypokalemia was also reported with a >5% incidence among patients receiving PAN. For patients in Study 181, hypokalemia was reported in 12% of patients on PAN and 5% on the no PAN arm.

Treatment related adverse events in the Oxaliplatin safety analysis and which occurred more frequently in the PAN arm included rash, dermatitis acneiform, hypomagnesemia and anorexia. There was an essentially equal incidence of these in both the wild-type and mutant *KRAS* groups. Nevertheless a higher incidence (by >5%) of neutropenia, rash, paresthesia, stomatitis was apparent in the wild-type *KRAS* group relative to the mutant *KRAS* group in the PAN arm. Again treatment related events which were newly identified in relation to PAN treatment were anorexia, PPE and decreased weight.

The most common treatment related adverse events in the Irinotecan safety analysis set, all PAN group, was diarrhoea. Other treatment related adverse events occurring more frequently in the PAN arm than the no PAN arm in Study 181 included skin toxicities, stomatitis, mucosal inflammation and anorexia. Once again, the newly identified risks of anorexia, PPE and decreased weight were reported with a higher incidence in patients receiving PAN compared to the no PAN arm.

Table 22. Subject incidence of adverse events with a 5% difference in rates between treatment arms in Phase III studies in descending order of preferred term. Irinotecan Safety Analysis Set.

	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	491 (98)	295 (98)	232 (79)	368 (97)	227 (96)	191 (78)	926 (97)	566 (96)	448 (75)
Diarrhoea	353 (70)	200 (66)	167 (57)	251 (66)	147 (62)	138 (56)	650 (68)	377 (64)	329 (55)
Rash	231 (46)	158 (52)	23 (8)	189 (50)	138 (58)	12 (5)	464 (49)	331 (56)	38 (6)
Dermatitis acneiform	173 (35)	83 (27)	2 (<1)	111 (29)	53 (22)	1 (<1)	295 (31)	141 (24)	3 (<1)
Pruritus	130 (26)	58 (19)	12 (4)	79 (21)	39 (16)	6 (2)	224 (24)	108 (18)	18 (3)
Dry skin	128 (26)	62 (21)	14 (5)	99 (26)	59 (25)	8 (3)	239 (25)	129 (22)	23 (4)
Anorexia	127 (25)	75 (25)	47 (16)	96 (25)	58 (24)	40 (16)	245 (26)	148 (25)	95 (16)
Hypomagnesaemia	124 (25)	78 (26)	8 (3)	59 (16)	36 (15)	5 (2)	194 (20)	122 (21)	15 (3)
Stomatitis	123 (25)	68 (23)	36 (12)	93 (25)	56 (24)	34 (14)	228 (24)	131 (22)	76 (13)
Abdominal pain	117 (23)	72 (24)	55 (19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mucosal inflammation	111 (22)	60 (20)	40 (14)	100 (26)	55 (23)	29 (12)	226 (24)	123 (21)	72 (12)
Paronychia	98 (20)	58 (19)	2 (<1)	61 (16)	34 (14)	1 (<1)	174 (18)	101 (17)	3 (<1)
	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Skin fissures	98 (20)	56 (19)	2 (<1)	67 (18)	35 (15)	1 (<1)	172 (18)	94 (16)	3 (<1)
Anaemia	86 (17)	46 (15)	67 (23)	0 (0)	0 (0)	0 (0)	161 (17)	82 (14)	113 (19)
Hypokalaemia	84 (17)	42 (14)	14 (5)	0 (0)	0 (0)	0 (0)	149 (16)	69 (12)	27 (5)
Conjunctivitis	79 (16)	49 (16)	5 (2)	39 (10)	27 (11)	6 (2)	127 (13)	81 (14)	11 (2)
Erythema	73 (15)	48 (16)	8 (3)	52 (14)	39 (16)	8 (3)	133 (14)	92 (16)	16 (3)
Acne	72 (14)	42 (14)	4 (1)	53 (14)	31 (13)	4 (2)	136 (14)	80 (14)	10 (2)
Alopecia	0 (0)	0 (0)	0 (0)	95 (25)	47 (20)	66 (27)	0 (0)	0 (0)	0 (0)
Nail disorder	0 (0)	0 (0)	0 (0)	27 (7)	19 (8)	5 (2)	70 (7)	43 (7)	8 (1)
Palmar-plantar erythrodysaesthesia syndrome	0 (0)	0 (0)	0 (0)	40 (11)	24 (10)	9 (4)	86 (9)	54 (9)	22 (4)
Pyrexia	0 (0)	0 (0)	0 (0)	73 (19)	51 (22)	40 (16)	0 (0)	0 (0)	0 (0)
Weight decreased	0 (0)	0 (0)	0 (0)	56 (15)	27 (11)	11 (4)	136 (14)	61 (10)	29 (5)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.
Zeroes (0 (0)) will be displayed for treatment groups that have differences less than 5% in rows where other treatment groups have a 5% or greater difference.

The incidence of Grade III/IV adverse events occurring in at least 5% of the PAN treated patients in the Oxaliplatin safety analysis set is summarised in Table 23.

The overall incidence of Grade III or IV adverse events is higher in the PAN arm compared to the no PAN arm (87% versus 76%). It was noted that the PAN arm of patients in the mutant *KRAS* group had a >5% higher incidence of Grade III/IV dehydration than the no PAN arm but this was not the case in the wild-type *KRAS* group. Grade III/IV fatigue was more common in the PAN treated patients in the wild-type *KRAS* group but less so in the mutant *KRAS* group. Similarly, neutropenia was less frequent in the PAN treated patients in the mutant *KRAS* group but similar in both arms of the wild-type *KRAS* group. Several of the most common Grade III or higher events associated with FOLFOX chemotherapy were not exacerbated by the addition of PAN, including neutropenia, paresthesia, vomiting and thrombocytopenia.

Table 23. Subject incidence of Grade III or IV adverse events in descending order of preferred term (for events with ≥5% incidence in Panitumumab group of All Subjects set. Oxaliplatin Safety Analysis set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	285 (89)	246 (75)	189 (87)	166 (76)	510 (87)	442 (76)
Neutropenia	131 (41)	131 (40)	77 (35)	101 (46)	221 (38)	245 (42)
Diarrhoea	59 (18)	29 (9)	43 (20)	22 (10)	108 (18)	55 (9)
Rash	55 (17)	1 (<1)	29 (13)	0 (0)	90 (15)	1 (<1)
Dermatitis acneiform	33 (10)	0 (0)	16 (7)	0 (0)	50 (9)	0 (0)
Hypokalaemia	33 (10)	15 (5)	19 (9)	8 (4)	53 (9)	26 (4)
Fatigue	31 (10)	10 (3)	16 (7)	11 (5)	48 (8)	24 (4)
Paraesthesia	28 (9)	21 (6)	17 (8)	17 (8)	47 (8)	39 (7)
Hypomagnesaemia	21 (7)	1 (<1)	14 (6)	1 (<1)	38 (6)	2 (<1)
Neuropathy peripheral	18 (6)	18 (6)	11 (5)	10 (5)	32 (5)	30 (5)
Abdominal pain	17 (5)	13 (4)	9 (4)	6 (3)	27 (5)	22 (4)
Asthenia	16 (5)	11 (3)	10 (5)	8 (4)	28 (5)	20 (3)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

Subject Incidences of Grade III and IV Adverse Events with at least 5% difference in incidence between treatment arms in Phase III studies in Descending order of Preferred term. Oxaliplatin Safety Analysis Set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	167 (52)	50 (15)	139 (64)	115 (53)	243 (42)	57 (10)
Diarrhoea	59 (18)	29 (9)	43 (20)	22 (10)	108 (18)	55 (9)
Rash	55 (17)	1 (<1)	29 (13)	0 (0)	90 (15)	1 (<1)
Dermatitis acneiform	33 (10)	0 (0)	16 (7)	0 (0)	50 (9)	0 (0)
Hypokalaemia	33 (10)	15 (5)	19 (9)	8 (4)	0 (0)	0 (0)
Fatigue	31 (10)	10 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Hypomagnesaemia	21 (7)	1 (<1)	14 (6)	1 (<1)	38 (6)	2 (<1)
Dehydration	0 (0)	0 (0)	12 (6)	1 (<1)	0 (0)	0 (0)
Neutropenia	0 (0)	0 (0)	77 (35)	101 (46)	0 (0)	0 (0)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.
Zeroes (0 (0)) will be displayed for treatment groups that have differences less than 5% in rows where other treatment groups have a 5% or greater difference.

The incidence of Grade III or IV adverse events in the Irinotecan safety analysis set is given in Table 24.

Table 24. Subject Incidences of Grade III and IV Adverse Events in Descending order of Preferred term (for events occurring in ≥5% in Panitumumab arm, Study 20050181. Irinotecan Safety Analysis Set.

	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	390 (78)	229 (76)	169 (57)	272 (72)	165 (70)	132 (54)	717 (75)	432 (74)	326 (55)
Neutropenia	96 (19)	59 (20)	68 (23)	61 (16)	32 (14)	43 (17)	180 (19)	110 (19)	122 (21)
Diarrhoea	82 (16)	41 (14)	27 (9)	57 (15)	32 (14)	26 (11)	154 (16)	82 (14)	56 (9)
Rash	60 (12)	46 (15)	0 (0)	48 (13)	39 (16)	1 (<1)	124 (13)	98 (17)	1 (<1)
Dermatitis acneiform	49 (10)	28 (9)	0 (0)	29 (8)	19 (8)	0 (0)	79 (8)	48 (8)	0 (0)
Fatigue	38 (8)	21 (7)	13 (4)	29 (8)	19 (8)	11 (4)	70 (7)	42 (7)	25 (4)
Hypokalaemia	30 (6)	20 (7)	3 (1)	26 (7)	9 (4)	2 (<1)	59 (6)	30 (5)	5 (<1)
Mucosal inflammation	20 (4)	14 (5)	4 (1)	24 (6)	17 (7)	4 (2)	45 (5)	31 (5)	9 (2)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

The incidence of Grade III or IV adverse events overall were higher in those receiving PAN (74% compared to 55% in the no PAN arm) in Study 181. Neutropenia was the most common Grade III or IV event and it had a similar incidence rate in the two treatment arms.

Grade III or IV adverse events occurring more frequently in the PAN arm were those well recognised as being adverse reactions associated with PAN administration.

There was a <5% difference between arms in the percentage of patients who discontinued all chemotherapy due to adverse events and the most common adverse events leading to discontinuation for PAN was skin toxicities.

A summary of the various events leading to treatment discontinuation in the overall Oxaliplatin safety analysis set is given in Table 25.

Table 25. Subject Incidences of Adverse Events leading to discontinuation from all chemotherapy (top) or Panitumumab (bottom) in descending order of Preferred Term in ≥1% of subjects in the Panitumumab arm (all subjects). Oxaliplatin Analysis set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	62 (19)	49 (15)	32 (15)	29 (13)	101 (17)	84 (14)
Paraesthesia	9 (3)	5 (2)	5 (2)	2 (<1)	14 (2)	7 (1)
Fatigue	7 (2)	0 (0)	0 (0)	2 (<1)	7 (1)	2 (<1)
Diarrhoea	6 (2)	0 (0)	2 (<1)	2 (<1)	8 (1)	2 (<1)
Hypersensitivity	5 (2)	4 (1)	2 (<1)	0 (0)	7 (1)	4 (<1)

	Wild-type KRAS	Mutant KRAS	All Subjects
	Panitumumab (N = 322)	Panitumumab (N = 217)	Panitumumab (N = 585)
Preferred Term	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	61 (19)	38 (18)	107 (18)
Rash	15 (5)	10 (5)	25 (4)
Dermatitis acneiform	5 (2)	4 (2)	9 (2)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

The most common events leading to FOLFOX discontinuation were paresthesia, fatigue, diarrhoea and hypersensitivity. The pattern of adverse events leading to discontinuation was similar in the Wild type and mutant KRAS groups. In Study 203, 18% of patients discontinued PAN due to an adverse event, the most common of these being rash (4%) and dermatitis acneiform (2%).

Review of the Irinotecan safety analysis set revealed that adverse events leading to discontinuation from all chemotherapy occurred in 15% of patients on the PAN arm of Study 181, 11% of patients on the no PAN arm and 17% of patients on the all PAN group. This is illustrated in Table 26.

Table 26. Subject Incidences of Adverse Events leading to discontinuation from all chemotherapy (top, Study 20050181 Panitumumab arm) or Panitumumab (bottom, All-Panitumumab group) in descending order of Preferred Term in ≥1% of subjects in the Panitumumab arm (all subjects). Irinotecan Analysis set.

	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	93 (19)	46 (15)	37 (13)	60 (16)	31 (13)	25 (10)	165 (17)	87 (15)	64 (11)
Diarrhoea	17 (3)	4 (1)	3 (1)	11 (3)	4 (2)	0 (0)	30 (3)	10 (2)	3 (<1)
Fatigue	7 (1)	4 (1)	4 (1)	8 (2)	5 (2)	1 (<1)	15 (2)	9 (2)	6 (1)
Asthenia	4 (<1)	2 (<1)	1 (<1)	3 (<1)	3 (1)	0 (0)	8 (<1)	6 (1)	1 (<1)
Rash	3 (<1)	2 (<1)	1 (<1)	9 (2)	8 (3)	0 (0)	13 (1)	11 (2)	1 (<1)

	Wild-type KRAS		Mutant KRAS		All Subjects	
	All Panit. (N = 501)	Panit. in 181 (N = 302)	All Panit. (N = 379)	Panit. in 181 (N = 237)	All Panit. (N = 951)	Panit. in 181 (N = 587)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	95 (19)	49 (16)	71 (19)	39 (16)	180 (19)	98 (17)
Rash	13 (3)	8 (3)	18 (5)	13 (5)	36 (4)	25 (4)
Diarrhoea	8 (2)	2 (<1)	7 (2)	4 (2)	16 (2)	7 (1)
Dermatitis acneiform	5 (<1)	1 (<1)	9 (2)	7 (3)	14 (1)	8 (1)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

Adverse events causing chemotherapy discontinuation in at least 1% of patients in the PAN arm of Study 181 were diarrhoea, fatigue, asthenia and rash. Diarrhoea led to discontinuation slightly more frequently in the PAN arm than in the no PAN arm. There were no important differences from the above pattern noted in the wild-type or mutant *KRAS* groups.

A review of the deaths that occurred in the two Phase III studies revealed that in Study 203 the rates were 7% for the PAN arm and 5% for the no PAN arm while in Study 181 the rates were 6% in the PAN arm and 5% for the no PAN arm. In the all PAN group the rate was 7%. In both studies, the treatment related fatal adverse events occurred in 1% of patients from each treatment arm.

The incidence of fatal adverse events in wild-type *KRAS* patients was similar between the treatment arms in both studies. However, in the mutant *KRAS* group in Study 203 the incidence of fatal adverse events in the PAN arm was higher than in the no PAN arm (8% versus 3%, with a hazard ratio 2.58). This difference was not as marked in Study 181 (7% for PAN and 5% for no PAN in the mutant *KRAS* group).

Treatment related fatal adverse events were infrequent and reported in a similar proportion of patients in both treatment arms in Study 203 (1% in each arm). Most of these events were a direct consequence of disease progression. Other on treatment fatal adverse events had various causes but few occurred in more than one patient. The incidence of fatal adverse events was similar between treatment arms in the wild-type *KRAS* group but was again higher in the PAN arm of the mutant *KRAS* group (8% versus 3%). The hazard ratio was 2.58. Deaths were due to a variety of causes including mCRC.

These fatal adverse events were generally consistent with the course of mCRC. It is noted that non disease progression fatal adverse events which occurred in more than one subject in the PAN arm were renal failure (n=2), hepatic failure (n=2) and cardio-respiratory arrest (n=2). Nevertheless pneumonitis and bilateral pneumonia were the only two fatal adverse events reported as related to PAN. Both events occurred in subjects in the wild-type *KRAS* groups. No apparent pattern of fatal adverse events could be determined in patients in the wild-type and mutant *KRAS* groups. Furthermore, the deaths

related to hepatic failure occurred in patients with recognised liver metastases and they were not considered to be related to PAN. Two patients in the PAN arm of therapy experienced pulmonary embolism as a fatal adverse event but neither were considered to be related to PAN administration. Similarly, the two cardio respiratory deaths and the two renal failure deaths were not considered to be related to PAN therapy either.

Three patients died from fatal infection events and this included febrile neutropenia in patient in the mutant *KRAS* group which was considered to be related to treatment (including PAN).

A review of the deaths that occurred in the Irinotecan safety analysis set indicated similar proportions of patients with on treatment fatal adverse events in the PAN (6%) and no PAN (5%) arms of Study 181 and in the all PAN group (7%). The rate of fatal adverse events was 4% and 6% in the PAN and no PAN arms, respectively, in the wild-type *KRAS* group, and 7% and 5%, respectively, for PAN and no PAN patients in the mutant *KRAS* group. Disease progression was the most frequent on treatment fatal adverse event. The type of the other on treatment fatal adverse events varied and few occurred in more than one patient.

As in Study 203, the cause of deaths was generally consistent with the course typical of patients with advanced mCRC.

In Study 181, one patient in the PAN arm of study died from diarrhoea which was considered related to treatment. Another patient in the PAN arm also died due to disease progression and associated Grade IV diarrhoea.

In Study 314, one patient died from haematemesis which was considered as possibly related to PAN. Another patient from the same study died from rectal bleeding. Both these patients were from the wild-type *KRAS* group.

In Study 277, one patient in the wild-type *KRAS* group developed Grade IV diarrhoea and acute renal failure and ultimately died of septic shock which was considered as likely to be related to PAN plus chemotherapy. A further patient in Study 314 experienced fatal vena cava thrombosis which was considered as possibly related to PAN plus chemotherapy.

A review of other serious adverse events revealed that diarrhoea occurred with higher frequency in the PAN arm than the no PAN arm in both pivotal trials. Furthermore, diarrhoea was the only serious event that had a >5 times higher incidence when PAN was given in combination with FOLFOX in Study 203. In Study 181 the rate of diarrhoea was 2% higher in the PAN plus FOLFIRI arm.

