NAME OF THE MEDICINE

Tecentriq®

atezolizumab (rch)

CAS: 1380723-44-3

Tecentriq is an engineered, humanised, monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors. Tecentriq is a non-glycosylated IgG1 immunoglobulin that has a calculated molecular mass of 145 kDa.

DESCRIPTION

Tecentriq is supplied as a single-use vial containing 20 mL preservative-free, colourless to slightly yellow solution, at a concentration of 60 mg/mL. Each vial contains a total of 1200 mg atezolizumab with the following excipients: histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injections.

PHARMACOLOGY

Pharmacodynamics

Binding of PD-L1 to the PD-1 and B7.1 receptors found on T cells suppresses cytotoxic T-cell activity through the inhibition of T-cell proliferation and cytokine production. PD-L1 may be expressed on tumour cells and tumour-infiltrating immune cells, and can contribute to the inhibition of the anti-tumour immune response in the microenvironment.

Atezolizumab is an Fc-engineered humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and blocks interactions with the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 pathway-mediated inhibition of the immune response, including reactivating the anti-tumour immune response. Atezolizumab leaves the PD-L2/PD-1 interaction intact, allowing PD-L2/PD-1 mediated inhibitory signals to persist. In syngeneic mouse tumour models, blocking PD-L1 activity resulted in decreased tumour growth.

Pharmacokinetics

The pharmacokinetics of atezolizumab has been characterised in patients in multiple clinical trials at doses 0.01 mg/kg to 20 mg/kg every 3 weeks including the fixed dose 1200 mg. Exposure to atezolizumab increased dose proportionally over the dose range 1 mg/kg to 20 mg/kg. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range 1 - 20 mg/kg with a linear two-compartment disposition model with first-order elimination. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the curve (AUC), maximum concentration (C_{max}) and trough concentration (C_{min}) was 1.91, 1.46 and 2.75-fold, respectively.

Based on analyses of population pharmacokinetics and exposure-safety and -efficacy relationships, the following factors have no clinically relevant effect: age (21 - 89 years), body weight, gender, positive anti-therapeutic antibody (ATA) status, albumin levels, tumour

burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or Eastern Cooperative Oncology Group (ECOG) status. No dose adjustments are recommended.

Absorption

Tecentriq is administered as an intravenous (IV) infusion. There have been no studies performed with other routes of administration.

Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution (V_1) is 3.28 L and volume at steady-state (V_{ss}) is 6.91 L in the typical patient.

Metabolism

The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism.

Excretion

A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life ($t_{1/2}$) is 27 days.

Pharmacokinetics in Special Populations

Children

No studies have been conducted to investigate the pharmacokinetics of Tecentriq in children.

Elderly

No dedicated studies of Tecentriq have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing atezolizumab pharmacokinetics based on patients of age range of 21 - 89 years (n = 472), and median of 62 years of age. No clinically important difference was observed in the pharmacokinetics of atezolizumab among patients < 65 years (n = 274), patients between 65 - 75 years (n = 152) and patients > 75 years (n = 46) (see *DOSAGE AND ADMINISTRATION*).

Renal impairment

No dedicated studies of Tecentriq have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2; n = 208) or moderate (eGFR 30 to 59 mL/min/1.73 m2; n = 116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m^2; n = 140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2; n = 8) (see *DOSAGE AND ADMINISTRATION*).

Hepatic impairment

No dedicated studies of Tecentriq have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 to 1.5 X ULN and any AST, n = 71) and normal

hepatic function (bilirubin and AST ≤ ULN, n = 401). No data are available in patients with either moderate (bilirubin>1.5 to 3.0 ´ ULN and any AST) or severe (bilirubin>3.0 ´ ULN and any AST) hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction (see *DOSAGE AND ADMINISTRATION*).

CLINICAL TRIALS

GO28915

A phase III, open-label, multi-centre, international, randomised study, GO28915 (OAK), was conducted to evaluate the efficacy and safety of Tecentriq compared with docetaxel in patients with locally advanced or metastatic NSCLC who have progressed during or following a platinum-containing regimen. A total of 1225 patients were enrolled, with the primary analysis population consisting of the first 850 randomised patients. Eligible patients were stratified by PD-L1 expression status in tumour-infiltrating immune cells (IC), by the number of prior chemotherapy regimens, and by histology. Patients were randomised (1:1) to receive either Tecentriq or docetaxel. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrollment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment. Tumour assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter.

The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-quarters of patients had non-squamous disease (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had CNS metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy five percent of patients received only one prior platinum-based therapeutic regimen.

Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator. Docetaxel was administered at 75 mg/m^2 by IV infusion on day 1 of each 21 day cycle until disease progression. For all treated patients, the median duration of treatment was 2.1 months for the docetaxel arm and 3.4 months for the Tecentriq arm.

The primary efficacy endpoint was OS. The key results of this study with a median survival follow-up of 21 months are summarised in Table 1. Kaplan-Meier curves for OS in the ITT population are presented in Figure 1. Figure 2 summarises the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with Tecentriq in all subgroups, including the TC0/IC0 subgroup (PD-L1 expression < 1% in TC and IC).