In the Oxaliplatin safety analysis set the subject incidence of serious adverse events was higher in the PAN treated arm compared with the no PAN arm (45% versus 34%) and this is shown in Table 27.

Table 27. Subject incidence of serious adverse events in descending order of Preferred Term (for events with ≥2% incidence in the Panitumumab group of All Subjects set). Oxaliplatin Safety Analysis set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	135 (42)	118 (36)	103 (47)	65 (30)	262 (45)	198 (34)
Diarrhoea	29 (9)	9 (3)	24 (11)	6 (3)	58 (10)	17 (3)
Abdominal pain	9 (3)	5 (2)	4 (2)	3 (1)	14 (2)	10 (2)
Vomiting	9 (3)	10 (3)	9 (4)	2 (<1)	18 (3)	12 (2)
Dehydration	8 (2)	4 (1)	11 (5)	0 (0)	20 (3)	5 (<1)
Intestinal obstruction	8 (2)	9 (3)	8 (4)	1 (<1)	18 (3)	12 (2)
Pulmonary embolism	8 (2)	3 (<1)	6 (3)	6 (3)	14 (2)	10 (2)
Pyrexia	8 (2)	11 (3)	7 (3)	4 (2)	16 (3)	15 (3)
Nausea	7 (2)	2 (<1)	5 (2)	1 (<1)	12 (2)	3 (<1)
Neutropenia	7 (2)	7 (2)	4 (2)	3 (1)	11 (2)	10 (2)
Rash	6 (2)	1 (<1)	3 (1)	1 (<1)	10 (2)	2 (<1)
Sepsis	6 (2)	5 (2)	2 (<1)	2 (<1)	12 (2)	7 (1)
Colorectal cancer metastatic	5 (2)	5 (2)	4 (2)	0 (0)	9 (2)	5 (<1)
Deep vein thrombosis	5 (2)	4 (1)	3 (1)	1 (<1)	9 (2)	5 (<1)
Febrile neutropenia	5 (2)	8 (2)	7 (3)	5 (2)	15 (3)	14 (2)
Pneumonia	5 (2)	6 (2)	3 (1)	1 (<1)	10 (2)	8 (1)
Anorexia	3 (<1)	1 (<1)	5 (2)	1 (<1)	9 (2)	2 (<1)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

The most frequent serious adverse events in the PAN arm were diarrhoea (10% versus 3% in the no PAN arm), febrile neutropenia (3% versus 2%, respectively), pyrexia (3% versus 3%, respectively), dehydration (3% versus <1%, respectively) and intestinal obstruction (3% versus 2%, respectively) and vomiting (3% versus 2%, respectively). Serious adverse events were deemed treatment related in 28% and 15% of patients in the PAN and no PAN arms, respectively. Diarrhoea was the most common treatment related serious adverse event.

In Study 203 a greater difference between the PAN and no PAN treatment arms was observed with respect to serious adverse events in the mutant *KRAS* group (47% on PAN versus 30% in the no PAN arm) compared to the wild-type *KRAS* groups (42% and 36%, respectively). No single event appeared to account for this difference. The incidence of dehydration, diarrhoea, pyrexia and intestinal obstruction were 2 to 3% higher in PAN treated patients in the mutant *KRAS* group relative to those in the wild-type *KRAS* groups.

Serious adverse events among patients who received PAN in the Irinotecan safety analysis set are summarised in Table 28.

Table 28. Subject incidence of serious adverse events in descending order of Preferred Term (for events with ≥2% incidence in the Panitumumab group of All Subjects set). Irinotecan Safety Analysis set.

	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with any adverse event[a] - n(%)	214 (43)	124 (41)	91 (31)	152 (40)	88 (37)	74 (30)	398 (42)	232 (40)	175 (29)
Diarrhoea	41 (8)	21 (7)	11 (4)	21 (6)	10 (4)	11 (4)	67 (7)	33 (6)	23 (4)
Dehydration	27 (5)	12 (4)	4 (1)	18 (5)	6 (3)	6 (2)	49 (5)	20 (3)	11 (2)
Pulmonary embolism	19 (4)	11 (4)	4 (1)	12 (3)	5 (2)	6 (2)	32 (3)	17 (3)	10 (2)
Pyrexia	18 (4)	11 (4)	9 (3)	17 (4)	12 (5)	5 (2)	36 (4)	24 (4)	16 (3)
Vomiting	15 (3)	7 (2)	5 (2)	15 (4)	8 (3)	8 (3)	32 (3)	17 (3)	13 (2)
Abdominal pain	14 (3)	7 (2)	7 (2)	8 (2)	4 (2)	4 (2)	23 (2)	12 (2)	13 (2)
Nausea	10 (2)	7 (2)	2 (<1)	10 (3)	5 (2)	3 (1)	20 (2)	12 (2)	5 (<1)
Deep vein thrombosis	9 (2)	3 (<1)	1 (<1)	4 (1)	2 (<1)	1 (<1)	15 (2)	7 (1)	2 (<1)
Febrile neutropenia	9 (2)	6 (2)	8 (3)	6 (2)	4 (2)	7 (3)	17 (2)	11 (2)	16 (3)
Neutropenia	9 (2)	3 (<1)	5 (2)	8 (2)	3 (1)	5 (2)	19 (2)	6 (1)	12 (2)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

In Study 181, 40% and 29% of patients in the PAN and no PAN arms, respectively, had serious adverse events, the most common being diarrhoea. The percentage of patients with serious adverse events of dehydration, pulmonary embolism, pyrexia and vomiting was higher in the PAN arm. Furthermore, treatment related serious adverse events occurred in 21% and 15% of patients in the PAN and no PAN arms, respectively, with diarrhoea, dehydration, vomiting, pyrexia, nausea and febrile neutropenia being the most common.

The subject incidence of serious adverse events and treatment related serious adverse events in the all PAN group was similar to those described from Study 181 above. The subject incidence of serious events was 41% in the PAN arm and 31% in the no PAN arm of the wild-type *KRAS* group. This can be compared to 37% (PAN) and 30% (no PAN), respectively, in the mutant *KRAS* group. The only events with at least a 2% difference between PAN treated patients in the wild-type *KRAS* and mutant *KRAS* groups were diarrhoea and pulmonary embolism.

Adverse events of specific interest for PAN, that is, those that occurred at a notably higher rate (+5%) in the PAN arms were the same in both of the randomised trials and included hypomagnesemia, diarrhoea, stomatitis/oral mucositis and skin and eye toxicities. Other events of interest such as infusion reactions, cardiac, pulmonary and vascular toxicities occurred with similar frequencies in the two arms.

The most frequently reported adverse event of interest in the Oxaliplatin safety analysis set was skin and eye toxicity affecting 96% and 42% of patients in the PAN and no PAN arms, respectively, as summarised in Tables 29 and 30.

Table 29. Subject incidence of adverse events of interest. Oxaliplatin Analysis set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Subjects with any adverse event of interest - n(%)	320 (99)	279 (85)	214 (99)	180 (83)	580 (99)	487 (83)
Hypomagnesemia	102 (32)	26 (8)	71 (33)	13 (6)	187 (32)	40 (7)
Hypocalcemia	19 (6)	8 (2)	10 (5)	4 (2)	32 (5)	12 (2)
Diarrhea	201 (62)	169 (52)	131 (60)	102 (47)	356 (61)	286 (49)
Cardiac Toxicity - Pre-specified	45 (14)	42 (13)	32 (15)	28 (13)	80 (14)	72 (12)
Cardiac Arrythmias - SMQ	30 (9)	24 (7)	20 (9)	21 (10)	53 (9)	46 (8)
Ischaemic Heart Disease - SMQ	1 (0)	4 (1)	6 (3)	2 (1)	7 (1)	6 (1)
Pulmonary Toxicity	65 (20)	96 (29)	46 (21)	41 (19)	124 (21)	143 (24)
Vascular Toxicity - Pre-specified	95 (30)	90 (28)	54 (25)	52 (24)	164 (28)	151 (26)
Vasculitis - SMQ	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Embolic and Thrombotic - SMQ[a]	47 (15)	37 (11)	29 (13)	24 (11)	81 (14)	66 (11)
Impaired or Delayed Wound Healing	4 (1)	0 (0)	3 (1)	0 (0)	8 (1)	0 (0)
Interstitial Lung Disease - SMQ	3 (1)	4 (1)	0 (0)	0 (0)	3 (1)	4 (1)
Stomatitis or Oral Mucositis	156 (48)	92 (28)	92 (42)	57 (26)	268 (46)	158 (27)
Integument and Eye Toxicities - Pre-specified	312 (97)	139 (43)	208 (96)	91 (42)	562 (96)	247 (42)
Skin Toxicity	312 (97)	107 (33)	207 (95)	64 (29)	560 (96)	183 (31)
Nail Toxicity	107 (33)	6 (2)	55 (25)	11 (5)	178 (30)	19 (3)
Hair Toxicity	61 (19)	30 (9)	35 (16)	22 (10)	106 (18)	56 (10)
Eye Toxicity	102 (32)	51 (16)	65 (30)	37 (17)	180 (31)	93 (16)
Cheilitis	12 (4)	5 (2)	8 (4)	7 (3)	21 (4)	12 (2)
Severe Cutaneous Adverse Reactions - SMQ	12 (4)	3 (1)	10 (5)	1 (0)	25 (4)	4 (1)
Infusion Reaction	94 (29)	96 (29)	52 (24)	58 (27)	164 (28)	164 (28)
USPI	30 (9)	39 (12)	16 (7)	18 (8)	55 (9)	60 (10)
CTCAE	85 (26)	84 (26)	47 (22)	53 (24)	147 (25)	147 (25)
Reported AE	30 (9)	39 (12)	19 (9)	21 (10)	57 (10)	63 (11)

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[a] Includes: Embolic and thrombotic events, arterial; Embolic and thrombotic events, venous; Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous.

Table 30. Subject incidence of Grade III or higher adverse events of interest. Oxaliplatin Analysis set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Subjects with any adverse event of interest - n(%)	214 (66)	81 (25)	136 (63)	58 (27)	375 (64)	152 (26)
Hypomagnesemia	21 (7)	1 (0)	14 (6)	1 (0)	38 (6)	2 (0)
Hypocalcemia	3 (1)	1 (0)	2 (1)	0 (0)	6 (1)	1 (0)
Diarrhea	59 (18)	29 (9)	43 (20)	22 (10)	108 (18)	56 (10)
Cardiac Toxicity - Pre-specified	14 (4)	10 (3)	11 (5)	9 (4)	26 (4)	20 (3)
Cardiac Arrythmias - SMQ	9 (3)	6 (2)	9 (4)	8 (4)	20 (3)	14 (2)
Ischaemic Heart Disease - SMQ	1 (0)	3 (1)	4 (2)	0 (0)	5 (1)	3 (1)
Pulmonary Toxicity	11 (3)	14 (4)	7 (3)	2 (1)	19 (3)	19 (3)
Vascular Toxicity - Pre-specified	37 (11)	24 (7)	20 (9)	14 (6)	62 (11)	44 (8)
Vasculitis - SMQ	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Embolic and Thrombotic - SMQ[a]	39 (12)	24 (7)	22 (10)	15 (7)	65 (11)	43 (7)
Impaired or Delayed Wound Healing	0 (0)	0 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Interstitial Lung Disease - SMQ	2 (1)	2 (1)	0 (0)	0 (0)	2 (0)	2 (0)
Stomatitis or Oral Mucositis	28 (9)	2 (1)	13 (6)	6 (3)	42 (7)	9 (2)
Integument and Eye Toxicities - Pre-specified	130 (40)	9 (3)	72 (33)	3 (1)	212 (36)	13 (2)
Skin Toxicity	119 (37)	7 (2)	68 (31)	3 (1)	197 (34)	10 (2)
Nail Toxicity	17 (5)	0 (0)	5 (2)	0 (0)	23 (4)	0 (0)
Hair Toxicity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Eye Toxicity	8 (2)	2 (1)	4 (2)	0 (0)	13 (2)	3 (1)
Cheilitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe Cutaneous Adverse Reactions - SMQ	2 (1)	0 (0)	2 (1)	0 (0)	4 (1)	0 (0)
Infusion Reaction	12 (4)	8 (2)	6 (3)	10 (5)	20 (3)	20 (3)
USPI	8 (2)	5 (2)	4 (2)	7 (3)	14 (2)	14 (2)
CTCAE	9 (3)	4 (1)	4 (2)	5 (2)	15 (3)	10 (2)
Reported AE	8 (2)	6 (2)	4 (2)	10 (5)	14 (2)	18 (3)

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[a] Includes: Embolic and thrombotic events, arterial; Embolic and thrombotic events, venous; Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous.

In Study 203 the most frequently reported adverse event of interest included skin toxicity (96% and 31%, respectively), diarrhoea (61% and 49%, respectively), stomatitis (46% and 27%, respectively) and hypomagnesemia (32% and 7%, respectively) in the PAN and no PAN treatment arms. Only diarrhoea (in 18%) and skin toxicity (in 34%) reached significant Grade III levels of toxicity as indicated in Table 30 (above). The pattern of toxicities was similar between the wild-type and mutant *KRAS* groups.

The adverse events of interest in the Irinotecan safety analysis set are summarised in Tables 31 and 32 below.

The common event of interest in this group was skin and eye toxicity affecting 93% and 45% of patients in the PAN and no PAN arms, respectively. In Study 181, skin toxicity was reported in 92% and 28% of patients in the PAN and no PAN arms, respectively. Other common events were diarrhoea (in 64% and 55% of patients, respectively), stomatitis (in 44% and 25%, respectively) and hypomagnesemia (in 23% and 3% of patients, respectively). Adverse events of interest with a Grade III or higher severity were noted in 54% and 24% of the PAN and no PAN arms, respectively, in Study 181. Skin toxicity (34% and 2%, respectively), diarrhoea (14% and 9%, respectively), stomatitis (8% and 3%, respectively) and hypomagnesemia (4% and <1%, respectively) occurred more frequently in PAN treated patients. A Grade III or higher severity of pulmonary toxicity occurred in 4% and 3% of patients in the PAN and no PAN arms, respectively, of Study 181, and in 3% of patients in the all PAN group. A Grade III or higher severity of cardiac toxicity occurred in 2% of patients in each arm of Study 181 and in 3% of patients in the all PAN group. Severe cutaneous adverse reactions occurred in 1% and 0% of the PAN and no PAN arms, respectively, of Study 181, and in 1% of patients of the all PAN group.

Table 31. Subject incidence of adverse events of interest. Irinotecan Analysis set.

	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Subjects with any adverse event of interest - n(%)	495 (99)	297 (98)	253 (86)	370 (98)	230 (97)	202 (82)	936 (98)	575 (98)	491 (83)
Hypomagnesemia	130 (26)	82 (27)	8 (3)	68 (18)	41 (17)	5 (2)	211 (22)	133 (23)	15 (3)
Hypocalcemia	32 (6)	18 (6)	2 (1)	21 (6)	16 (7)	6 (2)	55 (6)	36 (6)	9 (2)
Diarrhea	353 (70)	200 (66)	167 (57)	251 (66)	147 (62)	138 (56)	650 (68)	377 (64)	329 (55)
Cardiac Toxicity - Pre-specified	60 (12)	31 (10)	20 (7)	41 (11)	16 (7)	19 (8)	108 (11)	52 (9)	43 (7)
Cardiac Arrythmias - SMQ	35 (7)	21 (7)	13 (4)	22 (6)	8 (3)	13 (5)	62 (7)	33 (6)	29 (5)
Ischaemic Heart Disease - SMQ	2 (0)	1 (0)	5 (2)	3 (1)	3 (1)	3 (1)	5 (1)	4 (1)	9 (2)
Pulmonary Toxicity	104 (21)	63 (21)	60 (20)	77 (20)	44 (19)	40 (16)	191 (20)	114 (19)	104 (18)
Vascular Toxicity - Pre-specified	115 (23)	59 (20)	65 (22)	89 (23)	51 (22)	42 (17)	221 (23)	121 (21)	113 (19)
Vasculitis - SMQ	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Embolic and Thrombotic - SMQ[a]	65 (13)	28 (9)	29 (10)	47 (12)	20 (8)	20 (8)	124 (13)	58 (10)	49 (8)
Impaired or Delayed Wound Healing	2 (0)	1 (0)	1 (0)	2 (1)	1 (0)	0 (0)	5 (1)	2 (0)	2 (0)
Interstitial Lung Disease - SMQ	2 (0)	2 (1)	2 (1)	1 (0)	0 (0)	1 (0)	4 (0)	2 (0)	3 (1)
Stomatitis or Oral Mucositis	235 (47)	134 (44)	79 (27)	192 (51)	113 (48)	62 (25)	450 (47)	261 (44)	149 (25)
Integument and Eye Toxicities - Pre-specified	472 (94)	283 (94)	145 (49)	353 (93)	220 (93)	108 (44)	885 (93)	545 (93)	267 (45)
Skin Toxicity	471 (94)	282 (93)	99 (34)	345 (91)	215 (91)	55 (22)	876 (92)	539 (92)	165 (28)
Nail Toxicity	140 (28)	82 (27)	9 (3)	99 (26)	58 (24)	7 (3)	261 (27)	155 (26)	16 (3)
Hair Toxicity	139 (28)	76 (25)	65 (22)	106 (28)	53 (22)	67 (27)	259 (27)	138 (24)	137 (23)
Eye Toxicity	164 (33)	93 (31)	28 (10)	92 (24)	60 (25)	25 (10)	269 (28)	159 (27)	54 (9)
Cheilitis	28 (6)	21 (7)	4 (1)	18 (5)	15 (6)	2 (1)	50 (5)	38 (6)	9 (2)
Severe Cutaneous Adverse Reactions - SMQ	29 (6)	10 (3)	0 (0)	13 (3)	4 (2)	0 (0)	44 (5)	14 (2)	0 (0)
Infusion Reaction	79 (16)	42 (14)	37 (13)	53 (14)	31 (13)	31 (13)	141 (15)	80 (14)	72 (12)
USPI	6 (1)	6 (2)	8 (3)	7 (2)	4 (2)	2 (1)	14 (1)	11 (2)	11 (2)
CTCAE	77 (15)	41 (14)	33 (11)	49 (13)	29 (12)	31 (13)	135 (14)	77 (13)	68 (11)
Reported AE	5 (1)	4 (1)	8 (3)	4 (1)	3 (1)	1 (0)	10 (1)	8 (1)	10 (2)

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[a] Includes: Embolic and thrombotic events, arterial; Embolic and thrombotic events, venous; Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous.

Table 32. Subject incidence of Grade III or higher adverse events of interest. Irinotecan Analysis set.

	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Subjects with any adverse event of interest - n(%)	287 (57)	164 (54)	75 (26)	203 (54)	126 (53)	58 (24)	530 (56)	318 (54)	141 (24)
Hypomagnesemia	21 (4)	9 (3)	1 (0)	15 (4)	12 (5)	0 (0)	41 (4)	25 (4)	1 (0)
Hypocalcemia	10 (2)	3 (1)	0 (0)	7 (2)	5 (2)	1 (0)	18 (2)	9 (2)	1 (0)
Diarrhea	83 (17)	42 (14)	27 (9)	58 (15)	32 (14)	26 (11)	156 (16)	83 (14)	56 (9)
Cardiac Toxicity - Pre-specified	16 (3)	5 (2)	7 (2)	10 (3)	5 (2)	3 (1)	28 (3)	12 (2)	12 (2)
Cardiac Arrythmias - SMQ	11 (2)	4 (1)	7 (2)	5 (1)	1 (0)	1 (0)	19 (2)	8 (1)	9 (2)
Ischaemic Heart Disease - SMQ	1 (0)	1 (0)	1 (0)	3 (1)	3 (1)	2 (1)	4 (0)	4 (1)	3 (1)
Pulmonary Toxicity	15 (3)	12 (4)	12 (4)	13 (3)	8 (3)	6 (2)	30 (3)	22 (4)	18 (3)
Vascular Toxicity - Pre-specified	51 (10)	22 (7)	21 (7)	34 (9)	16 (7)	15 (6)	94 (10)	45 (8)	36 (6)
Vasculitis - SMQ	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Embolic and Thrombotic - SMQ[a]	52 (10)	22 (7)	22 (7)	35 (9)	14 (6)	14 (6)	97 (10)	44 (7)	36 (6)
Impaired or Delayed Wound Healing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Interstitial Lung Disease - SMQ	2 (0)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	1 (0)
Stomatitis or Oral Mucositis	37 (7)	23 (8)	8 (3)	31 (8)	22 (9)	9 (4)	70 (7)	46 (8)	19 (3)
Integument and Eye Toxicities - Pre-specified	180 (36)	115 (38)	9 (3)	122 (32)	80 (34)	3 (1)	325 (34)	211 (36)	13 (2)
Skin Toxicity	170 (34)	111 (37)	7 (2)	111 (29)	75 (32)	2 (1)	302 (32)	201 (34)	10 (2)
Nail Toxicity	25 (5)	13 (4)	1 (0)	20 (5)	10 (4)	0 (0)	49 (5)	24 (4)	1 (0)
Hair Toxicity	1 (0)	0 (0)	1 (0)	3 (1)	0 (0)	0 (0)	4 (0)	0 (0)	1 (0)

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	Wild-type KRAS			Mutant KRAS			All Subjects		
	All Panit. (N = 501)	Panit. in 181 (N = 302)	No Panit. 181 (N = 294)	All Panit. (N = 379)	Panit. in 181 (N = 237)	No Panit. 181 (N = 246)	All Panit. (N = 951)	Panit. in 181 (N = 587)	No Panit. 181 (N = 594)
Eye Toxicity	16 (3)	12 (4)	0 (0)	2 (1)	1 (0)	1 (0)	21 (2)	15 (3)	1 (0)
Cheilitis	3 (1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)	3 (1)	0 (0)
Severe Cutaneous Adverse Reactions - SMQ	6 (1)	1 (0)	0 (0)	6 (2)	3 (1)	0 (0)	13 (1)	4 (1)	0 (0)
Infusion Reaction	7 (1)	4 (1)	2 (1)	1 (0)	1 (0)	1 (0)	8 (1)	5 (1)	4 (1)
USPI	1 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (0)	1 (0)
CTCAE	5 (1)	3 (1)	1 (0)	1 (0)	1 (0)	1 (0)	6 (1)	4 (1)	3 (1)
Reported AE	3 (1)	2 (1)	1 (0)	0 (0)	0 (0)	0 (0)	3 (0)	2 (0)	1 (0)

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[a] Includes: Embolic and thrombotic events, arterial; Embolic and thrombotic events, venous; Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous.

Except for two events (hypomagnesemia and eye toxicity) which were higher in the PAN treated patients in the wild-type *KRAS* group relative to the mutant *KRAS* group, the incidences of adverse events of interest were similar in the Irinotecan wild-type and mutant *KRAS* safety analysis sets. A review of individual adverse events revealed that hypomagnesemia, which is a known effect of EGFR inhibitors, was most frequent in PAN treated patients across all the studies but of equal in incidence in both the wild-type and mutant *KRAS* groups as illustrated in Table 33.

The severity of hypomagnesemia was generally Grade I and there were no Grade V events. Subject incidences of hypomagnesemia by worst grade for the Oxaliplatin safety analysis set are given in Table 34 below.

Table 33. Summary of hypomagnesemia.

Percent of panitumumab-treated Subjects with Adverse Events	Hypomagnesemia[a]	
	Oxaliplatin Safety Analysis Set (N = 585)	Irinotecan Safety Analysis Set (N = 951)
Incidence of Worst Grade ≥ 3	6%	4%
Fatal	0	0
Serious	1%	1%
Treatment-related	28% hypomagnesemia, 2% blood magnesium decreased	19% hypomagnesemia, 2% blood magnesium decreased
Causing panitumumab discontinuation	< 1%	< 1%
Causing panitumumab dose adjustment	1%	1% hypomagnesemia, < 1% blood magnesium decreased
Causing chemotherapy discontinuation	< 1%	< 1%
Causing chemotherapy dose delays or adjustment	2% hypomagnesemia, < 1% blood magnesium decreased	1% hypomagnesemia, < 1% blood magnesium decreased
[a] Event of interest preferred terms: hypomagnesemia, blood magnesium decreased, and magnesium deficiency		

Table 34. Subject incidence of hypomagnesemia by worst grade. Oxaliplatin Analysis set.

Subjects with any adverse event[a] - n(%)						
	Wild-type KRAS		Mutant KRAS		All Subjects	
Grade	Panit. (N=322)	No Panit. (N=327)	Panit. (N=217)	No Panit. (N=218)	Panit. (N=585)	No Panit. (N=584)
any	102 (32)	26 (8)	71 (33)	13 (6)	187 (32)	40 (7)
1	57 (18)	22 (7)	36 (17)	10 (5)	104 (18)	33 (6)
2	24 (7)	3 (1)	21 (10)	2 (1)	45 (8)	5 (1)
3	17 (5)	1 (0)	12 (6)	1 (0)	30 (5)	2 (0)
4	4 (1)	0 (0)	2 (1)	0 (0)	8 (1)	0 (0)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

Hypomagnesemia led to discontinuation or removal from the study of two patients in the wild-type *KRAS* group and one in the mutant *KRAS* group.

The incidence of hypomagnesemia by worse grade in the Irinotecan safety analysis set is given in Table 35. Again most of these events were Grade I in severity. When grouped by severity, the incidence was similar in the all PAN group and in the wild-type versus mutant *KRAS* groups. Hypomagnesemia led to discontinuation or removal from study of three patients in the PAN group (compared to no patients in the no PAN arm) of Study 181 and in six in the all PAN group (n=2 in the wild-type *KRAS* group, n=2 in the mutant *KRAS* and n=2 in the unknown *KRAS* status groups).

Table 35. Subject incidence of hypomagnesemia by worst grade. Irinotecan Analysis set.

	Subjects with any adverse event[a, b] - n(%)								
	Wild-type KRAS			Mutant KRAS			All Subjects		
Grade	All Panit. (N=501)	Panit. in 181 (N=302)	No Panit. 181 (N=294)	All Panit. (N=379)	Panit. in 181 (N=237)	No Panit. 181 (N=246)	All Panit. (N=951)	Panit. in 181 (N=587)	No Panit. 181 (N=594)
any	130 (26)	82 (27)	8 (3)	68 (18)	41 (17)	5 (2)	211 (22)	133 (23)	15 (3)
1	72 (14)	52 (17)	7 (2)	41 (11)	25 (11)	4 (2)	119 (13)	81 (14)	12 (2)
2	37 (7)	21 (7)	0 (0)	12 (3)	4 (2)	1 (0)	51 (5)	27 (5)	2 (0)
3	10 (2)	3 (1)	0 (0)	8 (2)	7 (3)	0 (0)	22 (2)	13 (2)	0 (0)
4	11 (2)	6 (2)	1 (0)	7 (2)	5 (2)	0 (0)	19 (2)	12 (2)	1 (0)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

[b] Four subjects in Study 20050181 had a magnesium value of 0 mmol/L recorded at a site where the analyzer could not evaluate values below the lower limit of normal of 0.65 mmol/L (Subjects 203604005 and 203604002 [panitumumab arm, wild-type *KRAS*], and 2 subjects in the no-panitumumab arm, Subject 203604001 [wild-type *KRAS*] and Subject 203604003 [unknown *KRAS*]). The laboratory data captured the magnesium values of 0 mmol/L and these were assigned a CTCAE toxicity grade of 4. However, adverse events of hypomagnesemia were not reported for any of these subjects.

Hypocalcaemia of any grade occurred in 5% and 6% of patients in the PAN arm. It was mostly described as Grade II in severity. Hypocalcaemia was serious in one subject in the PAN arm of each pivotal study. It was reported with a higher subject incidence in the PAN arm than in the no PAN arm of both studies. There was no difference in the number of hypocalcaemia adverse events between the wild-type and the mutant *KRAS* groups. The incidence of hypocalcaemia for All PAN subjects was similar to that in the PAN arm of Study 181.

Diarrhoea, a frequently observed adverse effect of chemotherapy regimens commonly used for treatment of mCRC and in patients treated with other EGFR inhibitors, occurred sooner and with an approximately 10% higher subject incidence in the PAN arm compared to the no PAN arm. The increased incidence was primarily due to Grade II or III events. Diarrhoea was considered as related to PAN treatment in 56% of patients receiving Oxaliplatin in combination with PAN and in 65% of patients given Irinotecan.

Grade IV diarrhoea occurred in 10 subjects (2%) receiving PAN and two (<1%) patients receiving chemotherapy alone in Study 203. In Study 181 the subject incidence was similar in both treatment arms (1%). Within both studies there was only one fatal adverse event of diarrhoea in a subject from Study 181. This event was considered as related to chemotherapy but not to PAN.

Diarrhoea was a serious adverse event in 10% of patients receiving PAN and 3% of patients in the no PAN arm in Study 203 and 6% and 4%, respectively, in Study 181. Diarrhoea (of any grade) was not a frequent reason to discontinue study treatment in any treatment arm. This indicates that these events were managed with appropriate medical intervention and very few patients discontinued treatment as a result of an adverse event (eight and two patients in Study 203 versus twelve and three patients in Study 181, in the PAN and no PAN arms, respectively).

The incidences of diarrhoea were similar in the wild-type and mutant *KRAS* groups in both the Oxaliplatin and Irinotecan Safety analysis sets.

It is noted that in Study 203, one patient died of complications associated with diarrhoea which was considered related to therapy. A further patient in Study 181 also developed Grade IV diarrhoea ultimately resulting in death associated with ileus. This event was considered to be related to chemotherapy but not to PAN by the study investigators.

Adverse events related to cardiac toxicity were generally balanced across treatment arms in both Study 203 and 181. Cardiac toxicity events overall were 1 to 2% points higher in

PAN treated patients in both the Oxaliplatin and Irinotecan safety analysis set. Cardiac events were not dominated by a particular event or type of event.

A review of the patients in the PAN arm with cardiac toxicity did not identify any new safety signals. Most of the patients had a significant pre existing cardiac disease or confounding illnesses contributing to the cardiac events. In many of the cases the cardiac events resolved and treatment with PAN was continued.

The incidence of cardiac toxicity was slightly higher in the PAN arm (9% compared to 7% in the no PAN arm) in Study 181. The subject incidence in the all PAN group was 11%. The majority of these events were Grade I and II in severity and the pattern in the wild-type and mutant *KRAS* groups was similar. One patient in the no PAN arm of Study 181 and one patient in the All PAN group experienced a fatal cardiac arrest. Three other patients in Study 181 (two given PAN and one not) experienced sudden death. It was considered that some of these events may have been related to hypomagnesemia. In relation to this it is noted that the subject incidence of cardiac arrhythmia in the PAN arm was 8% among subjects with hypomagnesemia reported on or before the date of arrhythmia versus 4% in patients without hypomagnesemia. Nevertheless, only one of these events was considered as related to study treatment by the study investigators.

A review of the incidence of pulmonary toxicity revealed that this adverse event was reported with a similar incidence in the PAN and no PAN arms and most of these events were of a Grade I or II in severity. A small number of patients (n=14 overall) developed interstitial lung disease (ILD) and the incidence was similar in the PAN and no PAN arms.

Overall, pulmonary toxicity was reported in 21% and 24% of patients in the PAN and no PAN arms, respectively, in Study 203. These were mostly of a Grade I or II in severity. In the wild-type *KRAS* group fewer patients in the PAN arm than the no PAN arm had pulmonary toxicities (20% versus 29%). In contrast, the incidence was similar in the mutant *KRAS* groups. It is noted that one patient in the no PAN arm discontinued treatment due to pulmonary fibrosis, one patient in the PAN arm discontinued treatment due to ILD and one patient in the PAN arm discontinued treatment due to pneumonitis. All patients belonged to the wild-type *KRAS* group.

The Grade V pulmonary toxicities included broncho-pneumonia (n=1 no PAN); pneumonia (n=1 PAN and n=3 no PAN); dyspnoea (n=1 no PAN); hypoxia (n=1 no PAN); ILD (n=1 PAN); pleural effusion (n=1 PAN); pneumonitis (n=1 PAN); pulmonary fibrosis (n=1 no PAN) and respiratory failure (n=1 PAN).

Pulmonary toxicity events were reported in 19% and 18% of patients in the PAN and no PAN arms, respectively, of Study 181. Most events were of a Grade I or II in severity. The findings were similar in the wild-type and mutant *KRAS* groups. The types of Grade III and IV events were comparable across the arms and the incidences did not exceed the 1% difference. The type of subject incidence of Grade V events were comparable across treatment groups with four Grade V events in the PAN arm (n=1 cardiopulmonary failure, n=2 pneumonia and n=1 dyspnoea) and three events in the no PAN arm (n=1 pneumonia, n=1 pneumothorax and n=1 respiratory failure).

A review of vascular toxicity revealed that in relation to thromboembolic events in Studies 203 and 181, the incidence of vascular toxicity did not appear to increase markedly with the addition of PAN to chemotherapy. The overall incidence of vascular toxicities is slightly higher in the PAN arm compared to the no PAN arm but only two patients had events of vasculitis; one Grade II event in Study 203 and one Grade IV cerebral vasculitis in Study 181.

The Oxaliplatin analysis set revealed that in Study 203 the incidence of vascular toxicity was similar in the PAN and no PAN arms (28% and 26%, respectively) with Grade III or IV events occurring in 10% and 7% of patients, respectively. The trends were the same in the

wild-type and mutant *KRAS* groups and only one patient, on PAN with a mutant *KRAS* diagnosis, experienced Grade II vasculitis. There were two Grade V events of pulmonary embolism; both occurring in the PAN arm.

In the Irinotecan safety analysis set the subject incidence of vascular toxicity was similar for the two arms of Study 181. Grade III and IV events occurred in 8% and 5% of the PAN and no PAN arms, respectively. In Study 181 there was one Grade V event (a venous thrombosis of the limb in patient in the PAN arm) and five Grade V events in the no PAN arm (one CVA, two pulmonary embolisms, one embolism and one venous embolism). In Study 181 the difference between the Pan and no PAN treatment groups was greater in the mutant *KRAS* group (22% versus 17%) than in the wild-type *KRAS* group (20% versus 22%). One patient with wild-type *KRAS* in Study 314 experienced a Grade IV event of cerebral vasculitis.

The incidence of arteriovenous embolic and thrombotic adverse events were similar between the PAN and no PAN arms in the Oxaliplatin and Irinotecan safety analysis sets, with the overall incidence being very small (see Table 36).

Table 36. Summary of subject incidence of embolic and thrombotic events.

	Arterial Embolic and Thrombotic Events		Venous Embolic and Thrombotic Events	
Chemotherapy/ Study	Panitumumab	No Panitumumab	Panitumumab	No Panitumumab
Oxaliplatin (Study 20050203)	8 (1%)	9 (2%)	54 (9%)	45 (8%)
Irinotecan (Study 20050181)	2 (< 1%)	4 (1%)	38 (6%)	30 (5%)

Among the more frequently reported adverse events in the Oxaliplatin analysis set were pulmonary embolism (3% of patients in each treatment arm, 3% and 2% in PAN and no PAN arms, respectively, of the wild-type *KRAS* group and 4% in each arm of the mutant *KRAS* group) and deep vein thrombosis (4% and 3% in each treatment arm). There were two cases of fatal pulmonary embolism, both of which occurred in the PAN arm (one each in the wild-type and mutant *KRAS* groups).

In the Irinotecan safety analysis set venous embolic and thrombolic events were reported in 6% and 5% of patients in the PAN and no PAN arms, respectively, in Study 181. A fatal adverse event (fatal venous thrombosis of a limb) occurred in one patient in the PAN arm of Study 181. One patient in the all PAN group (Study 314) died of vena cava thrombosis. Two patients in the no PAN arm of Study 181 died from pulmonary embolism and one in the no PAN arm of Study 181 died from venous embolism. The pattern was similar across the wild-type and mutant *KRAS* groups.

Skin and eye toxicities were consistent with the known safety profile of PAN and affected more than 90% of PAN treated patients. Generally, these events were mild to moderate in severity. These events consisted mainly of rash and dermatitis acneiform. Hand/foot syndrome (PPE) occurred in 5% more patients treated with PAN than patients receiving chemotherapy alone and it is considered as a newly identified risk of PAN.