Table 1. Summary of Efficacy in the Primary Analysis Population (GO28915)

Efficacy endpoints	Tecentriq	Docetaxel
Primary Efficacy Endpoint		
OS		
All comers*	n = 425	n = 425
No. of deaths (%)	271 (64%)	298 (70%)
Median time to events (months)	13.8	9.6
95% CI	(11.8, 15.7)	(8.6, 11.2)
Stratified[#] hazard ratio (95% CI)	0.73 (0.62, 0.87)	
p-value**	0.0003	
12-month OS (%)	218 (55%)	151 (41%)
18-month OS (%)	157 (40%)	98 (27%)
TC1/2/3 or IC1/2/3	n = 241	n = 222
No. of deaths (%)	151 (63%)	149 (67%)
Median time to events (months)	15.7	10.3
95% CI	(12.6, 18.0)	(8.8, 12.0)
Stratified[#] hazard ratio (95% CI)	0.74 (0.58, 0.93)	
p-value**	0.0102	
12-month OS (%)	58%	43%
18-month OS (%)	44%	29%
Secondary Endpoints		
Investigator-assessed PFS (RECIST v1.1)		
All comers*	n = 425	n = 425
No. of events (%)	380 (89%)	375 (88%)
Median duration of PFS (months)	2.8	4.0
95% CI	(2.6, 3.0)	(3.3, 4.2)
Stratified[#] hazard ratio (95% CI)	0.95 (0.82, 1.10)	
Investigator-assessed ORR (RECIST v1.1)		
All comers*	n = 425	n = 425
No. of responders (%)	58 (14%)	57 (13%)
95% CI	(10.5, 17.3)	(10.3, 17.0)
Investigator-assessed DOR (RECIST v1.1)		
All comers*	n = 58	n = 57
Median in months	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

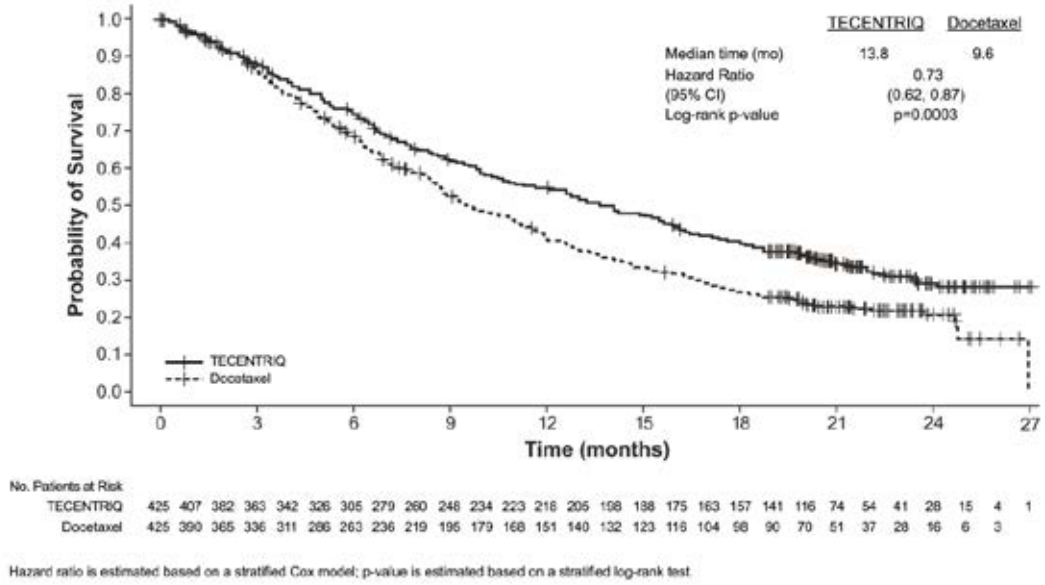
CI = confidence interval; DOR = duration of objective response; IC = tumor-infiltrating immune cells; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors v1.1; TC = tumour cells.

* All comers refers to the primary analysis population consisting of the first 850 randomised patients

[#] Stratified by PD-L1 expression in ICs, the number of prior chemotherapy regimens, and histology

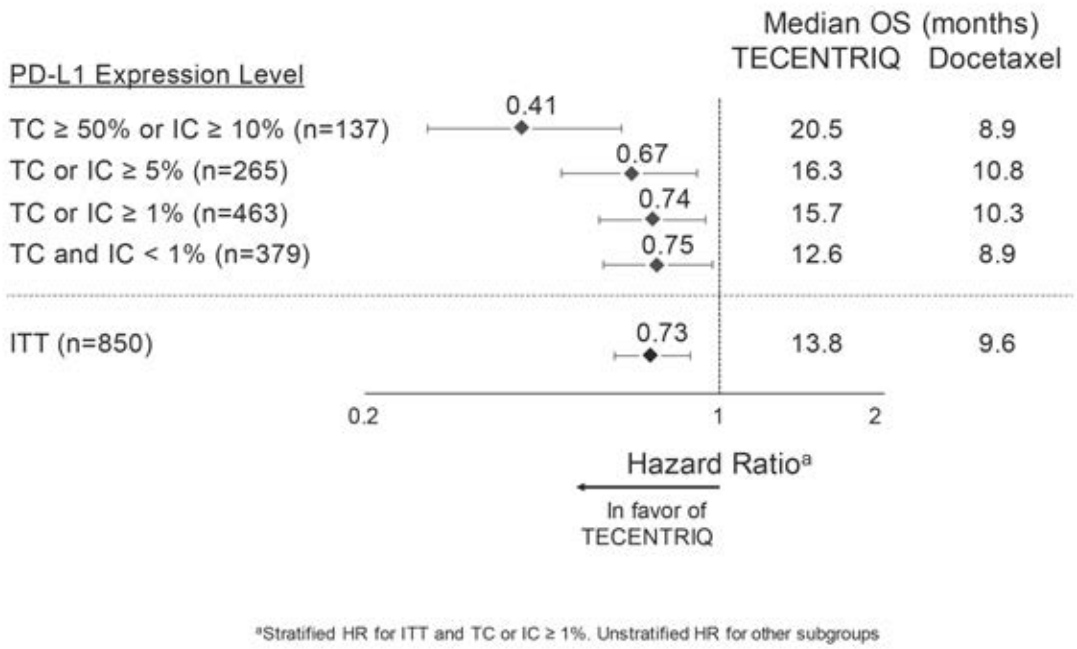
** Based on the stratified log-rank test