Grade III or IV skin toxicities occurred in approximately 30% of patients in each Phase III study and were reported with a higher incidence in the PAN arm compared to the no PAN arm of both studies. Generally, the skin toxicity was manageable and rarely required dose adjustments. However, 8% of patients had skin related adverse events leading to discontinuation of PAN.

A review of skin toxicities reported in the Oxaliplatin safety analysis set in Study 203 revealed that 96% and 31% of patients experienced skin toxicity in the PAN and no PAN arms, respectively. This was most often a rash. Nail toxicity, most commonly paronychia, affected 30% and 3% of patients in the PAN and no PAN arms, respectively, while hair

toxicity occurred in 18% and 10%, and cheilitis in 4% and 2% of patients in the treatment arms, respectively. Eye toxicity occurred in 31% and 16% of patients in the PAN and no PAN arms, respectively, and was Grade III in severity in 2% and 1% of patients, respectively. The most common eye toxicity was conjunctivitis.

In the Irinotecan safety analysis set, skin and eye toxicities were again common in the PAN arm of treatment. The same pattern was observed in the wild-type and mutant *KRAS* groups. The overall incidence and pattern of skin and eye toxicities seen in the Irinotecan safety analysis set are similar to those described above for the Oxaliplatin safety analysis set.

Severe skin reactions, including exfoliative dermatitis and toxic skin eruption, occurred in 4% of patients in the PAN arm and 1% of patients on the no PAN arm of Study 181. No event was greater than Grade III in severity. The severity of these events was similar in the wild-type and mutant *KRAS* groups.

Impaired or delayed wound healing was reported in 13 patients in the All Analysis sets combined and the most severe event was Grade III (n=1). In the Oxaliplatin safety analysis set all eight patients experiencing impaired or delayed wound healing were in the PAN arm of the studies. The most severe case was a patient with Grade III wound dehisence. In the Irinotecan safety analysis set the incidence was low and none of the events were serious.

Some 46% and 27% of patients in the Oxaliplatin safety analysis set had the adverse events of stomatitis, mouth ulceration or mucosal inflammation. Generally these events were Grade I or II in severity. No event was more severe than Grade III. Mucosal inflammation was reported as a serious adverse event in six PAN treated patients and in two patients receiving chemotherapy alone. Stomatitis was a serious adverse event in four patients in the PAN arm (there were no such reports in the no PAN arm). The incidence of stomatitis was slightly higher in the PAN arm of the wild-type *KRAS* group (48% on PAN and 28% on no PAN) relative to the mutant group (42% and 26%, respectively).

In the Irinotecan safety analysis set the incidence of mucosal toxicities was 44% and 25% of patients in the PAN and no PAN arms, respectively, of Study 181. These were usually considered as Grade I or II. Two episodes of mucosal inflammation were considered as serious adverse events in the PAN arm. Four such episodes were reported in the no PAN arm of the study. Stomatitis was reported as a serious adverse event in one patient of the PAN arm and in three patients of the no PAN arm of study.

Similar numbers of subjects receiving PAN plus chemotherapy or chemotherapy alone experienced infusion reactions and none of these appeared to be influenced by the addition of PAN to chemotherapy. A total of 14 patients in the Oxaliplatin safety analysis set had Grade III or IV infusion reactions and two of these were considered as related to PAN. Neither of these events was considered as life threatening or serious. In the Irinotecan safety analysis set one patient on the no PAN arm of Study 181 had a Grade III event of pyrexia. A PAN treated patient had a Grade IV anaphylactic reaction which was considered as possibly related to PAN. The event was considered to be life threatening and no further therapy was administered to this patient who died of a cerebrovascular accident (CVA) nine days later.

A review of safety with long term exposure indicated that in 700 patients who received PAN in combination with Oxaliplatin or Irinotecan for at least six months, there were no apparent differences in the types of adverse events reported for patients with longer or shorter duration of exposure. However, the frequency of some events increased with time on treatment.

A review of laboratory toxicities in the Oxaliplatin safety analysis set indicated that the incidence of worse post baseline Grade III or higher haematologic parameters in the PAN

and no PAN arms were similar with no differences in trends. These results are presented Table 37.

Table 37. Worst post baseline Grade III or higher based on the CTCAE v3.0. Oxaliplatin Safety Analysis set.

		Worst Post-Baseline Grade N (%)					
		Panitumumab (N=585)			No Panitumumab (N=584)		
Lab Assessment (Std Unit)	Direction of Toxicity	Grade 3	Grade 4	Grade 3 or Higher	Grade 3	Grade 4	Grade 3 or Higher
Chemistry							
Alanine Amino Transferase (U/L)	Increase	8 (1)	0 (0)	8 (1)	5 (1)	0 (0)	5 (1)
Albumin (g/L)	Decrease	21 (4)	0 (0)	21 (4)	11 (2)	0 (0)	11 (2)
Alkaline Phosphatase (U/L)	Increase	40 (7)	0 (0)	40 (7)	44 (8)	0 (0)	44 (8)
Aspartate Amino Transferase (U/L)	Increase	15 (3)	1 (0)	16 (3)	10 (2)	0 (0)	10 (2)
Bicarbonate (mmol/L)	Decrease	0 (0)	2 (0)	2 (0)	1 (0)	5 (1)	6 (1)
Calcium (mmol/L)	Decrease	19 (3)	20 (3)	39 (7)	6 (1)	12 (2)	18 (3)
	Increase	0 (0)	7 (1)	7 (1)	2 (0)	7 (1)	9 (2)
Creatinine (umol/L)	Increase	3 (1)	2 (0)	5 (1)	3 (1)	1 (0)	4 (1)
Magnesium (mmol/L)	Decrease	39 (7)	28 (5)	67 (11)	6 (1)	11 (2)	17 (3)
	Increase	13 (2)	4 (1)	17 (3)	17 (3)	1 (0)	18 (3)
Phosphorus (mmol/L)	Decrease	42 (7)	3 (1)	45 (8)	45 (8)	0 (0)	45 (8)
Potassium (mmol/L)	Decrease	71 (12)	16 (3)	87 (15)	36 (6)	5 (1)	41 (7)
	Increase	9 (2)	0 (0)	9 (2)	6 (1)	1 (0)	7 (1)
Sodium (mmol/L)	Decrease	29 (5)	2 (0)	31 (5)	20 (3)	3 (1)	23 (4)
	Increase	0 (0)	1 (0)	1 (0)	2 (0)	0 (0)	2 (0)
Total Bilirubin (umol/L)	Increase	19 (3)	2 (0)	21 (4)	17 (3)	2 (0)	19 (3)
Uric Acid (umol/L)	Increase	0 (0)	15 (3)	15 (3)	0 (0)	18 (3)	18 (3)
Hematology							
Absolute Neutrophil Count (10^9 /L)	Decrease	154 (26)	58 (10)	212 (36)	150 (26)	61 (10)	211 (36)
Hemoglobin (g/L)	Decrease	11 (2)	0 (0)	11 (2)	16 (3)	2 (0)	18 (3)
Lymphocytes (10^9 /L)	Decrease	35 (6)	6 (1)	41 (7)	43 (7)	5 (1)	48 (8)
Platelets (10^9 /L)	Decrease	7 (1)	4 (1)	11 (2)	15 (3)	2 (0)	17 (3)
Total Neutrophils (10^9 /L)	Decrease	149 (25)	58 (10)	207 (35)	148 (25)	60 (10)	208 (36)
White Blood Cells (10^9 /L)	Decrease	43 (7)	4 (1)	47 (8)	52 (9)	4 (1)	56 (10)

CTCAE: Common Terminology Criteria for Adverse Events version 3.0. Data presented are n (%).

Consistent with the known haematologic toxicities of FOLFOX and the rates of neutropenia reported as an adverse event, 36% of patients in both treatment arms had a decrease in absolute neutrophil count (ANC) with a worst post baseline Grade of III or higher.

As might be expected decreases in serum magnesium were more common in the PAN arm; (11% of PAN patients had a worse baseline Grade III or greater decrease in magnesium compared to 3% of patients in the no PAN arm). The same was true for decreases in serum calcium. Grade III decreases in potassium were also more frequent among patients in the PAN arm (15% compared to 7 % in the no PAN arm). Of the 67 patients treated with PAN in the Oxaliplatin safety analysis set who experienced a worst Grade III or IV hypomagnesemia, seven patients also had Grade III or IV hypocalcaemia and nine patients had Grade III or IV hypokalemia. There was no difference in the incidence of worst post baseline Grade III or higher increases in creatinine. The rate was 1% in each treatment arm.

Findings were similar in the Oxaliplatin wild-type *KRAS* safety analysis set. Grade III or IV hypomagnesemia was reported in 12% and 3% of patients in the PAN arm and no PAN arm, respectively. Similar trends were noted for hypocalcemia and hypokalemia (in 7% and 2% of the PAN and no PAN arms, respectively, and in 17% and 7% of the PAN and no PAN arms, respectively).

The incidence of treatment emergent laboratory toxicities for the Irinotecan Safety Analysis set is given Table 38.

Table 38. Worst post baseline Grade II or higher based on CTCAE v3.0. Irinotecan Safety Analysis set.

		Worst Post-Baseline Grade N (%)								
		All-Panitumumab Group (N=951)			Study 20050181					
					Panitumumab Arm (N=587)			No Panitumumab Arm (N=594)		
Lab Assessment (Std Unit)	Increase/ Decrease	Grade 3	Grade 4	Grade 3 or Higher	Grade 3	Grade 4	Grade 3 or Higher	Grade 3	Grade 4	Grade 3 or Higher
Chemistry										
Alanine Amino Transferase (U/L)	Increase	19 (2)	1 (0)	20 (2)	16 (3)	1 (0)	17 (3)	11 (2)	2 (0)	13 (2)
Albumin (g/L)	Decrease	12 (1)	0 (0)	12 (1)	7 (1)	0 (0)	7 (1)	13 (2)	0 (0)	13 (2)
Alkaline Phosphatase (U/L)	Increase	70 (7)	6 (1)	76 (8)	54 (9)	5 (1)	59 (10)	61 (10)	1 (0)	62 (10)
Aspartate Amino Transferase (U/L)	Increase	32 (3)	1 (0)	33 (3)	27 (5)	1 (0)	28 (5)	21 (4)	1 (0)	22 (4)
Bicarbonate (mmol/L)	Decrease	4 (0)	3 (0)	7 (1)	4 (1)	3 (1)	7 (1)	1 (0)	3 (1)	4 (1)
Calcium (mmol/L)	Decrease	46 (5)	37 (4)	83 (9)	35 (6)	27 (5)	62 (11)	11 (2)	19 (3)	30 (5)
	Increase	2 (0)	8 (1)	10 (1)	2 (0)	5 (1)	7 (1)	1 (0)	5 (1)	6 (1)
Creatinine (umol/L)	Increase	3 (0)	6 (1)	9 (1)	2 (0)	1 (0)	3 (1)	2 (0)	1 (0)	3 (1)
Magnesium (mmol/L)[a]	Decrease	63 (7)	46 (5)	109 (11)	39 (7)	27 (5)	66 (11)	9 (2)	10 (2)	19 (3)
	Increase	25 (3)	1 (0)	26 (3)	25 (4)	1 (0)	26 (4)	19 (3)	3 (1)	22 (4)
Phosphorus (mmol/L)	Decrease	89 (9)	7 (1)	96 (10)	63 (11)	2 (0)	65 (11)	32 (5)	4 (1)	36 (6)
Potassium (mmol/L)	Decrease	86 (9)	12 (1)	98 (10)	56 (10)	9 (2)	65 (11)	14 (2)	5 (1)	19 (3)
	Increase	8 (1)	3 (0)	11 (1)	6 (1)	3 (1)	9 (2)	6 (1)	2 (0)	8 (1)
Sodium (mmol/L)	Decrease	45 (5)	6 (1)	51 (5)	36 (6)	6 (1)	42 (7)	31 (5)	5 (1)	36 (6)
	Increase	7 (1)	6 (1)	13 (1)	7 (1)	6 (1)	13 (2)	5 (1)	1 (0)	6 (1)
Total Bilirubin (umol/L)	Increase	18 (2)	6 (1)	24 (3)	16 (3)	4 (1)	20 (3)	24 (4)	1 (0)	25 (4)
Uric Acid (umol/L)	Increase	0 (0)	26 (3)	26 (3)	0 (0)	21 (4)	21 (4)	0 (0)	24 (4)	24 (4)

		Worst Post-Baseline Grade N (%)								
		All-Panitumumab Group (N=951)			Study 20050181					
					Panitumumab Arm (N=587)			No Panitumumab Arm (N=594)		
Lab Assessment (Std Unit)	Increase/ Decrease	Grade 3	Grade 4	Grade 3 or Higher	Grade 3	Grade 4	Grade 3 or Higher	Grade 3	Grade 4	Grade 3 or Higher
Hematology										
Absolute Neutrophil Count (10^9/L)	Decrease	115 (12)	38 (4)	153 (16)	86 (15)	26 (4)	112 (19)	81 (14)	35 (6)	116 (20)
Hemoglobin (g/L)	Decrease	16 (2)	8 (1)	24 (3)	11 (2)	5 (1)	16 (3)	17 (3)	2 (0)	19 (3)
Lymphocytes (10^9/L)	Decrease	71 (7)	10 (1)	81 (9)	51 (9)	4 (1)	55 (9)	56 (9)	1 (0)	57 (10)
Platelets (10^9/L)	Decrease	4 (0)	0 (0)	4 (0)	3 (1)	0 (0)	3 (1)	4 (1)	1 (0)	5 (1)
Total Neutrophils (10^9/L)	Decrease	116 (12)	40 (4)	156 (16)	84 (14)	26 (4)	110 (19)	78 (13)	33 (6)	111 (19)
White Blood Cells (10^9/L)	Decrease	47 (5)	3 (0)	50 (5)	36 (6)	2 (0)	38 (6)	39 (7)	3 (1)	42 (7)

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Data presented are n(%).

[a] Four subjects in Study 20050181 had a magnesium value of 0 mmol/L recorded at a site where the analyzer could not evaluate values below the lower limit of normal of 0.65 mmol/L (Subjects 203604005 and 203604002 [panitumumab arm, wild-type KRAS], and 2 subjects in the no-panitumumab arm, Subject 203604001 [wild-type KRAS] and Subject 203604003 [unknown KRAS]). The laboratory data captured the magnesium values of 0 mmol/L and these were assigned a CTCAE toxicity grade of 4. However, adverse events of hypomagnesemia were not reported for any of these subjects.

There were no obvious differences in the incidence of worst post baseline Grade III or higher haematologic parameters between subjects in the two treatment arms (PAN and no PAN arm). Decreases in serum magnesium, calcium and potassium were more common in the patients in the PAN arm.

In the PAN arm of Study 181, a high proportion of patients had Grade III or worse post baseline values for decreases in serum calcium (11%), magnesium (11%), phosphorus (11%) and potassium (11%). These numbers were all greater than those observed in the no PAN arm of study.

In the Irinotecan wild-type *KRAS* safety analysis set the findings were similar, with an excess of Grade III or higher decreases in the PAN arm.

The adverse event of hepatotoxicity was reported in 14% and 10% of patients in the PAN and no PAN arms, respectively, in the Oxaliplatin safety analysis set (Study 203). These results are shown in Table 39.

Table 39. Subject incidence of hepatotoxicity. Oxaliplatin Safety Analysis set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with Hepatotoxicity - n(%)	44 (14)	37 (11)	33 (15)	17 (8)	83 (14)	56 (10)
Hyperbilirubinaemia (5%, 2%)	10 (3)	7 (2)	14 (6)	5 (2)	27 (5)	14 (2)
Ascites (2%, < 1%)	8 (2)	3 (<1)	5 (2)	2 (<1)	13 (2)	5 (<1)
Hypoalbuminaemia (3%, 1%)	8 (2)	4 (1)	9 (4)	3 (1)	17 (3)	7 (1)
Alanine aminotransferase increased	5 (2)	5 (2)	2 (<1)	2 (<1)	8 (1)	7 (1)
Aspartate aminotransferase increased	5 (2)	5 (2)	3 (1)	3 (1)	9 (2)	8 (1)
Hepatic pain	3 (<1)	1 (<1)	0 (0)	0 (0)	3 (<1)	1 (<1)
Hepatomegaly	3 (<1)	3 (<1)	3 (1)	1 (<1)	7 (1)	5 (<1)
Jaundice	3 (<1)	0 (0)	3 (1)	1 (<1)	7 (1)	1 (<1)
Gamma-glutamyltransferase increased	2 (<1)	3 (<1)	2 (<1)	1 (<1)	4 (<1)	4 (<1)
Hepatic failure	2 (<1)	3 (<1)	1 (<1)	0 (0)	3 (<1)	3 (<1)
Hypertransaminasaemia	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)
International normalised ratio increased	2 (<1)	0 (0)	1 (<1)	0 (0)	3 (<1)	0 (0)
Blood alkaline phosphatase increased	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)
Blood bilirubin increased	1 (<1)	3 (<1)	1 (<1)	1 (<1)	2 (<1)	4 (<1)
Hepatic enzyme increased	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
Liver palpable subcostal	1 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)

	Wild-type KRAS		Mutant KRAS		All Subjects	
	Panitumumab (N = 322)	No Panitumumab (N = 327)	Panitumumab (N = 217)	No Panitumumab (N = 218)	Panitumumab (N = 585)	No Panitumumab (N = 584)
Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Transaminases increased	1 (<1)	0 (0)	2 (<1)	0 (0)	3 (<1)	0 (0)
Cholestasis	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Hepatic cirrhosis	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Hepatic cyst	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Hepatic function abnormal	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)
Jaundice cholestatic	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)
Liver disorder	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	2 (<1)
Liver function test abnormal	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)	2 (<1)
Ocular icterus	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)
Prothrombin level decreased	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)

It is noted that the incidence of hepatotoxicity in the wild-type *KRAS* group (14% for the PAN arm and 11% for the no PAN arm) was similar to that noted for the overall study population. In the mutant *KRAS* group the difference between treatment arms was greater, being 15% for the PAN arm and 8% for the no PAN arm. This was mostly due to reports of hyperbilirubinemia.

Three patients receiving PAN in Study 203 died of hepatic failure. These deaths were not considered to be related to PAN. One of these deaths was however considered to be related to chemotherapy.

Further review of the PAN arm of the Oxaliplatin safety analysis set revealed that of the 575 patients reviewed, 10 possible cases meeting laboratory criteria for potential drug induced liver injury were identified. Each case had baseline liver metastases and eight of the cases had a marked increased in alkaline phosphatase at the time of elevated levels of other liver enzymes. Of the remaining three cases with alkaline phosphatase abnormalities, there were two cases of treatment discontinuation due to disease progression and one death due to mCRC. Upon discontinuation of study therapy, seven of the patients continued to have elevated levels of total bilirubin indicating a likely alternate aetiology rather than drug induced toxicity. Of the other three cases, bilirubin levels subsequently returned to normal while the patients were still receiving PAN, indicating that PAN therapy was not playing a causative role. In the no PAN arm of the Oxaliplatin safety analysis set seven cases of possible hepatic toxicity were identified. Each had baseline liver metastases and six reported evidence of disease progression. It was

considered that none of them unequivocally satisfied the criteria for potential drug induced liver injury.

Among the Irinotecan safety analysis set, adverse events categorised as hepatotoxicity occurred in 12% and 11% of patients in the PAN and no PAN arms, respectively, of Study 181, and in 11% of patients in the all PAN group as indicated in Table 40.

Ascites and hyperbilirubinemia were the two most frequent events. One patient receiving PAN in Study 314 died of hepatic failure. The study investigators considered the hepatic failure and subsequent death to be unrelated to PAN. The incidences of adverse events in were similar between PAN subjects of the wild-type and mutant *KRAS* groups.

In the overall Irinotecan safety analysis set, 15 cases possibly met laboratory criteria for potential drug induced liver injury. All 15 had baseline liver metastases. Upon discontinuation of study therapy, 13 had persistent elevations in bilirubin indicating alternate aetiology. In the remaining two cases, bilirubin levels resolved while the patient remained on treatment indicating a likely alternate aetiology. In the no PAN arm of the Irinotecan safety analysis set there were five cases meeting the laboratory criteria for potential drug induced liver injury; four had liver metastases and one had a history of on study cholestasis. Overall no cases unequivocally satisfied the criteria for potential drug induced liver injuries.

With regards to potential renal toxicity very few patients (3% on each treatment arm) had events of renal toxicity and there were an equal number of patients in each treatment arm with renal failures. There is no obvious evidence that the addition of PAN to chemotherapy influenced the development of renal dysfunction. Adverse events related to renal function in the Oxaliplatin safety analysis set are shown in Table 41.

Table 40. Subject incidence of hepatotoxicity. Irinotecan Analysis set.

	Wild-type KRAS			Mutant KRAS			All Subjects		
Preferred Term	All Panit. (N = 501) n (%)	Panit. in 181 (N = 302) n (%)	No Panit. 181 (N = 294) n (%)	All Panit. (N = 379) n (%)	Panit. in 181 (N = 237) n (%)	No Panit. 181 (N = 246) n (%)	All Panit. (N = 951) n (%)	Panit. in 181 (N = 587) n (%)	No Panit. 181 (N = 594) n (%)
Subjects with Hepatotoxicity - n(%)	53 (11)	30 (10)	31 (11)	43 (11)	31 (13)	27 (11)	106 (11)	68 (12)	63 (11)
Ascites	13 (3)	5 (2)	4 (1)	6 (2)	4 (2)	3 (1)	23 (2)	11 (2)	11 (2)
Hyperbilirubinaemia	10 (2)	7 (2)	4 (1)	12 (3)	11 (5)	8 (3)	25 (3)	21 (4)	12 (2)
Aspartate aminotransferase increased	7 (1)	6 (2)	4 (1)	7 (2)	6 (3)	6 (2)	15 (2)	13 (2)	11 (2)
Hypoalbuminaemia	7 (1)	5 (2)	1 (<1)	8 (2)	5 (2)	3 (1)	16 (2)	11 (2)	4 (<1)
Alanine aminotransferase increased	6 (1)	5 (2)	3 (1)	3 (<1)	2 (<1)	5 (2)	11 (1)	8 (1)	8 (1)
Hepatic pain	5 (<1)	4 (1)	2 (<1)	2 (<1)	1 (<1)	0 (0)	7 (<1)	5 (<1)	2 (<1)
Blood alkaline phosphatase increased	3 (<1)	2 (<1)	3 (1)	6 (2)	5 (2)	5 (2)	9 (<1)	7 (1)	9 (2)
Hepatomegaly	3 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (<1)	4 (<1)	2 (<1)	4 (<1)
Jaundice	3 (<1)	3 (<1)	3 (1)	1 (<1)	1 (<1)	0 (0)	4 (<1)	4 (<1)	3 (<1)
Blood bilirubin increased	2 (<1)	2 (<1)	1 (<1)	2 (<1)	2 (<1)	1 (<1)	4 (<1)	4 (<1)	2 (<1)
Cholestasis	2 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	2 (<1)	2 (<1)
Hepatic failure	2 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)
Prothrombin time prolonged	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)
Gamma-glutamyltransferase increased	1 (<1)	1 (<1)	0 (0)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	1 (<1)
Hepatic function abnormal	1 (<1)	1 (<1)	1 (<1)	2 (<1)	1 (<1)	0 (0)	4 (<1)	3 (<1)	1 (<1)
Hepatic lesion	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)
Hepatic steatosis	1 (<1)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	2 (<1)
International normalised ratio increased	1 (<1)	0 (0)	1 (<1)	7 (2)	1 (<1)	1 (<1)	8 (<1)	1 (<1)	2 (<1)
Liver palpable subcostal	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	3 (1)	1 (<1)	1 (<1)	4 (<1)
Cytolytic hepatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)
Hepatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)
Jaundice cholestatic	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)
Liver operation	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)
Prothrombin level decreased	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)

Table 41. Renal and Urinary disorders SOC. Oxaliplatin Safety Analysis set.

	Wild-type KRAS		Mutant KRAS		All Subjects	
Grade	Panit. (N=322)	No Panit. (N=327)	Panit. (N=217)	No Panit. (N=218)	Panit. (N=585)	No Panit. (N=584)
any	36 (11)	38 (12)	28 (13)	25 (11)	65 (11)	68 (12)
1	20 (6)	17 (5)	16 (7)	19 (9)	37 (6)	38 (7)
2	7 (2)	13 (4)	6 (3)	6 (3)	13 (2)	21 (4)
3	5 (2)	7 (2)	4 (2)	0 (0)	9 (2)	8 (1)
4	4 (1)	0 (0)	0 (0)	0 (0)	4 (1)	0 (0)
5	0 (0)	1 (0)	2 (1)	0 (0)	2 (0)	1 (0)

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[a] Adverse events were coded using the MedDRA dictionary V12. Severity graded using the CTCAE v3.0, with the exception of some dermatology/skin adverse events that were graded using the Common Terminology Criteria for Adverse Events version 3.0 with modifications.

Overall the two treatment arms of study appeared balanced for Grade III or higher Renal Disorders. The most frequent event was renal failure (1% in each treatment arm). The renal toxicity events were considered to have multiple plausible aetiologies. Two (renal failure) events in the PAN arm and one event in the no PAN arm resulted in death. Four cases of renal failure were reported as treatment related, with two of these having Grade III increased blood creatinine levels (one in the PAN arm and one in the no PAN arm).

Reviewing the Irinotecan safety analysis set with regards to renal dysfunction, the overall incidence in Study 181 was 9% in each arm of study and 11% in the all PAN group. The incidence of serious renal failure was balanced between the two arms (n=1 in the PAN arm and n=2 in the no PAN arm in Study 181). There were multiple potential aetiologies for this nephro toxicity. One fatal event of acute rental failure was reported in the no PAN arm. No such events were reported in the PAN arm of study.

A review of changes in vital signs throughout these studies did not reveal any significant changes. In general terms, vital signs changes reported as adverse events were uncommon and occurred at a similar frequency in the PAN and no PAN arms of therapy.

A review of sub group analyses revealed no major differences in the adverse event profile with respect to age, sex, race or baseline disease characteristics in the Oxaliplatin or the Irinotecan safety analysis sets.

The rate of Grade III adverse events was somewhat higher in women than men, due primarily to a higher subject incidence of Grade IV events in women in the PAN arm of Study 203. As might be expected, subgroup analysis also indicated that patients with a poorer ECOG performance status tended to have a greater incidence of serious and fatal adverse events. Furthermore, patients with moderate or severe renal impairment at baseline appeared to have a higher proportion of serious and fatal adverse events relative to those with mild impairment or normal renal function.

Serious adverse events that occurred with ≥ 2% higher subject incidence in the panitumumab arm in the mutant *KRAS* group relative to the wild-type *KRAS* group in Study 20050203 were diarrhea, dehydration and intestinal obstruction. It was also noted that in the mutant *KRAS* group fatal adverse events were reported somewhat more frequently in the PAN arm (8%) compared to the no PAN arm (3%).

In Study 181 the subject incidence of fatal adverse events was 4% for the PAN arm and 6% for the no PAN arm of the wild-type *KRAS* group and 7% for the PAN arm and 5% for the no PAN arm of the mutant *KRAS* group.

It was considered that the differences in toxicities observed in the patients with mutant *KRAS* tumours receiving FOLFOX chemotherapy in Study 203 was not attributable to any particular increase in toxicity but rather due to a variety of conditions reflective of end stage mCRC.

A separate study, Study 20040249[2] (a randomised open label controlled clinical trial of chemotherapy and Bevacizumab with and without PAN in the first line treatment of patients with metastatic colorectal cancer), was not included in the overall safety analyses. This study was conducted at 200 sites across the US with a start date of 10 March 2005 and a data cut off date of 31 May 2007.

The design of the study involved initial randomisation to either Oxaliplatin based or Irinotecan based chemotherapy in conjunction with Bevacizumab. Subsequent randomisation was to PAN or no PAN within each separate chemotherapy stratum. Primary efficacy endpoint was PFS with safety analysis being an important secondary objective.

For the Oxaliplatin stratum, 823 patients were randomised to either the PAN arm (413 patients) or the control arm (410 patients). For the Irinotecan stratum, 230 patients were randomised to either the PAN arm (115 patients) or the control arm (115 patients).

When reviewing the safety results of this trial across both chemotherapy strata, more toxicity was seen in the PAN group. This toxicity manifested itself as a greater incidence of Grade III and higher adverse events and a greater incidence of serious adverse events and more overall deaths relative to the control group. Similar safety trends were seen for the Oxaliplatin and Irinotecan strata separately.

Within the PAN treatment group, 95% of patients had one or more adverse events considered related to PAN. Twenty percent of patients discontinued all components of first line treatment due to an adverse event. This was similar between treatment groups, that is, PAN or control, across both chemotherapy strata combined (22% versus 20%) and for the Oxaliplatin stratum alone (23% versus 24%). In contrast, the Irinotecan stratum displayed a difference between treatment groups (17% versus 5%).

Serious adverse events were reported by 59% in the PAN group and 37% of the control group with a higher incidence in the PAN group of dehydration, diarrhoea, pulmonary embolism, nausea and vomiting. Serious infections overall displayed a treatment difference of 15% versus 9% but no one specific type of infection could be pin pointed for this difference. Nineteen percent of patients receiving PAN experienced a serious event that was considered related to PAN. The most common of these were diarrhoea, dehydration and vomiting.

More deaths occurred in the PAN group relative to the control group with all deaths 32% versus 25% and deaths due to disease progression 25% versus 20% while deaths due to adverse events were 7% versus 4% and deaths occurring on treatment 8% versus 3%. Of the 35 patients (23 PAN patients and 12 control patients) who died on or within 30 days of the last dose of first line treatment because of an event other than disease progression, differences between treatment groups were noted in the number of deaths due to cardiac causes (10 versus 4), sepsis (6 versus 3), intestinal perforation (3 versus 0) and pulmonary embolism (3 versus 0).

Among adverse events of special interest, higher incidences were observed in the PAN group across both chemotherapy strata for skin and eye events as a whole, diarrhoea, hypomagnesemia, hypocalcaemia and mucositis/stomatitis and to a lesser extent cardiac, pulmonary and vascular events specifically pulmonary embolism. In the Irinotecan stratum, diarrhoea had, as expected, a higher overall incidence relative to the Oxaliplatin stratum. A higher incidence of Grade III diarrhoea was also noted in the PAN group relative to the control group.

Three other ongoing trials (Studies 20070509; 20060141 and study 20070820) have also been assessed for adverse reactions.

Study 509 was a randomised multicentre Phase II study to compare the efficacy of PAN in combination with FOLFOX-6 to the efficacy of Bevacizumab in combination with FOLFOX-6 in patients with previously untreated *KRAS* wild-type unresectable metastatic colorectal cancer. Data cut off for this trial was the 15 October 2009. The number of patients enrolled was 32. In relation to safety to date, five cases have been identified with serious adverse events reported for five patients who received PAN or Bevacizumab in combination with chemotherapy. These included oesophagitis, dehydration, fracture, transient ischaemic attack and acute renal failure. The events of the oesophagitis, dehydration and transient ischaemic attack were reported as possibly treatment related.

Study 20060141 was a multicentre open label randomised Phase II clinical trial evaluating safety and efficacy of FOLFIRI with either PAN or Bevacizumab as second line treatment in subjects with metastatic colorectal cancer with wild-type *KRAS* tumours. This study was conducted at six sites in the US with the study data cut off period being 15 October 2009. To date, a total of 197 patients have been enrolled in this trial. The primary endpoint is PFS. An interim report indicates that in relation to safety as of the cut off date, 87 cases were identified with 192 serious adverse events reported for 69 patients. The most

common serious adverse events were Gastrointestinal (63 events), Metabolism and Nutritional Disorders (20 events) and Respiratory, Thoracic and Mediastinum Disorders (19 events) and Infections and Infestations (18 events). The most commonly reported serious adverse events were diarrhoea and dehydration (12 events each), small intestinal obstruction and vomiting (8 events each), abdominal pain (7 events) and dyspnoea and malignant neoplasm progression (6 events).

Twenty-three events in 14 patients were considered by the study investigators to be related to either PAN or Bevacizumab. These events were dehydration (2 events), diarrhoea (2 events), rectal ulcer, pain in the oesophagus, difficulty swallowing, mucositis, infection, febrile neutropenia, atrial fibrillation and hypomagnesemia. As of the data cut off date, 59 fatal adverse events were reported for 21 patients, the most common being progression of malignancy. Others included dehydration and sepsis. Four adverse events for two patients were considered by the investigator to be related to treatment, one being a patient receiving Bevacizumab in combination with FOLFIRI dying from respiratory failure and the other patient receiving PAN in combination with FOLFIRI who had a fatal adverse event of nausea, vomiting and dehydration.

The third study (Study 20070820) was a Phase II study of PAN plus Irinotecan followed by PAN plus AMG479 in patients with metastatic colorectal cancer expressing wild-type *KRAS* and refractory to Oxaliplatin or Irinotecan and Oxaliplatin chemotherapy regimens. The study aim was to evaluate mechanisms of acquired resistance to PAN. Five sites in Europe had at least one patient each enrolled. The cut off date was the 15 October 2009. The total number of patients enrolled to date was eight.

In relation to safety, two patients were identified with two serious adverse events of diarrhoea and general physical deterioration. Neither event was considered by the study investigators to be related to PAN.

Evaluator's comment:

The overall safety data together has essentially confirmed the recognised safety profile for PAN. It is clear that the addition of PAN to either Oxaliplatin based or Irinotecan based chemotherapy results in an increased spectrum and degree of toxicities. In general terms these toxicities had already been recognised and are normally managed in an appropriate manner. Nevertheless, there does appear to be increased potential for certain toxicities, in particular diarrhoea, dehydration and electrolyte imbalances (in particular hypomagnesemia). It is also noted that the incidence of hand/foot syndrome appears to have increased with the addition of PAN to either Oxaliplatin based or Irinotecan based chemotherapy. All of these adverse events therefore require careful monitoring and appropriate prophylactic and interventional management. There is no apparent evidence of any new fatal or Grade III/IV adverse events developing that could not have been anticipated in relation to the development of combinations involving PAN plus chemotherapy. Accordingly the clinical evaluator did not consider that the adverse effect profile identified for this PAN drug related combination was a sufficient offset to the potential benefits for this combination in the management of metastatic colorectal carcinoma.

Postmarketing experience

As of the 30 September 2009, PAN had been approved for use in 33 countries. Cumulatively since the inception of the PAN development program an estimated 35,952 patients have been exposed to the drug. The Amgen safety data base has received a total of 524 postmarketing individual safety reports of which 206 were serious and 318 not serious.

There were 32 cases who reported a fatal outcome of which the majority were considered to be disease progression. There were two cases of reported fatal outcomes in the setting of a hypersensitivity reaction and based on these two cases the Core Reference Safety Document has been updated. Further, as a result of the cumulative review of postmarketing events, the adverse events of increased blood pressure and cardio-respiratory arrest in the setting of infusion reactions will be added to the postmarketing experience section of the Core Reference Safety Document.

The most frequently reported adverse events were of the Skin and Subcutaneous Disorders class. A review of severe cutaneous adverse events identified two events of skin necrosis that was suggestive of a causal drug event association with PAN. There was one event of ulcerative keratitis and one event of chorioretinopathy reported in the postmarketing experience.

Review of other events of interest has not identified any additional safety signals to warrant revision of the Core Reference Safety Document.

In relation to non-Amgen sponsored studies, 10/22 non-Amgen sponsored studies were in the setting of colorectal cancer. There have been a total of 437 serious adverse events reported to Amgen in patients who received PAN in these non-sponsored studies. A review of these serious adverse events including fatal outcomes did not identify any new safety signals.

Clinical summary and conclusions

The current Australian submission proposed a new indication for PAN (Vectibix).

"for the treatment of patients with wild-type KRAS mCRC in combination with chemotherapy as first and subsequent lines of treatment."

Previously approval has been for the use of PAN as monotherapy for the treatment of EGFR expressing metastatic colorectal cancer in patients with wild-type *KRAS* who have disease progression following treatment with Fluoropyrimidine, Oxaliplatin and Irinotecan based chemotherapy.