Figure 1. Kaplan-Meier Plot for Overall Survival in the Primary Analysis Population (all comers) (GO28915)



Hazard ratio is estimated based on a stratified Cox model; p-value is estimated based on a stratified log-rank test

Figure 2. Forest Plot of Overall Survival by PD-L1 Expression in the Primary Analysis Population (GO28915)



[a]Stratified HR for ITT and TC or IC ≥ 1%. Unstratified HR for other subgroups

An improvement in OS was observed with Tecentriq compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for Tecentriq and docetaxel, respectively) and squamous NSCLC patients (HR of 0.73, 95% CI: 0.54, 0.98; median OS of 8.9 vs. 7.7 months for Tecentriq and docetaxel, respectively). The observed OS improvement was consistently demonstrated across

subgroups of patients including those with brain metastases at baseline (HR of 0.54, 95% CI: 0.31, 0.94; median OS of 20.1 vs. 11.9 months for Tecentriq and docetaxel respectively) and patients who were never smokers (HR of 0.71, 95% CI: 0.47, 1.08; median OS of 16.3 vs. 12.6 months for Tecentriq and docetaxel, respectively). However, patients with EGFR mutations did not show improved OS with Tecentriq compared to docetaxel (HR of 1.24, 95% CI: 0.71, 2.18; median OS of 10.5 vs. 16.2 months for Tecentriq and docetaxel respectively).

Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with Tecentriq compared with docetaxel (HR 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ-LC13 was similar between Tecentriq and docetaxel. The average global health status and functioning scores (i.e. physical, role, social, emotional, and cognitive) as measured by the EORTC QLQ-C30 did not show clinically meaningful deterioration over time for both treatment groups, suggesting maintained health-related quality of life and patient-reported functioning for patients remaining on treatment.

GO28753

A phase II, multi-centre, international, randomised, open-label, controlled study, GO28753 (POPLAR), was conducted in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression. The primary efficacy outcome was overall survival, defined as the time from randomisation to death from any cause. Eligible patients were stratified by PD-L1 IC status (IC0, IC1, IC2, and IC3), by the number of prior chemotherapy regimens (1 vs. 2), and by histology (non-squamous vs. squamous) and then randomised 1:1 to receive either Tecentriq or docetaxel. Patients were excluded if they had a history of autoimmune disease, active brain metastasis, administration of a live, attenuated vaccine within 28 days prior to enrolment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to enrollment.

A total of 287 patients were randomised. The demographic and baseline disease characteristics of the overall patient population were generally well balanced between the treatment arms, and were reflective of the expected characteristics in the previously treated NSCLC population. The median age was 62.0 years for both docetaxel and Tecentriq and a higher proportion of patients were male (53% vs. 65% in docetaxel and Tecentriq). Most patients were White (81% vs. 76% in docetaxel and Tecentriq). More than half of patients had non-squamous disease (66% in both docetaxel and Tecentriq). Most patients were current or previous smokers (80% vs. 81% in docetaxel and Tecentriq). Approximately two-thirds of patients had ECOG score of 1 (68% in both docetaxel and Tecentriq). More than half of patients were 2L (67% vs. 65% in docetaxel and Tecentriq), with the remainder being 3L patients.

Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator.

The primary analysis occurred after 173 deaths were observed in the intent-to-treat (ITT) population. The median duration of treatment was 2.1 months for the docetaxel arm and 3.7 months for the Tecentriq arm. The median survival follow-up was 15.7 months for the

docetaxel arm and 14.8 months for the Tecentriq arm. The key results of this study are summarised in Tables 2 and 3. Kaplan-Meier curves for the ITT population are presented in Figure 3.

Table 2. Summary of efficacy from GO28753

Efficacy endpoint	Tecentriq	Docetaxel
Primary Efficacy Endpoint		
Overall Survival		
All Comers	n = 144	n = 143
No. of deaths (%)	78 (54.2%)	95 (66.4%)
Median time to events (months)	12.6	9.7
95% CI	9.7, 16.4	8.6, 12.0
Stratified hazard ratio[†] (95% CI)	0.73 (0.53, 0.99)	
Secondary Efficacy Endpoints		
Investigator-assessed PFS		
All Comers	n = 144	n = 143
No. of events (%)	124 (86.1%)	121 (84.6%)
Median duration of PFS (months)	2.7	3.0
95% CI	(2.0, 4.1)	(2.8, 4.1)
Stratified hazard ratio (95% CI)	0.94 (0.72, 1.23)	
Investigator-assessed ORR (RECIST v1.1)		
All Comers	n = 144	n = 143
No. of responders (%)	21 (14.6%)	21 (14.7%)
95% CI	(9.3, 21.4)	(9.3, 21.6)
Investigator-assessed DOR (RECIST v1.1)		
All Comers	n = 21	n = 21
Median in months	14.3	7.2
95% CI	11.6, NE	5.6, 12.5