Data to support the new indication included one pharmacokinetic interaction study, two pivotal Phase III efficacy and safety studies and three supportive single arm Phase II studies regarding efficacy. A further four studies have also been provided with the current submission to assist in the evaluation of safety in conjunction with the above studies.

The submitted pharmacokinetic study was a drug to drug interaction trial (Study 200622010) which was a Phase I open label study to determine the effect of PAN on the pharmacokinetics of Irinotecan in subjects with unresectable metastatic colorectal cancer. These were conducted at six sites in the US and Canada between the 28 March 2008 and the 16 July 2009. The primary objective of the study was to determine if PAN affects the pharmacokinetic profile of Irinotecan. The patients on trial had unresectable metastatic colorectal cancer and no prior exposure to EGFR inhibitors. PAN was administered at 6 mg/kg every two weeks and Irinotecan at 180 mg/m^2 every two weeks until disease progression or intolerance to treatment occurred.

The primary endpoint of the pharmacokinetic phase of the trial was the maximum observed concentration (C_{max}) and the area under concentration time curve (AUC) of Irinotecan with and without concomitant PAN administration.

Twenty-eight patients were enrolled in the study and 27 received at least one dose of therapy. Nineteen of these patients fit the criteria for inclusion into the pharmacokinetic analysis sets.

The Irinotecan pharmacokinetic data also revealed that the ratio of geometric means (Irinotecan with PAN versus Irinotecan alone) $AUC_{0\text{-inf}}$ was 0.898 and for $AUC_{0\text{-last}}$ was 0.897 and for C_{max} was 0.980. Although the magnitude of $AUC_{0\text{-inf}}$ and $AUC_{0\text{-last}}$ Irinotecan was smaller when administered with PAN, the 90% CI of geometric mean ratios for the $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} Irinotecan were all within the pre specified interval of 70-143% demonstrating there was no clinically significant difference in Irinotecan pharmacokinetics with or without concomitant PAN administration. Similar results were also observed for the active metabolite of Irinotecan, SN-38.

Assessment for efficacy in the current submission involved two pivotal clinical trials and three supportive Phase II studies.

The first of the pivotal trials was Study 20050203, which was a Phase III open label, randomised controlled study in previously untreated patients with mCRC to compare the efficacy of PAN in combination with FOLFOX to the efficacy of FOLFOX alone. The second pivotal trial was Study 20050181, which was a Phase III open label, randomised controlled study in subjects previously treated for mCRC to compare the efficacy of PAN in combination with FOLFIRI to efficacy of FOLFIRI alone. A total of 1183 patients were enrolled in Study 203 and 1186 patients were enrolled in Study 181. Both studies were well controlled and prospectively evaluated the treatment effect of PAN in combination with chemotherapy by *KRAS* mutation status. *KRAS* mutation status was assessed by an independent central laboratory blinded to subject treatment assignments and outcomes to minimise any potential bias. The ascertainment rate for *KRAS* mutation status was high, being >90%, and balanced between treatment arms in both studies and comparison of baseline characteristics and key efficacy parameters between the overall enrolled population in subjects evaluable for *KRAS* and showed no apparent difference.

Tumour assessments were determined according to the modified RECIST criteria by an independent central radiological review in both studies.

The primary objective in Study 20050203 was to assess the influence on PFS of PAN in combination with FOLFOX versus FOLFOX alone as first line therapy for metastatic colorectal cancer in patients with both wild-type *KRAS* tumours and mutant *KRAS* tumours. Secondary objectives included assessment of overall survival, objective response rate, duration of response, time to disease progression and safety.

A total of 1183 patients were randomised onto trial, with 593 receiving PAN plus FOLFOX and 590 FOLFOX alone.

For the wild-type *KRAS* efficacy analysis set for the primary endpoint, 61% of patients in the PAN plus FOLFOX arm and 65% in the FOLFOX alone arm had disease which had progressed or they had died. The estimated median PFS was 9.6 months in the PAN plus FOLFOX arm and eight months in the FOLFOX alone arm. PFS was significantly improved with the P value by stratified log rank test being P=0.023. The estimated hazard ratio was 0.798.

Results of overall survival analysis revealed a median overall survival for the PAN plus FOLFOX patients of 23.9 months which can be compared to 19.7 months for the FOLFOX alone patients with a P value of 0.0723 and hazard ratio of 0.825.

In relation to response rates, 55% of patients in the combined arm achieved complete and partial response which can be compared to 48% of patients in the FOLFOX alone arm with an odds ratio of 1.35. There was only one CR in all of these responses seen in the FOLFOX alone arm.

In relation to the mutant *KRAS* efficacy analysis set, 76% in the combination and 157 patients in the FOLFOX alone had disease which had progressed or they had died. The estimated median PFS was 7.3 months in the combination arm and 8.8 months in the

FOLFOX alone arm with a P value of 0.0227 and an estimated hazard ratio of 1.294 favouring the FOLFOX alone arm.

In relation to overall survival the estimated median OS was 15.1 months for the combination and 18.7 months for FOLFOX alone arm with a P value of 0.0034 and a hazard ratio of 1.534 favouring the FOLFOX alone arm.

Response rates were 40% in the combination arm and 40% in the FOLFOX alone arm with an odds ratio of 0.98. All responses were partial.

In Study 181 (a multicentre trial conducted in 190 centres in the US, Australia, Western Europe, Eastern Europe and Japan), the patients enrolled had received one prior chemotherapy regimen for mCRC consisting of first line FU based chemotherapy and had developed radiographically documented disease progression during or <6 months after last dose of first line chemotherapy. Eligible patients were randomised to receive PAN plus FOLFIRI or FOLFIRI alone. Two primary objectives evaluated in this trial were PFS and OS. Secondary objectives were to evaluate the overall objective response rate.

A total of 1186 patients were randomised, 591 to PAN plus FOLFIRI and 595 to FOLFIRI alone. Efficacy results for the wild-type *KRAS* efficacy analysis set revealed that 59% of patients in the combination arm and 69% of patients in the FOLFIRI alone arm had disease that had progressed or they had died. The estimated median PFS times were 5.9 months in the combination arm and 3.9 months in the FOLFIRI alone arm. Hazard ratio was 0.732 favouring the combination arm. This difference was significant with a P value of 0.0036 by stratified log rank test. The estimated median OS was 14.5 months in the combination arm and 12.5 months in FOLFIRI alone arm with a P value of P=0.1154. The hazard ratio was 0.854.

The objective response rate was 35% for patients receiving the combination and 10% for patients receiving FOLFIRI alone with all responses being partial. The odds ratio was 5.33.

For the mutant *KRAS* efficacy analysis set, 68% of patients in the combination arm and 65% of the patients in the FOLFIRI alone arm had disease that had progressed or they had died by the time of data cut off. The estimated median PFS times were 5.0 months in the combination arm and 4.9 months in the FOLFIRI alone arm with a hazard ratio of 0.846 and a P value of 0.1448. The estimated median OS was 11.8 months in the combination arm and 11.1 months in the FOLFIRI alone arm with a hazard ratio of 0.939.

The objective responses observed were 13% and 14% in the combination versus FOLFIRI alone arms, respectively, and all responses were partial.

Of the three supportive trials the first (Study 20060314) was a single arm multicentre Phase II study of PAN in combination with FOLFIRI in patients who had not received any prior systemic therapy for metastatic colorectal cancer. The primary objective of the study was to estimate the effect of *KRAS* mutation status on the objective response rate and other measures of efficacy. A total of 150 subjects comprised the full analysis set; overall 49% of these patients achieved a complete or partial response with a median duration of response being 9.2 months. The median time to disease progression was 7.8 months. A higher percentage of patients with wild-type *KRAS* achieved either complete or partial tumour response compared to the mutant *KRAS* group, with the objective response rate for patients in the wild-type *KRAS* group being 56.5% versus 37.9%. The median duration of response was longer for patients in the wild-type *KRAS* compared with the mutant group (13 months versus 7.4 months) and the median PFS was 8.9 months in the wild-type *KRAS* group as compared to 7.2 months in the mutant *KRAS* group.

The second supportive study (Study 20060277) was a multicentre open label single arm trial evaluating PAN in combination with FOLFIRI therapy following first line FOLFOX and Bevacizumab treatment of metastatic colorectal cancer. The primary objective of study was to estimate the effect of *KRAS* mutation status on efficacy endpoints. A total of 116

patients were enrolled onto trial, 65 patients with wild-type *KRAS* tumours and 45 patients with mutant *KRAS* tumours. Review of response rates revealed that patients with wild-type *KRAS* tumours had a 23% partial response rate compared to a 16% partial response rate for those in the mutant *KRAS* stratum. The median duration of response for the wild-type group was 29 weeks compared to 23 weeks in the mutant *KRAS* group and the median PFS was 26 weeks in the wild-type stratum compared to 19 weeks for the mutant *KRAS* stratum. The median OS time was 50 weeks for the wild-type stratum which can be compared to 31 weeks for the mutant *KRAS* stratum.

Study 20025409[10]. was an early study (initiated in July 2002) where patients were to receive PAN in combination with Irinotecan. This study was terminated early after 19 patients had ended therapy because of high levels of toxicity. The study was continued (Part II) and the safety and efficacy of PAN in combination with FOLFIRI in patients with metastatic CRC with no prior treatment for disease in the metastatic setting was analysed. Analyses of *KRAS* mutation status were not undertaken in this trial. A total of 24 patients were enrolled on trial. The overall objective response rate was 42% with a median PFS of 47 weeks. Median survival was 22.5 months.

Review of the safety profile of PAN in combination with chemotherapy was undertaken in relation to the above five efficacy studies together with five other Phase II and Phase III trials that were either complete or ongoing at the time of this analysis.

The adverse event profile of PAN when administered with Oxaliplatin or Irinotecan based chemotherapy reflected the additive effect of combining two pharmacodynamically active agents. Overall a higher incidence of adverse events was observed for PAN administered in combination with chemotherapy relative to chemotherapy alone. In general terms however, the adverse effects documented were consistent with the known safety profile of both the chemotherapies utilised and EGFR inhibitors.

Almost all patients experienced at least one adverse event. There was no evidence that PAN increased the dose limiting toxicities associated with chemotherapy or interfered with the delivery of PAN chemotherapy doses. In both the Oxaliplatin and Irinotecan safety analysis sets, higher grade (Grade III/IV) adverse events occurred with a higher frequency in patients receiving the combination treatment and these were generally consistent with the known safety profile of PAN plus the associated chemotherapy. In relation to PAN, the already documented adverse effects of skin rash and dermatitis acneiform were noted to have a >5% higher incidence in patients receiving the combination versus chemotherapy alone. Similarly, the degree of hypomagnesemia and diarrhoea were also increased by >5% for the combination treatment of PAN plus Oxaliplatin chemotherapy versus chemotherapy alone.

The rate of serious adverse events was higher in the PAN arms primarily due to a higher incidence of diarrhoea. It appeared to be predominantly related to the cytoxic chemotherapy but was also influenced by the addition of PAN to treatment. Nevertheless, the rate of treatment discontinuation was similar between the two treatment arms in the large pivotal trials.

In Study 20050203, essentially all patients experienced adverse events and serious adverse events were documented in 45% and 34% of patients in the combination and chemotherapy alone arms, respectively. The serious adverse events were deemed treatment related in 28% and 15% of patients, respectively.

Adverse events caused permanent discontinuation of treatment in 23% and 14% of patients in the combination versus chemotherapy alone arms, respectively. A fatal adverse event occurred in 7% and 5% of patients in the combination versus chemotherapy alone

[10] Sponsor comment: Study 20025409 was not a supportive study.

arms, respectively. There were few fatal adverse events deemed as treatment related (n=8 in the PAN arm and n=5 in the no PAN arm).

It is noted that the subject incidence of fatal adverse events was similar between the treatment arms for patients with wild-type *KRAS* tumours (5% versus 6%) whereas there was a higher incidence of fatal events in PAN treated patients with mutant *KRAS* tumours (8% versus 3%). Nevertheless, there was no clear pattern of fatal adverse events observed.

Three adverse events were noted to appear in the combination therapy treated patients that had not previously been recognised as part of the likely spectrum of toxicities with PAN alone; palmar/plantar erythrodysaesthesia syndrome (PPE), anorexia and decreased weight. It would appear that these particular adverse effects are increased in potential when combining Oxaliplatin based chemotherapy with PAN. These events were rarely reported as serious and rarely led to treatment discontinuation. It was also noted that when PAN was added to chemotherapy, hypokalemia became more frequent with an incidence of 20% for the combination treatment arm as compared to 13% for the chemotherapy alone arm. Again, very few of the hypokalemia events were serious and no subject in either arm discontinued treatment due to hypokalemia.

Nearly all patients in both arms of Study 20050181 experienced adverse events and serious adverse events occurred in 40% and 29% of patients in the combination versus the chemotherapy alone arms, respectively. The latter were deemed to be treatment related in 21% and 15% of patients, respectively. Adverse events causing permanent discontinuation of therapy occurred in 21% and 11% of patients in the PAN and no PAN treatment arms, respectively. Fatal adverse events and treatment related fatal adverse events occurred with similar rates in the PAN and no PAN arms.

The adverse effects of PPE, anorexia and decreased weight were increased in the combination therapy arm versus the chemotherapy alone arm to levels above those previously recognised for PAN alone. The incidence of hypokalemia was increased over and above that to be expected for PAN alone in the PAN plus FOLFIRI arm.

Unlike Study 20050203, the incidence of severe and fatal adverse events for the wild-type *KRAS* group versus the mutant *KRAS* group were equivalent in Study 20050181.

These data have therefore shown that in terms of efficacy, the addition of PAN to combination chemotherapy involving either Oxaliplatin or Irinotecan is associated with a modest but significant improvement in PFS and a significant improvement in objective response rate. At the time of this evaluation, there was no clear evidence of improvement in OS, although the follow up of the two pivotal trials was ongoing. The safety profile for combining PAN with chemotherapy certainly reflects an additive nature of the two agents, thereby increasing the overall levels of toxicity including to some extent the serious toxicities. Nevertheless, in general terms these toxicities appear to be manageable. There was a very low incidence of fatal adverse effects and no clear indication of an increase of these when combining PAN with chemotherapy.

Benefit/risk assessment

As indicated above, the efficacy studies have demonstrated improvements in PFS and objective response rates. The benefits in relation to PFS are modest, being of the order of two months improvement. Nevertheless, because of the large nature of the two pivotal trials these data are significant. It is noteworthy that there has been no evidence of significant improvement in OS at this time despite ongoing review of the data. The toxicity profiles demonstrated represent an additive increase when combining chemotherapy with PAN. In general terms, these appear to be within the range of expectations and appropriately managed.

The clinical evaluator considered that the level of benefit achieved by combining PAN with chemotherapy in patients with metastatic colorectal cancer who have not received prior chemotherapy or only one line of chemotherapy for metastatic disease is likely to be real but again emphasising the modest improvement. Accordingly, the benefit risk ratio favours the use of the combination therapy but nevertheless other factors apart from clinical benefit may need to be considered.

Overall, the clinical evaluator supported the application for the proposed new indication for PAN (Vectibix) as being indicated for the treatment of patients with wild-type *KRAS* metastatic colorectal cancer in combination with chemotherapy. It is recognised that the previously approved indication as monotherapy in patients after failure of standard chemotherapy is appropriate to still remain.

V. Pharmacovigilance findings

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

A summary of the Ongoing Safety Concerns as specified by the sponsor are tabulated below (Table 42).

Table 42. Summary of Ongoing Safety Concerns for PAN.

Identified risks	· Integument and eye toxicities (including PPE) · Stomatitis and oral mucositis · Pulmonary toxicities · Hypomagnesaemia, hypocalcaemia, and hypokalaemia · Diarrhoea · Dehydration · Infusion reactions and other hypersensitivity reactions · Lack of response in patients with mCRC with mutant *KRAS* tumours · Negative effects in combination with oxaliplatin-containing chemotherapy in patients with mCRC with mutant *KRAS* tumours
Potential risks	· Vascular toxicities · Cardiac toxicities · Immunogenicity · Wound healing

Missing/limited information	· Pregnant women · Lactating women · Paediatric patients · Non-White patients · Patients with renal, hepatic, cardiac, or pulmonary impairment · Patients who receive PAN at a dose schedule that has not been evaluated extensively · Patients with cancer type other than refractory mCRC · Biomarkers for response to PAN therapy

Hypokalaemia and PPE are newly identified safety concerns that have been included in the European Union (EU) RMP (version 6.0)

OPR reviewer comment:

Pursuant to the evaluation of the clinical aspects of the safety specifications, this was considered acceptable.

Pharmacovigilance plan

The sponsor outlines adequate tools and activities used for conducting routine Pharmacovigilance (PhV). Routine PhV is proposed for all the Ongoing Safety Concerns except for issue regarding biomarkers for response to panitumumab therapy where routine PhV is not applicable. The following are identified as additional PhV actions by the Sponsor:

1. **Identified risk: Pulmonary toxicity**

   Enhanced monitoring of spontaneously reported interstitial lung disease adverse drug reactions (ADRs) will include the use of targeted questions (by questionnaire or by the use of clinical queries). Physicians treating patients presenting with events such as interstitial pneumonitis and/or pulmonary fibrosis in either clinical trials or the post market setting will be asked to respond to these questions.

2. **Identified risks: Lack of response in patients with mCRC with mutant *KRAS* tumours. Negative effects in combination with oxaliplatin-containing chemotherapy in patients with mCRC with mutant *KRAS* tumours**

   The sponsor is proposing 2 additional PhV actions for these identified risks:

   a. A physician survey to assess oncologist's awareness and understanding of panitumumab indication and the importance of tumour *KRAS* testing prior to therapy. The protocol synopsis is provided in the EU RMP (version 6.0). This will be a cross sectional survey across 5 European countries with a plan to have 150 participating oncologists. A questionnaire is to be developed. The study target outcome is that >80% of oncologists will answer the questions correctly at 12 months after the initiation of the study.

   b. A medical records review to describe the patterns of KRAS testing and panitumumab use in Europe. The protocol synopsis is provided in the EU RMP

(version 6.0). The study design is a cross sectional review of the existing medical records of up to 3 patients per participating oncologist. Sampling from 5 European countries with a total of 150 participating oncologists is planned. The data analysis will look at the overall testing results by number of patients and by oncologist.

3. Potential risk: Cardiac toxicity

In the RMP regarding PhV actions for cardiac toxicity the following is stated by the Sponsor: "*additional clinical study (to be planned)*". No further information or clarification is provided.

4. Missing/limited information: Paediatric patients

A Phase 2 open label study in paediatric patients (1 – 18 years) to examine the safety and pharmacokinetics of panitumumab in children with solid tumours. The study is due for completion in April 2011 and the final report expected in 2012. No other panitumumab clinical trials have been conducted in this population.

5. Missing/limited information: Biomarkers for response to panitumumab therapy

A direct measure of EGFR family hetero- and homo-dimers in mouse models of human disease suggests that this method may have some predictive ability. The sponsor states that they are currently evaluating a method for measuring EGF family receptor hetero and homo dimers in archival tumour tissue from subjects treated in panitumumab clinical studies. The level of receptor dimerisation will be evaluated against clinical response.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

Routine risk minimisation is proposed for all the Ongoing Safety Concerns through information contained in the PI. Additional risk minimisation activities are considered necessary, by the sponsor, for the following identified safety concerns:

1. Lack of response in patients with mCRC with mutant *KRAS* tumours.
2. Negative effects in combination with oxaliplatin-containing chemotherapy in patients with mCRC with mutant *KRAS* tumours.

As such, the Sponsor proposes additional risk minimisation activities for these. The Sponsor states that routine educational materials will be provided to health care practitioners in the EU describing the importance of *KRAS* ascertainment before treatment with panitumumab. This will provide further communication of what is provided in the PI. Furthermore, to minimize the risks of lack of response in patients with mCRC with mutant *KRAS* tumours, and negative effects in combination with oxaliplatin-based chemotherapy in subjects with mCRC with mutant *KRAS* tumours, the sponsor has provided initial funding to assist the European Society of Pathologists (ESP) to establish a quality assurance program in *KRAS* mutation testing in order to better ensure high quality testing of *KRAS* status in mCRC patients. The sponsor states that they maintain contact with the ESP program, and in line with commitments made to the CHMP, will update the CHMP on the progress of this program.

Summary of recommendations

It was recommended to the Delegate that once Vectibix RMP amendments and additions are agreed to and the RMP is accepted, a condition of registration be that the sponsor provides an updated RMP or an annex to the EU-RMP outlining the specific Australian

differences. It would be acceptable that this be provided at the time of submission of the next Periodic Safety Update Report (PSUR). It is also recommended that the Australian PI language is included for the routine risk minimisation activities in the *Summary of the Risk Management Plan* document. If there are specific safety related concerns identified from the clinical evaluation of the submission by the Office of Medicines Authorisation (OMA) that have not been identified in the RMP, it is recommended that the sponsor include these in the RMP along with sufficient monitoring and risk mitigation strategies.

The following is a summary of specific recommendations to the Delegate regarding the Vectibix RMP, version 6.0.

- Pharmacovigilance plan:
  - The physician survey and medical record review are audits intended to evaluate the use of *KRAS* testing and prescriber understanding of panitumumab in a sample of European oncologists. These may not be readily generalisable to the Australian situation as prescribing patterns might be different. It was recommended that the sponsor commit to undertaking additional PhV, such as an audit or drug utilisation study, to monitor the important identified risks of lack of therapeutic response to panitumumab in patients with mCRC with mutant *KRAS* tumours and the negative effects in combination with oxaliplatin containing chemotherapy in patients with mutant *KRAS* tumours, or adequately justify why this is not required.
  - It was recommended that the sponsor should clarify what is meant by the statement "*additional clinical study (to be planned)*" regarding the cardiac toxicity PhV activities. Details of any specific planned pharmacoepidemiological study into the cardiac safety of panitumumab should be provided including milestones for reporting of the results to the TGA.
  - With respect to the sponsor's evaluation of a method for EGF family receptor dimers in archival tumour tissue to evaluate biomarkers for response to panitumumab, it is recommended that the sponsor provide an update of this process and milestones for the reporting of findings, and any ensuing recommendations, to the TGA.
  - The sponsor has not made mention in the RMP of the Amgen Pregnancy Surveillance Programme that is identified in the draft Australian PI and CMI. The Sponsor should provide the protocol for this program for review.
- Risk minimisation plan: The sponsor has assessed that routine risk minimisation activities are not sufficient for the Ongoing Concerns regarding the safety in mCRC patients with mutant *KRAS* tumours. While the additional risk minimisation measures are considered appropriate, they are clearly European specific. As such the following recommendations to the Delegate are made:
  - The sponsor develops a secondary risk communication process in Australia for the education of expected prescribers (oncologists) on the importance of determining tumour *KRAS* status, or the sponsor should provide adequate justification against this recommendation. An overview of such a program, including the target population, estimation of participant uptake and a process for assessing the effectiveness of the intervention on mitigating the risk is suggested.
  - The sponsor identifies what measures are planned for quality assurance in *KRAS* mutation testing in Australia. It is suggested that the sponsor liaise with the Royal College of Pathologists of Australia (RCPA) to ascertain whether any program is in place to help ensure the accuracy and proficiency in *KRAS* mutation testing across Australia. The sponsor should outline what commitments will be made to the TGA regarding *KRAS* mutation testing quality assurance provision and monitoring in Australia.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacokinetics (PK)

The submission included one new interaction study (20062010) examining the effects of PAN on the PK of Irinotecan, and its active metabolite SN-38. Co administration of PAN resulted in no significant effect on the PK of irinotecan. There was a reduction in the AUC and C_{max} of SN-38 which was not considered clinically significant.

Pharmacodynamics - immunogenicity

The submission included an analysis of the immunogenicity of PAN in subjects receiving the drug in combination with chemotherapy, based on four of the submitted studies. Serum samples were collected at baseline and again at 30 days after the last study treatment. Samples were tested with two assays screening for binding antibodies. Samples testing positive were further tested for neutralising antibodies. Two PAN treated subjects (0.2%) developed positive neutralising antibodies, compared to 0% in the chemotherapy alone treatment group. There were no clinical sequelae associated with the development of antibodies.

Efficacy

Evidence for efficacy comes primarily from two randomised controlled trials which compared PAN in combination with chemotherapy to chemotherapy alone:

- Study 2005 0203 (aka the PRIME study) was conducted in the first line setting. The chemotherapy regimen used was a combination of oxaliplatin, 5-fluorouracil and folinic acid (FOLFOX-4);
- Study 2005 0181 was conducted in the second line setting. The chemotherapy regimen used was a combination of Irinotecan, 5-fluorouracil and folinic acid (FOLFIRI). Patients could only have received one prior line of chemotherapy for metastatic disease, which must have been fluoropyrimidine based, and which could not include Irinotecan.

The two studies have been published[11].

The primary endpoint for both studies was PFS, as assessed by a blinded independent review committee. OS was a co primary endpoint in Study 0181.

Both studies were commenced before the availability of data indicating that anti-EGFR antibodies are only effective in subjects with wild-type *KRAS* tumours. Once these data were available, the protocols for both studies were amended such that the primary analysis became an analysis of PFS in both the wild-type *KRAS* and mutant *KRAS* populations. These amendments were made prior to any analysis or unblinding of the data.

Study 0203: First line treatment

Wild-type KRAS population

PFS was significantly improved by the addition of PAN to FOLFOX-4 chemotherapy (hazard ratio 0.798 [95% CI: 0.656 – 0.971]; p = 0.0234). Median PFS was prolonged by 1.6 months (9.6 versus 8.0 months).

Overall response rate was also improved (55 versus 48%). There was a non significant trend towards improved OS. There was no significant difference in quality of life measures.

Mutant KRAS population

PFS was significantly worsened by the addition of PAN.

Study 181: Second line treatment

Wild-type KRAS population

PFS was significantly improved by the addition of PAN to FOLFIRI chemotherapy (hazard ratio 0.732 [95% CI: 0.593 – 0.903]; p = 0.0036). Median PFS was prolonged by 2.0 months (5.9 versus 3.9 months).

Overall response rate was also improved (35 versus 10%). There was a non significant trend towards improved OS. The clinical evaluator noted that there was an imbalance between arms in the proportion of patients who received anti-EGFR therapy after disease progression (10% versus 31%) and that this may have affected the OS outcome. There was no significant difference in quality of life measures.

Mutant KRAS population

There was no significant benefit associated with the addition of PAN.

Phase II studies

The submission included four supportive Phase II, single arm studies in which PAN was administered in conjunction with FOLFIRI chemotherapy. The data from these studies provide supportive evidence of greater efficacy in patients with Wild type KRAS tumours.

Safety

In the Phase II and III studies included in the submission, a total of 1536 patients were exposed to PAN in combination with chemotherapy (either oxaliplatin or Irinotecan based regimens). In the two pivotal studies the median duration of treatment was 26.0 weeks (Study 0203) and 21.1 weeks (Study 0181).

[11] Douillard J-Y *et al.* (2010). Randomized, Phase III Trial of Panitumumab With Infusional Fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX4) Versus FOLFOX4 Alone As First-Line Treatment in Patients With Previously Untreated Metastatic Colorectal Cancer: The PRIME Study. JCO 28:4697-4705, and Peeters M *et al* (2010). Randomized Phase III Study of Panitumumab With Fluorouracil, Leucovorin, and Irinotecan (FOLFIRI) Compared With FOLFIRI Alone As Second line Treatment in Patients With Metastatic Colorectal Cancer JCO 28:4706-4713.

The overall safety profile in terms of comparative incidence of adverse events is summarised in Tables 43-44.

Table 43. Study 20050203. First-line; oxaliplatin based chemotherapy – FOLFOX-4.

	Chemotherapy plus PAN (n = 585)	Chemotherapy alone (n=584)
Any adverse event (AE)	100 %	99%
Treatment-related AEs	99 %	97 %
Grade III AEs	56 %	51 %
Grade IV AEs	25 %	21 %
Serious AEs	45 %	34 %
AEs causing discontinuation of all chemotherapy	17 %	14 %
AEs causing discontinuation of PAN	18 %	-
Fatal AEs	7 %	5 %
Treatment-related fatal AEs	1 %	1 %

These data suggest that the addition of PAN to chemotherapy results in a moderate increase in toxicity with an increase in the incidence of serious adverse events of approximately 10%. Approximately 20% of patients discontinued PAN due to adverse events but only an additional 3 to 4% of patients in the PAN arm had to discontinue all chemotherapy treatment. There did not appear to be an increase in treatment related deaths.

Table 44. Study 20050181. Second line Irinotecan based chemotherapy FOLFIRI.

	Chemotherapy plus PAN (n = 585)	Chemotherapy alone (n=584)
Any adverse event (AE)	99 %	96 %
Treatment-related AEs	98 %	91 %
Grade III AEs	51 %	35 %
Grade IV AEs	18 %	15 %
Serious AEs	40 %	29 %
AEs causing discontinuation of all chemotherapy	15 %	11 %

	Chemotherapy plus PAN (n = 585)	Chemotherapy alone (n=584)
AEs causing discontinuation of PAN	19 %	-
Fatal AEs	6 %	5 %
Treatment-related fatal AEs	1 %	1 %

The pattern of individual adverse events seen in the pivotal studies was generally consistent with that previously documented for PAN. Toxicities which occurred more commonly in the PAN arms of the two studies were:

- Dermatological toxicities: rash, dermatitis acneiform, pruritus, dry skin, paronychia;
- Gastrointestinal (GIT) toxicities: diarrhoea, stomatitis, mucosal inflammation;
- Electrolyte disturbances: hypomagnesaemia, hypokalaemia;
- Eye toxicity: conjunctivitis.

Toxicities with increased incidence in the PAN arms and which had not previously been documented for PAN, were anorexia, palmar-plantar erythrodysesthesia (PPE), decreased weight and asthenia.

The toxicity profile of PAN in the Phase II studies was generally consistent with that observed in the Phase III trials.

The clinical evaluator considered that the toxicities of PAN observed in the submitted studies were consistent with the recognised safety profile of the drug and that these were manageable.

Risk management plan

The Risk Management Program proposed by the sponsor has been found to be generally acceptable by the TGA's Office of Product Review.

Risk-benefit analysis

Delegate considerations

Efficacy

The two pivotal studies have demonstrated a modest benefit in terms of improved PFS with the addition of PAN to standard chemotherapy regimens. PFS is an acceptable efficacy endpoint for Phase III trials according to the European Union (EU) guideline on anticancer agents which has been adopted by the TGA[12].

The magnitude of the efficacy benefit is small. The current application was recently rejected in Europe. One of the reasons given by the European Medicines Agency (EMA) was the questionable clinical relevance of the observed PFS benefits, particularly given the lack of improvement in overall survival or quality of life.

[12] Guideline on the evaluation of anticancer medicinal products in man. CPMP/EWP/205/95/Rev.3/Corr.

Although the efficacy benefits with PAN are small (a 1.6 to 2.0 month prolongation of median PFS), they would appear to be consistent with those observed for a similar product in similar studies. These studies were the basis for TGA approval of of this product for a similar indication. However, one difference between the results for the two agents was that an overall survival benefit was demonstrated in one trial.

Given that the TGA accepts PFS as an efficacy endpoint, and the magnitude of the PFS benefit observed is similar to that seen with a similar approved product, the Delegate did not consider that the lack of clinically significant efficacy was grounds for rejection.

Safety

The toxicity of PAN when used in combination with chemotherapy was consistent with that previously observed for the drug, and as assessed by the clinical evaluator, appeared manageable.

Patients with KRAS mutant disease

As indicated above, in Study 203 PAN had a detrimental effect on progression free survival in patients with mutant *KRAS* disease. The EMA stated that *"This is a concern because of the uncertainty about the current reliability of KRAS testing*." Presumably this refers to a concern regarding a potential harmful effect of the drug in patients who have a false negative result on *KRAS* mutation testing.

The sponsor was requested to address this issue in the pre ACPM response, with details of the *KRAS* testing methods used in the pivotal studies, the test methods being used in Australia, and the potential for harm in patients.

It is noted that the sponsor proposes to contraindicate the use of PAN (with FOLFOX-4) in patients with *KRAS* mutation positive disease and those whose *KRAS* mutation status is unknown. The RMP proposed by the sponsor also proposes educational measures for oncologists in Australia on the importance of *KRAS* testing. However neither of these measures will address the issue of potential harm to patients erroneously diagnosed as having wild type *KRAS* disease.

Indication – EGFR expression

The current monotherapy, 'last-line' indication is restricted to patients with EGFR expressing tumours. In the revised indication proposed with this Australian submission it was proposed to delete this restriction. In addition, for the new indication, no restriction to patients with EGFR-expressing tumours is proposed. In the pre ACPM response, the sponsor was requested to justify this approach.

Proposed action

The sponsor will need to adequately address the concerns regarding patients with mutant *KRAS* disease being inadvertently exposed to a harmful effect of the drug. If this can be done, the Delegate considered that the drug has a favourable risk-benefit ratio for the new indication, and the Delegate would propose approval of the application.

The advice of the ACPM was requested.

Response from Sponsor

Amgen supports the Delegate's recommendation regarding the use of Vectibix in combination with chemotherapy proposed in this application. Amgen recognises the importance of *KRAS* mutation testing to patient safety and addresses the TGA concerns in this response. The following concerns raised by the Delegate will be addressed in this response:

- *KRAS* testing

- Epidermal growth factor receptor (EGFR) expression
- Efficacy

KRAS testing

Details of KRAS testing methods used in pivotal studies

Diagnostic procedures and techniques for the deoxyribonucleic acid (DNA) based assays used in the ascertainment of *KRAS* status are based on well established and widely used molecular techniques. There are several *KRAS* test kits available that provide a reliable and effective mechanism for the detection of mutant *KRAS* tumours.

All samples from the three Amgen Phase III clinical trials (20020408, 20050181, 20050203) were tested in a Belgian government accredited central laboratory following validation of the TheraScreen: K-RAS Mutation Kit.

Potential risk for harm to patients

Current metastatic CRC (mCRC) therapy guidelines[13] support the need for *KRAS* testing in patients with mCRC prior to initiating treatment, and the accuracy of the *KRAS* test result is an important matter for anti-EGFR monoclonal antibodies. In patients with mutant *KRAS* mCRC, Vectibix in combination with FOLFOX was shown to have a detrimental effect on PFS and OS in Study 20050203 (n = 440 with mutant status; median PFS 7.3 versus 8.8 months; p = 0.0227; hazard ratio 1.294 [95% CI: 1.036, 1.616] and median OS 15.5 versus 19.3 months; p = 0.068; hazard ratio 1.241 [95% CI: 0.984, 1.566], all favouring the FOLFOX alone arm). A similar effect was demonstrated with cetuximab in combination with FOLFOX in patients with mutant *KRAS* status in the OPUS trial[14]. Negative outcomes are limited to patients receiving anti-EGFR monoclonal antibodies in combination with oxaliplatin based chemotherapy. In contrast, the addition of Vectibix or cetuximab to FOLFIRI in patients with mutant *KRAS* mCRC had no positive or negative effect on PFS or OS in Study 20050181 or in the CRYSTAL trial[15], respectively.

The potential for harm exists with a false negative *KRAS* test result. In this scenario, a patient with *KRAS* mutation would inappropriately be identified as wild-type and could receive Vectibix. False positive *KRAS* test results incorrectly identify mutant *KRAS* tumour status when *KRAS* is actually wild-type. These errors inappropriately prohibit patients from receiving anti-EGFR monoclonal antibodies but do not pose a risk for active harm.