[†] Stratified by IC levels, the number of prior chemotherapy regimens, and histology
CI = confidence interval; DOR = duration of objective response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

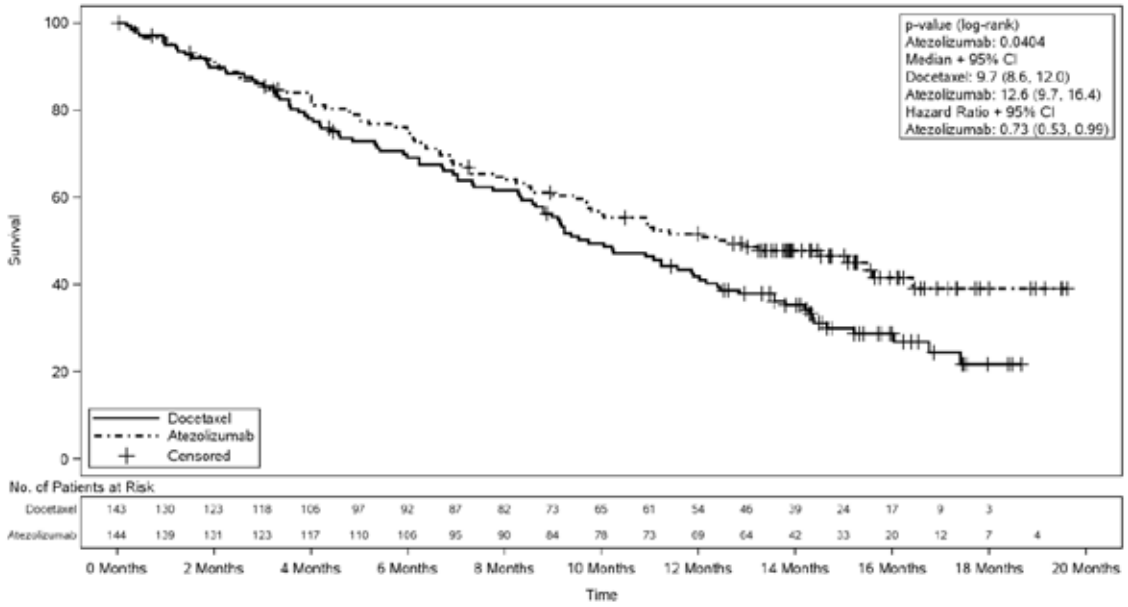
Table 3. Summary of efficacy from GO28753 based on PD-L1 expression

Efficacy endpoint	Tecentriq	Docetaxel
Primary Efficacy Endpoint		
Overall Survival		
TC3 or IC3	n = 24	n = 23
No. of deaths (%)	10 (41.7%)	16 (69.6%)
Median time to events (months)	15.5	11.1
95% CI	9.8, NE	6.7, 14.4
Unstratified hazard ratio (95% CI)	0.49 (0.22, 1.07)	
TC2/3 or IC2/3, excluding TC3 or IC3	n = 26	n = 32
No. of deaths (%)	15 (57.7%)	25 (78.1%)
Median time to events (months)	9.0	6.2
95% CI	6.9, NE	4.6, 9.0
Unstratified hazard ratio (95% CI)	0.59 (0.31, 1.12)	
TC1/2/3 or IC1/2/3, excluding TC2/3 or IC2/3	n = 43	n = 47
No. of deaths (%)	20 (46.5%)	28 (59.6%)
Median time to events (months)	15.6	12.4
95% CI	11.1, NE	8.8, 16.0
Unstratified hazard ratio (95% CI)	0.65 (0.37, 1.16)	
TC0 or IC0	n = 51	n = 41

Efficacy endpoint	Tecentriq	Docetaxel
No. of deaths (%)	33 (64.7%)	26 (63.4%)
Median time to events (months)	9.7	9.7
95% CI	(6.7, 12.0)	(8.6, 12.0)
Unstratified hazard ratio (95% CI)	1.04 (0.62, 1.75)	

CI = confidence interval; IC = tumour-infiltrating immune cells; OS = overall survival.

Figure 3. Kaplan-Meier Plot for Overall Survival (Primary Analysis – ITT Population)



An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with Tecentriq, vs. 9.7 months in patients treated with docetaxel (HR of 0.69, 95% CI: 0.52, 0.92). ORR was 15.3% vs. 14.7% and median DOR was 18.6 months vs. 7.2 months for Tecentriq vs. docetaxel, respectively.

GO28754

A phase II, multi-centre, international, single-arm clinical trial, GO28754 (BIRCH), was conducted in patients with PD-L1-selected locally advanced or metastatic NSCLC. Patients with TC2/3 or IC2/3 tumours were enrolled. Patients were excluded if they had a history of autoimmune disease, active brain metastasis, administration of a live, attenuated vaccine within 28 days prior to enrolment, administration of systemic immunostimulatory agents within 6 weeks or systemic immunosuppressive medications within 2 weeks. A total of 667 patients were enrolled into three cohorts: Cohort 1 included patients who had not received prior chemotherapy for advanced NSCLC (1L); Cohort 2 included patients who had received one platinum based chemotherapy regimen for advanced NSCLC (2L); Cohort 3 included patients who had received at least one platinum based chemotherapy and one additional regimen for advanced NSCLC (3L+).

There were 520 patients treated in Cohorts 2 and 3 (n = 267, 253 respectively). Patient demographics and baseline characteristics were representative of patients with previously treated locally advanced or metastatic NSCLC. In 2L+ treated patients, more than half were male (61%). The majority of patients were White (82%). Most patients were smokers (83%; current or previous). Almost two-thirds of patients had ECOG score of 1 (66%). Most patients had non-squamous disease (71%).

Tecentriq was administered as a fixed dose of 1200 mg by IV infusion every 3 weeks. No dose reduction was allowed. Patients in Cohorts 2 and 3 were treated until loss of clinical benefit as assessed by the investigator. The median duration of treatment was 4.1 months and median survival follow-up was 8.4 months for 2L+ TC2/3 or IC2/3.

The primary analysis was performed approximately 6 months after the last patient was enrolled. The primary efficacy endpoint was confirmed ORR as assessed by an IRF according to RECIST v1.1. Key efficacy results in all 2L+ treated patients are summarised in Table 4.

Table 4. Summary of efficacy from GO28754

Efficacy endpoint	**Cohorts 2 and 3 (2L+ in TC2/3 or IC2/3)**
Primary Efficacy Endpoint	
IRF-assessed ORR (RECIST v1.1)	n = 520
No. of Responders (%)	90 (17.3%)
95% CI	14.2, 20.8
Additional Efficacy Endpoints	
IRF-assessed DOR (RECIST v1.1)	n = 90
Median (months)	8.3
95% CI	6.9, NE
Range (months)	1.4* to 12.0*
IRF-assessed PFS (RECIST v1.1)	n = 520
Patients with events (%)	401 (77.1%)
Median duration of PFS (months)	2.8
95% CI	2.7, 2.9
6-month PFS rate	30.0%
95% CI	26.0, 34.1
1-year PFS rate	11.9%
95% CI	7.4, 16.4
OS[†]	n = 520
Patients with events (%)	187 (36%)
6-month OS rate	73.4%
95% CI	69.5, 77.3
1-year OS rate	55.3%
95% CI	49.5, 61.1
IRF-assessed time to onset of response (RECIST v1.1)	n = 90
Median (months)	2.6
95% CI	1.5, 2.7
Range (months)	1.1 to 9.6

[†] Median overall survival was not reached.

* denotes a censored value

CI = confidence interval; DOR = duration of objective response; IC = tumour-infiltrating immune cells; IRF = independent review facility; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

At the time of clinical data cut-off, 90 patients had responses, of which 57 (63.3%) had an ongoing response. In addition, 66.6% of responders had an ongoing response of 6 months or longer, using the Kaplan-Meier estimate.

With an additional 4 months of follow-up after the primary analysis cut-off date, the ORR as assessed by IRF per RECIST v1.1, was 18.7% (95% CI: 15.4, 22.3) and the median DOR was 11.3 months (95% CI: 8.3, 16.4) in 2L+ TC2/3 or IC2/3 NSCLC patients.

PD-L1 expression by immunohistochemistry

The VENTANA PD-L1 (SP142) Assay has been validated to detect PD-L1 expression in tumour-infiltrating immune cells (IC) and tumour cells (TC).

The test detects the presence of any discernible PD-L1 staining of any intensity.

Scoring for tumour cells was defined as TC0 (< 1%), TC1 (≥ 1% and < 5%), TC2 (≥ 5% and < 50%), and TC3 (≥ 50%). Scoring for tumour-infiltrating immune cells was defined as IC0 (< 1%), IC1 (≥ 1% and < 5%), IC2 (≥ 5% and < 10%) and IC3 (≥ 10%).

Immunogenicity

As with all therapeutic proteins, there is the potential for immune response to atezolizumab. In study GO28915, the post-baseline ATA rate was 30.4%. In study GO28753, the incidence of post-baseline ATAs was 54.5%. In study GO28754, the post-baseline ATA rate was 38.5%. Overall, ATA positivity appeared to have no clinically relevant impact on pharmacokinetics, efficacy or safety.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of incidence of antibodies to Tecentriq with the incidence of antibodies to other products may be misleading.

INDICATIONS

Tecentriq is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Tecentriq should be used after progression on or after targeted therapy.

CONTRAINDICATIONS

Tecentriq is contraindicated in patients with a known hypersensitivity to atezolizumab or any of the excipients.

PRECAUTIONS

Immune-related pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with Tecentriq (see *ADVERSE EFFECTS*). Patients should be monitored for signs and symptoms of pneumonitis.

Treatment with Tecentriq should be withheld for Grade 2 pneumonitis, and 1 - 2 mg/kg prednisone or equivalent per day should be started. If symptoms improve to ≤ Grade 1, taper

corticosteroids over ≥ 1 month. Treatment with Tecentriq may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with Tecentriq should be permanently discontinued for Grade 3 or 4 pneumonitis.

Immune-related hepatitis

Cases of hepatitis, some leading to fatal outcomes, have been observed in clinical trials with Tecentriq (see *ADVERSE EFFECTS*). Patients should be monitored for signs and symptoms of hepatitis. Monitor aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin prior to and periodically during treatment with Tecentriq. Appropriate management of patients with abnormal liver function tests (LFTs) at baseline should be considered.

Treatment with Tecentriq should be withheld if Grade 2 (ALT or AST > 3 x ULN or blood bilirubin > 1.5 x ULN) persists for more than 5 - 7 days, and 1 - 2 mg/kg prednisone or equivalent per day should be started. If LFTs improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month. Treatment with Tecentriq may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with Tecentriq should be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 3 x ULN).

Immune-related colitis

Cases of diarrhoea or colitis have been observed in clinical trials with Tecentriq (see *ADVERSE EFFECTS*). Patients should be monitored for signs and symptoms of colitis.