A recently published analysis compared the performance of the TheraScreen: K-RAS Mutation Kit with DNA sequencing targeting the 7 most prevalent *KRAS* mutations in codon 12 and 13. DNA was extracted from formalin fixed, paraffin embedded (FFPE) colorectal cancer samples of 511 patients. *KRAS* mutation assessment was successful in 510 samples, with the two methods generating the same results in 486 samples (95.3%). For the 24 discrepant results, the TheraScreen: K-RAS Mutation Kit assay result was considered false positive in 6 samples (1.2%) and false negative in 7 samples (1.4%), compared to the sequencing results of 1 sample (0.2%) and 9 samples (1.8%), respectively. The authors concluded that both sequencing and the TheraScreen:K-RAS Mutation Kit assay are reliable tests for *KRAS* mutation analysis in FFPE colorectal cancer

[13] Van Cutsem E, Nordlinger B, Cervantes A, ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. *Ann Oncol*. 2010;21(Suppl 5): v93-v97.
[14] Bokemeyer C, Bondarenko I, Hartmann, JT, *et al*. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol*. 2011; Advanced Access published January 12, 2011.
[15] Van Cutsem E, Claus-Henning K, Istvan L. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol*. 2011; Published Ahead of Print on April 18, 2011 as 10.1200/JCO.2010.33.5091

samples. These rigorously conducted, externally published results confirm the results of an internal comparability study[16].

A 2011 external quality assessment of the quality of *KRAS* testing of 59 laboratories in 8 European countries was recently reported. The laboratories were allowed to use their own preferred method for histological evaluation, DNA isolation, and mutation analysis. The false negative rate was 1% (6/590)[17].

The *KRAS* test characteristics and error rates for commercially available platforms are among the most sensitive and specific assays for biomarkers in oncology. By way of comparison, in breast cancer, the reported frequency of HER-2[18] positivity using the FDA approved HercepTest (DAKO) ranges from 30% to 60% in large cohort studies[19]. Furthermore, it has recently been reported that 20% of HER-2 assays performed in the field were incorrect [20], and that only 57% to 65% of participants in the United Kingdom National External Quality Assurance scheme quality audits using the DAKO HercepTest demonstrated acceptable performance[21]. By comparison, the semi quantitative *KRAS* test is far more accurate with substantially lower error rates compared with a qualitative test that requires observer interpretation that is, more susceptible to inter observer variability.

Amgen strongly believes that Vectibix should not be administered to patients with mutant *KRAS* tumours or patients who have not been evaluated for *KRAS* tumour status as per the proposed indication and contraindication. As Vectibix is currently not reimbursed in Australia, patients who received Vectibix until December 2010 were on an Amgen Access scheme, which required tumour *KRAS* status testing and limited eligibility for treatment to patients with wild-type *KRAS* mCRC.

This Access scheme has since been halted. Currently patients could potentially receive unfunded Vectibix, however, this would be very limited in numbers. Should an anti-EGFR monoclonal antibody be reimbursed through the Pharmaceutical Benefits Scheme (PBS) in Australia, there would be strict mechanisms in place to prevent patients with mutant *KRAS* tumours from receiving an anti- EGFR agent. In this instance, the prescribing doctor would need to ensure that the patient meets the defined reimbursement criteria which would include determination of the *KRAS* status of the tumour.

KRAS test methods currently used in Australia

Amgen acknowledges that in Australia, as well as in many other countries, multiple methodologies are used to detect *KRAS* mutations in tumour tissue samples prior to treatment with an anti-EGFR agent, including single strand conformation polymorphism analysis, pyrosequencing, and high resolution melting (HRM) analysis. In Australia, these tests are performed at National Association of Testing Authorities (NATA) accredited laboratories with test validation methodology compliant with ISO15189 – Medical Laboratories – Particular Requirements of Quality and Competence. The TheraScreen: K-RAS Mutation Kit used during the pivotal studies is not generally used in pathology laboratories in Australia due to cost and the kit is not currently reimbursed.

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[16] Oliner K, Juan T, Suggs S, *et al*. A Comparability Study of 5 Commercial KRAS Tests. *Diagn. Pathol* 2010;5:23.
[17] Bellon E, Ligtenberg JL, Tejpar S, *et al*. External quality assessment for KRAS testing Is needed: setup of a European program and report of the First Joined Regional Quality Assessment Rounds. *The Oncologist*. 2011;16:467-478.
[18] HER-2=human epidermal growth factor receptor 2. HER2 is expressed by, and involved in the growth of, some cancer cells. For example, some breast cancers express HER2 protein.
[19] Roche PC, Ingle JN. Increased HER2 with US Food and Drug Administration-approved antibody [correspondence]. *J Clin Oncol*. 1999;17:434.
[20] Wolff AC, Hammond ME, Schwartz JN, *et al*. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2007;25:118-145.
[21] UKNEQAS Immunocytochemistry Journal <http://www.ukneqasicc.ucl.ac.uk/neqasicc.shtml>

At this time, there is no nationally recognised Quality Assurance (QA) program in Australia that evaluates the performance and characteristics of sensitivity, specificity, and precision of the methods used to assess *KRAS* status in the individual laboratories. Four Australian laboratories participated in a multicentre blinded study in which six individual *KRAS* testing methods were evaluated: single strand conformation polymorphism analysis, pyrosequencing, HRM analysis, dideoxy sequencing, and two commercial kits, *KRAS* mutation detection kit (DxS Diagnostic Innovations; the same kit is now named TheraScreen: K-RAS Mutation Kit and is marketed by Qiagen who acquired DxS Diagnostics Innovations) and TIB Molbiol [22]. When one assay outlier (TIB Molbiol) was excluded, this study demonstrated a 96% degree of concordance between the *KRAS* mutation detection methodologies including the TheraScreen: K-RAS Mutation Kit and all those used by the Australian laboratories. The study concluded that a variety of techniques available at a number of clinical sites are suitable for *KRAS* mutation analysis.

To address the EMA's concern regarding the accuracy of *KRAS* testing and the detrimental consequences of acting upon a false negative result, Amgen has supported efforts in Europe to include Quality Assurance (QA) information for *KRAS* testing in practice guidelines. Amgen has also provided educational support to allow the European Society of Pathology to establish a QA program for *KRAS* testing in the EU to foster ongoing improvements in testing accuracy. Amgen would consider evaluating the relevance of a similar program in Australia.

Until an established Australian QA program can ensure appropriate standards for *KRAS* mutation test methodology in Australian pathology laboratories, Amgen will undertake to inform prescribers of the need for the *KRAS* status to be determined by an experienced laboratory using appropriate methodology. Accordingly, Amgen proposes to include a statement in the PI recommending the TheraScreen: *KRAS* Mutation Kit, as employed in the pivotal trials, or test methodologies with high concordance with the TheraScreen: *KRAS* Mutation Kit as established by the Whitehall *et al* (2009) study[22]. Because these other methodologies are viable alternatives to the TheraScreen: K-RAS Mutation Kit, Amgen believes that this proposal minimises the risk of false negatives and potential harm to patients erroneously diagnosed as wild-type *KRAS* mCRC.

Amgen considers the proposed indication, restricting use to patients with wild-type *KRAS* mCRC, contraindication, and recommended use of specific methodology for determining *KRAS* status, are appropriate and adequate measures to minimise the risk of potential harm to patients with mutant *KRAS* mCRC being inadvertently exposed to Vectibix in combination with oxaliplatin-based chemotherapy.

EGFR expression

As noted in Amgen's Clinical Overview, Amgen has systematically analysed the correlation between EGFR expression by immunohistochemistry (IHC) and outcome of Vectibix treatment in patients with mCRC in both monotherapy and combination therapy settings and has repeatedly and consistently failed to detect any difference in tumour response or progression free survival (PFS) between subjects with low/negative (1% to 9%/≤ 1%) versus high (≥ 10%) EGFR expression as detected by IHC. It is Amgen's position that this lack of association between efficacy and EGFR staining as detected by IHC demonstrates that IHC is inappropriate in this setting due to insensitivity of the IHC technology for useful detection of EGFR expression and tumour cell dependence on the EGFR pathway in colon cancer patients.

[22] Whitehall V, Tran K, Amapathy A, *et al*. (2009). A multicenter blinded study to evaluate KRAS mutation testing methodologies in the clinical setting. *J Mol Diagn* 11:543- 552.

Efficacy

Amgen agrees with the Delegate that Vectibix has demonstrated a statistically significant improvement in PFS in Phase III studies both when combined with FOLFOX in patients with previously untreated wild-type *KRAS* mCRC (Study 20050203) and when combined with FOLFIRI in patients who have failed a prior regimen for mCRC (Study 20050181). As FOLFOX and FOLFIRI are commonly used standards of care in initial or second line treatment of mCRC, the results from Studies 20050203 and 20050181 are relevant and generalisable to current clinical practice.

Studies 20050181 and 20050203 were designed with PFS as a co primary or primary endpoint. As discussed in our Clinical Overview, PFS was considered appropriate because it can be anticipated that an improvement in PFS predicts further survival benefit in the setting of mCRC. In addition, a literature review and assessment of mCRC trials of combination chemotherapy with targeted agents performed by Amgen has demonstrated that PFS strongly correlates with OS in modern mCRC trials (data on file). The observed correlation coefficient between PFS and OS in this analysis (0.88 based on a linear model between log[PFS] and log[OS]) for all trials) are consistent with that reported by [23] and [24], Spearman rank correlation coefficient). Taken together, these analyses strongly suggest that PFS and OS are highly correlated and that PFS may be a valid surrogate for OS in mCRC. PFS is the best direct measure of efficacy for a single line of therapy, and in contrast to OS, is less likely to be influenced by other effective post progression therapies. Disease progression is a direct indicator of tumour growth, which is linked with cancer associated morbidity and death, and is a highly clinically relevant endpoint because it is often associated with resistance to current therapy, and a need to switch to another line of treatment and regimen. In addition, disease progression is often associated with a deterioration of physical and emotional well being in cancer patients.

Additionally the improvements in PFS were complemented by positive trends in OS in favour of the Vectibix arms in subjects with wild-type *KRAS* tumours.

The overall benefits of Vectibix compare favourably with current standards of care. Thus, the totality of data support a clinically meaningful benefit of Vectibix administered in combination with chemotherapy for the first or second line treatment of patients with wild-type *KRAS* mCRC.

The sponsor added the following summary of study 184

*Study 184***.** Study 20050184 was a phase II, multi-centre, open-label, randomized clinical trial in subjects with mCRC for whom first-line treatment failed. The primary objective of the study was to obtain a preliminary estimate of the difference in incidence rates of specific ≥ Grade 2 skin toxicities of interest between mCRC subjects in the pre-emptive and reactive skin treatment arms during the 6-week skin treatment period. Secondary objectives were to evaluate additional preliminary assessments of skin toxicity events (including incidence of ≥ Grade 2 skin toxicities of any type, time to first occurrence of specific ≥ Grade 2 skin toxicities of interest, most severe specific ≥ Grade 2 skin toxicities of interest, time to the first most severe specific ≥ Grade 2 skin toxicities of interest, and incidence of panitumumab dose reduction due to the specific skin toxicities of interest), and the efficacy (response rate, ORR, PFS, disease control, time-to-treatment-failure, OS, PRO) and safety of panitumumab among subjects in the pre-emptive and reactive skin treatment arms.

[23] Buyse M, Burzkowski T, Carroll K, *et al*. Progression-free survival is a surrogate for survival in advanced colorectal cancer. *J Clin Oncol*. 2007; 25:5218-5224.
[24] Tang P, Bentzen SM, Chen EX, Siu LL. Surrogate end points for median overall survival in metastatic colorectal cancer: literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. *J Clin Oncol*. 2007; 25:4562-4568.

Conclusions of study 20050184

Study 20050184 shows that a pre-emptive skin toxicity regimen in patients treated with panitumumab reduced ≥grade 2 skin toxicities, delayed the onset time for skin toxicities, decreased the need for dose modification, and did not interfere with the anti-tumor efficacy of panitumumab.

In analyses by *KRAS* status, subjects with wild-type *KRAS* given panitumumab as part of second-line treatment demonstrated improvement in clinical outcomes relative to those with mutant *KRAS*, consistent with the results of the phase 3 studies (20050181 and 20050203).

Conclusion

Amgen supports the Delegate's recommendation regarding the use of Vectibix in combination with chemotherapy proposed in this application and recognises the importance of *KRAS* mutation testing for patient safety. As described above, with a single methodology exception not apparently used in Australia, *KRAS* testing methodologies are robust, sensitive, specific and one of the most accurate molecular diagnostic tests in oncology (compared to HER2 and EGFR testing). Amgen considers the proposed indication, restricting use to patients with wild-type *KRAS* mCRC, contraindication, and recommended use of specific methodology for determining *KRAS* status, are appropriate and adequate measures to minimise the risk of potential harm to patients with mutant *KRAS* mCRC being inadvertently exposed to Vectibix in combination with oxaliplatin-based chemotherapy.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission from Amgen Australia Pty Ltd to register PAN (Vectibix) injection 100 mg, 200 mg and 400 mg to include the proposed extension of indications use in the first (and later) line treatment of wild-type *KRAS* metastatic colorectal cancer, in combination with chemotherapy.
In making the recommendation that the overall risk benefit profile for this product was negative, the ACPM considered the following.

Efficacy

In both first and second line treatment with the addition of PAN to chemotherapy statistically significant improvements in progression free survival (PFS) and overall response rate were demonstrated in the *KRAS* wild type patient population. However, this was considered clinically to be an extremely limited improvement. There was only a non significant trend towards improved overall survival (OS) and no significant difference in quality of life measures.

Efficacy results for the mutant *KRAS* population in Study 203 showed PFS was significantly worsened by the addition of PAN in first line treatment and no benefit in second line treatment.

Safety

Safety data suggest that the addition of PAN to chemotherapy results in an increase in toxicity with an increase in the incidence of serious adverse events of approximately 10%. Approximately 20% of patients discontinued PAN due to adverse events; an additional 3 to 4% of patients in the PAN arm had to discontinue all chemotherapy treatment.

The ACPM was of the opinion that the marginal benefit conferred by the addition of PAN treatment was outweighed by the increase in toxicity.

The ACPM, taking into account the submitted evidence of safety and efficacy, considered this product has unfavourable benefit-risk profile for the proposed indication.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the application for extension of indications for Vectibix (Panitumumab) 100 mg/5 mL, 200 mg/10 mL and 400 mg/20 mL Concentrated Solution for Injection.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The following is an excerpt from the Delegate of the Minister's report.

The Delegate of the Minister made some findings which are summarised below. The Delegate noted that some of those matters were only clearly apparent from information that was not available to the Committee. Some analysis had been prepared for a review requested in Europe, where initially the Committee for Medicinal Products for Human Use (CHMP) had reached a similar view as the Committee.

Efficacy

Concerning efficacy of the use of the combination of panitumumab and FOLFOX, the Delegate has come to the view that such use in first line treatment of subjects with ECOG performance status of 0 or 1 has a median Progression-free Survival Time benefit of 2.4 months. In addition to being statistically significant, I am of the view that although it is a modest difference it would be regarded as a worthwhile additional benefit by many patients as well as their treating oncologists. On the other hand, the information derived from small numbers of subjects with ECOG status 2 suggests that use of the combination in this subgroup is deleterious. Further, the median Overall Survival in subjects with ECOG 0 or 1 status was 25.8 months with the combination and 20.7 months with FOLFOX alone (difference of 5.1 months). The P-value for the Log-rank test was 0.0176, the Hazard Ratio 0.767 (95% CI: 0.616; 0.955) and the P value for treatment effect 0.0179. In this subset of subjects, there was a consistency between the observed median Progression-free Survival Time and the median Observed Survival Time. This is sufficient to demonstrate efficacy in this first-line indication.

Concerning efficacy of the use of the combination of panitumumab and FOFIRI, the Delegate noted that the use of the combination in subjects with an ECOG status of 0 or 1 conferred a median gain of 2 months in Progression-free Survival Time. In addition to being statistically significant, the Delegate is of the view that although it is a very modest difference it would be regarded as a worthwhile additional benefit by many patients as well as their treating oncologists. It is of concern that the median gain in Overall Survival in subjects with ECOG status of 0 or 1 was borderline (1.9 months) and not statistically significant. The Delegate noted the apparent disconnection between median Overall Survival Time and Objective Response Rates, and that there may be merit in the proposition that the imbalances in the use and timing of use of subsequent anti-EGFR monoclonal antibody therapy between the two treatment arms may have had the effect of decreasing the calculated median Overall Survival time. The Delegate decided that, on

balance, the corpus of information is just sufficient to demonstrate efficacy in subjects with ECOG performance status 0 or 1 in this second line indication.

Concerning use in subjects with ECOG status 2, use of the combination with FOLFOX in first- line therapy appeared to be deleterious, while use of the combination with FOLFIRI in second line therapy failed any reasonable expectation of efficacy. The Delegate was of the view that it is important that these matters should be adequately highlighted in the Product Information.

Safety

The Delegate stated that it is beyond doubt that adverse events are particularly more common when panitumumab is combined with either FOLFOX or FOLFIRI. As noted in the Minutes of the ACPM, use of the combination was associated with an increase in the incidence of serious adverse events of approximately 10%. With the exception of palmar/plantar erythrodysaesthesia syndrome (PPE), anorexia and decreased weight, however, the adverse effects have been documented with panitumumab used as monotherapy. The Delegate noted the view of the Clinical Evaluator and of the two specialist oncologists who provided statements in support of the appeal that the adverse effects conferred on the combinations by panitumumab can be managed appropriately when the combinations are given by specialist oncologists.

The Delegate was of the view that it is important that the adverse effects should be adequately documented in the Product Information.

Notwithstanding that the evidence of efficacy of panitumumab in first-line and second line combination therapies is modest and that there are increased incidences of adverse effects that will require appropriate management the Delegate was of the view that the requirements of efficacy and safety in *the Act* have been met for both uses.

In approving the extension of indications, the Delegate imposed certain conditions for the additional indications as first line therapy with FOLFOX and second line therapy with FOLFIRI. These conditions were to do with amendments to the proposed Product Information, so as to adequately convey the matters referred to above.

Vectibix (Panitumumab) 100 mg/5 mL, 200 mg/10 mL and 400 mg/20 mL Concentrated Solution for Injection was approved for the following indications:

Vectibix is indicated for the treatment of patients with wild-type KRAS metastatic colorectal cancer (mCRC).

- *As first line therapy in combination with FOLFOX. Efficacy is influenced by patient performance status (see Clinical Trials; Precautions).*
- *As second line therapy in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). Efficacy may be influenced by patient performance status (see Clinical Trials).*
- *As monotherapy in patients after the failure of standard chemotherapy.*

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Therapeutic Goods Administration

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