Treatment with Tecentriq should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, start 1 - 2 mg/kg prednisone or equivalent per day. Treat Grade 3 diarrhoea or colitis with IV corticosteroids (1 - 2 mg/kg/day methylprednisolone or equivalent) and convert to oral corticosteroids (prednisone 1-2 mg/kg or equivalent per day) after improvement. If symptoms improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month. Treatment with Tecentriq may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with Tecentriq should be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis.

Immune-related endocrinopathies

Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, including diabetic ketoacidosis, have been observed in clinical trials with Tecentriq (see *ADVERSE EFFECTS*). Patients should be monitored for clinical signs and symptoms of endocrinopathies and for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation). Patients may present with the following: fatigue, headache, mental status changes, heat or cold intolerance, tachycardia or bradycardia, unusual bowel habits, weight change, polyuria/polydipsia, blurred vision. Unless an alternate aetiology has been identified, signs and symptoms of endocrinopathies should be conservatively considered immune-related. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered.

Asymptomatic patients with abnormal thyroid function tests can receive Tecentriq. For symptomatic hypothyroidism, Tecentriq should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, Tecentriq should be withheld and an anti-thyroid drug such as carbimazole should be initiated as needed. Treatment with a beta blocker may also be considered. Treatment with Tecentriq may be resumed when symptoms are controlled and thyroid function is improving.

For symptomatic adrenal insufficiency, Tecentriq should be withheld and treatment of 1 - 2 mg/kg per day of IV methylprednisolone or equivalent should be started. Once symptoms improve, follow with 1 - 2 mg/kg per day of oral prednisone or equivalent. If symptoms improve to ≤ Grade 1, taper corticosteroids over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone or equivalent per day and patient is stable on replacement therapy (if required).

Treatment with Tecentriq should be withheld for Grade 2 or Grade 3 hypophysitis. Treatment with 1 - 2 mg/kg per day IV methylprednisolone or equivalent should be started, and hormone replacement should be initiated as needed. Once symptoms improve, convert to 1 - 2 mg/kg per day of oral prednisone or equivalent. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg per day of oral prednisone or equivalent and patient is stable on replacement therapy (if required). Treatment with Tecentriq should be permanently discontinued for Grade 4 hypophysitis.

Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose greater than 13.9 mmol/L), Tecentriq should be withheld. Treatment with Tecentriq may be resumed if metabolic control is achieved on insulin replacement therapy.

Immune-related meningoencephalitis

Meningoencephalitis has been observed in clinical trials with Tecentriq (see *ADVERSE EFFECTS*). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis.

Treatment with Tecentriq should be permanently discontinued for any grade of meningitis or encephalitis. Treat with 1 - 2 mg/kg IV methylprednisolone or equivalent per day. Convert to 1 - 2 mg/kg oral prednisone or equivalent per day once the patient has improved. If symptoms improve to ≤ Grade 1, taper corticosteroids over ³ 1 month.

Immune-related neuropathies

Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life-threatening, were observed in patients receiving Tecentriq (see *ADVERSE EFFECTS*). Patients should be monitored for symptoms of motor and sensory neuropathy.

Treatment with Tecentriq should be permanently discontinued for any grade of myasthenic syndrome / myasthenia gravis or Guillain-Barré syndrome. Consider initiation of systemic corticosteroids at a dose of 1 - 2 mg/kg oral prednisone or equivalent per day.

Immune-related pancreatitis

Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with Tecentriq (see *ADVERSE EFFECTS*). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.

Treatment with Tecentriq should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2.0 ULN), or Grade 2 or 3 pancreatitis, and treatment with 1 - 2 mg/kg IV methylprednisolone or equivalent per day, should be started. Once symptoms improve, follow with 1 - 2 mg/kg oral prednisone or equivalent per day. Treatment with Tecentriq may be resumed when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day. Treatment with Tecentriq should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

Immune related myocarditis

Myocarditis has been observed in clinical trials with Tecentriq. Patients should be monitored for signs and symptoms of myocarditis. Treatment with Tecentriq should be withheld for Grade 2 myocarditis. Consider initiation of treatment with systemic corticosteroids. Treatment with Tecentriq should be permanently discontinued for Grade 3 or 4 myocarditis.

Infusion related reactions

Infusion related reactions (IRRs) have been observed in clinical trials with Tecentriq (see *ADVERSE EFFECTS*).

The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion related reactions. Tecentriq should be permanently discontinued in patients with Grade 3 or 4 infusion related reactions. Patients with Grade 1 or 2 infusion related reactions may continue to receive Tecentriq with close monitoring; premedication with an antipyretic and antihistamines may be considered.

Patients with autoimmune disease

Patients with autoimmune disease were excluded from clinical trials with Tecentriq. In the absence of data, Tecentriq should be used with caution in patients with autoimmune disease, after assessment of the potential risk-benefit.

Use in renal impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see *DOSAGE AND ADMINISTRATION* and *PHARMACOLOGY*).

Use in hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment (see *DOSAGE AND ADMINISTRATION* and *PHARMACOLOGY*). There are no data in patients with moderate or severe hepatic impairment.

Effects on fertility

No fertility studies have been conducted with atezolizumab; however assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Atezolizumab had an effect on menstrual cycles in all female monkeys in the 50 mg/kg dose group characterised by an irregular cycle pattern during the dosing phase and correlated with the lack of fresh corpora lutea in the ovaries at the terminal necropsy; this effect was reversible during the dose-free recovery period. The AUC at the no effect level was approximately 5 times that anticipated in patients. . There was no effect on the male reproductive organs.

Use in pregnancy – Category D

Based on the mechanism of action, the use of Tecentriq may cause foetal harm. Administration of Tecentriq is expected to have an adverse effect on pregnancy and poses a risk to the human foetus, including embryofoetal lethality. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to an increased risk of immune-related rejection of the developing foetus resulting in foetal death.

No dedicated reproductive or teratogenicity studies in animals have been conducted with atezolizumab.

There are no clinical studies of Tecentriq in pregnant women. Tecentriq is not recommended during pregnancy unless the potential benefit for the mother outweighs the potential risk to the foetus. Pregnant women should be advised of the potential risk to the foetus.

Women of childbearing potential should use highly effective contraception during treatment with Tecentriq and for 5 months after the last dose.

The safety of Tecentriq during labor and delivery has not been established.

Use in lactation

It is not known whether atezolizumab is excreted in human breast milk. No studies have been conducted to assess the impact of atezolizumab on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, a decision must be made to either discontinue breast-feeding or discontinue Tecentriq therapy.

Paediatric use

The safety and efficacy of Tecentriq in children and adolescents below 18 years of age has not been established.

Use in the elderly

No overall differences in safety or efficacy were observed between patients ≥ 65 years of age and younger patients (see *DOSAGE AND ADMINISTRATION* and *PHARMACOLOGY*).

Genotoxicity

No genotoxicity studies have been conducted with atezolizumab.

Carcinogenicity

No carcinogenicity studies have been conducted with atezolizumab.

Effect on laboratory tests

See sections *PRECAUTIONS, Immune-related hepatitis* and *Immune-related endocrinopathies* for management of the following:

- AST, ALT, bilirubin
- thyroid function.

Ability to drive and use machines

No studies on the effects on the ability to drive and to use machines have been performed.

INTERACTIONS WITH OTHER MEDICINES

No formal pharmacokinetic drug-drug interaction studies have been conducted with Tecentriq.

ADVERSE EFFECTS

The safety of Tecentriq is based on pooled data in 1636 patients with NSCLC, with supporting data from the estimated cumulative exposure in 6000 patients across all clinical trials in multiple tumour types.

Table 5 summarises the adverse drug reactions (ADRs) that have been reported in association with the use of Tecentriq during treatment. The following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 5. Summary of ADRs occurring in patients treated with Tecentriq in clinical trials

System Order Class/ ADR (MedDRA Preferred Term)	Tecentriq (n = 1636)			
	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
Blood and Lymphatic System Disorders				
Thrombocytopenia	31 (1.9%)	7 (0.4%)	0 (0%)	Common
Endocrine Disorders				
Hypothyroidism [a]	76 (4.6 %)	3 (0.2%)	0 (0%)	Common
Hyperthyroidism [b]	30 (1.8%)	0 (0%)	0 (0%)	Common
Adrenal insufficiency [c]	6 (0.4%)	0 (0%)	0 (0%)	Uncommon
Hypophysitis	1 (< 0.1%)	0 (0%)	0 (0%)	Rare
Diabetes mellitus [d]	5 (0.3%)	3 (0.2%)	0 (0%)	Uncommon
Gastrointestinal Disorders				
Diarrhoea	287 (17.5%)	14 (0.9%)	0 (0%)	Very Common
Dysphagia	52 (3.2%)	10 (0.6%)	0 (0%)	Common
Colitis [e]	15 (0.9%)	4 (0.2%)	0 (0%)	Uncommon
Nausea	359 (21.9 %)	17 (1.0%)	0 (0%)	Very Common
Vomiting	231 (14.1%)	14 (0.9%)	0 (0%)	Very Common
Abdominal pain	86 (5.3%)	6 (0.4%)	0 (0%)	Common
Pancreatitis [f]	4 (0.2%)	3 (0.2%)	0 (0%)	Uncommon
Amylase increased	1 (< 0.1%)	1 (< 0.1%)	0 (0%)	Rare
Lipase increased	3 (0.2%)	2 (0.1%)	0 (0%)	Uncommon

System Order Class/ ADR (MedDRA Preferred Term)	Tecentriq (n = 1636)			
	All Grades (%)	Grade 3 - 4 (%)	Grade 5 (%)	Frequency (All Grades)
General Disorders and Administration				
Chills	77 (4.7%)	1 (< 0.1%)	0 (0%)	Common
Fatigue	514 (31.4 %)	47 (2.9%)	0 (0%)	Very Common
Asthenia	240 (14.7%)	22 (1.3%)	0 (0%)	Very Common
Influenza like illness	93 (5.7%)	0 (0.0%)	0 (0%)	Common
Pyrexia	287 (17.5%)	7 (0.4%)	0 (0%)	Very Common
Infusion related reaction	19 (1.2%)	5 (0.3%)	0 (0%)	Common
Hepatobiliary Disorders				
ALT increased	73 (4.5%)	14 (0.9%)	0 (0%)	Common
AST increased	80 (4.9%)	16 (1.0%)	0 (0%)	Common
Hepatitis [g]	5 (0.3%)	4 (0.2%)	0 (0%)	Uncommon
Immune System Disorders				
Hypersensitivity	20 (1.2%)	1 (< 0.1%)	0 (0%)	Common
Metabolism and Nutrition Disorders				
Decreased appetite	406 (24.8%)	12 (0.7%)	0 (0%)	Very Common
Hypokalemia	80 (4.9%)	17 (1.0%)	0 (0%)	Common
Hyponatremia	74 (4.5%)	42 (2.6%)	0 (0%)	Common
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	220 (13.4%)	11 (0.7%)	0 (0%)	Very Common
Musculoskeletal pain	158 (9.7%)	8 (0.5%)	0 (0%)	Common
Nervous System Disorders				
Guillain-Barré syndrome [h]	5 (0.3%)	4 (0.2%)	0 (0%)	Uncommon
Noninfective encephalitis [i]	2 (0.1%)	2 (0.1%)	0 (0%)	Rare
Meningitis noninfective[j]	3 (0.2%)	2 (0.1%)	0 (0%)	Uncommon
Myasthenic syndrome [k]	-	-	-	Rare
Respiratory, Thoracic, and Mediastinal Disorders				
Dyspnoea	386 (23.6%)	68 (4.2%)	1 (< 0.1%)	Very Common
Hypoxia	47 (2.9%)	21 (1.3%)	0 (0%)	Common
Nasal congestion	39 (2.4%)	0 (0%)	0 (0%)	Common
Pneumonitis [l]	56 (3.4%)	19 (1.2%)	1 (< 0.1%)	Common
Skin and Subcutaneous Tissue Disorders				
Rash [m]	303 (18.5%)	15 (0.9%)	0 (0%)	Very Common
Pruritus	163 (10.0%)	3 (0.2%)	0 (0%)	Common
Vascular Disorders				
Hypotension	53 (3.2%)	8 (0.5%)	0 (0%)	Common
Cardiac Disorders				
Myocarditis[k]	-	-	-	Rare

[a] Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased
[b] Includes reports of hyperthyroidism, blood thyroid stimulating hormone increased, thyroiditis, blood thyroid stimulating hormone decreased, endocrine ophthalmopathy, exophthalmus, thyroid function test abnormal, thyroiditis acute, thyroxine decreased
[c] Includes reports of adrenal insufficiency, primary adrenal insufficiency, and Addison's disease
[d] Includes reports of diabetes mellitus and type 1 diabetes mellitus
[e] Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic
[f] Includes reports of pancreatitis and pancreatitis acute
[g] Includes reports of autoimmune hepatitis, hepatitis, hepatitis acute
[h] Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy
[i] Includes reports of encephalitis
[j] Includes reports of meningitis
[k] Reported in studies outside the NSCLC dataset. The frequency is based on the program-wide exposure
[l] Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis
[m] Includes reports of rash maculo-papular, erythema, rash pruritic, dermatitis acneiform, eczema, rash papular, rash macular, dermatitis, rash erythematous, acne, rash pustular, skin exfoliation, skin ulcer, seborrhoeic dermatitis, erythema multiforme, dermatitis bullous, rash generalised, skin toxicity, exfoliative rash, dermatitis allergic, drug eruption, dermatitis exfoliative, palmar-plantar erythrodysaesthesia syndrome, rash papulosquamous, toxic skin eruption, erythema of eyelid, eyelid rash, folliculitis, furuncle, rash

Tables 6 and 7 summarise safety information from the GO28915 (OAK) study that evaluated Tecentriq compared with docetaxel in patients with locally advanced or metastatic NSCLC. Table 6 summarises adverse reactions that occurred in at least 10% of Tecentriq-treated patients and at a higher incidence than in the docetaxel arm. Table 7 summarises selected laboratory abnormalities worsening from baseline that occurred in ≥ 10% of Tecentriq-treated patients and at a higher incidence than in the docetaxel arm.

Table 6. Adverse reactions occurring in ≥ 10% of Tecentriq-treated patients in GO28915 and at a higher incidence than in the docetaxel arm (between arm difference of ≥ 5% [all grades] or ≥ 2% [grades 3 - 4])

	Tecentriq (n = 609)		**docetaxel (n = 578)**	
Adverse Reaction	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**
	Percentage (%) of Patients			
Respiratory, thoracic and mediastinal disorders				
Cough	26	0.5	21	0.2

Table 7. Selected laboratory abnormalities worsening from baseline occurring in ≥ 10% of Tecentriq-treated patients in GO28915 and at a higher incidence than in the docetaxel arm (between arm difference of ≥ 5% [all grades] or ≥ 2% [grades 3 - 4])

	Percentage of patients with worsening laboratory test from baseline	
	Tecentriq	**docetaxel**

Test	All grades %	Grade 3–4 %	All grades %	Grade 3–4 %
Hyponatremia	42	7	31	6
ALP increased	39	2	25	1
AST increased	31	3	16	1
ALT increased	27	3	14	1
Magnesium decreased	26	1	21	1
Creatinine increased	23	2	16	1
Hypokalemia	15	2	9	2

Additional information for selected adverse reactions

See *PRECAUTIONS* for management of the following:

Immune-related pneumonitis

Pneumonitis occurred in 3.4% (56/1636) of patients who received Tecentriq. Of the 56 patients, one event was fatal. The median time to onset was 3.3 months (range: 3 days to 18.7 months). The median duration was 1.6 months (range 0 days to 15.1* months; where * denotes a censored value). Pneumonitis led to discontinuation of Tecentriq in 9 (0.6%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.8% (29/1636) of patients receiving Tecentriq.

Immune-related hepatitis

Hepatitis occurred in 0.3% (5/1636) of patients who received Tecentriq. The median time to onset was 1.1 months (range 9 days to 7.9 months). The median duration was 22 days (range: 9 days to 1.9* months; where * denotes a censored value). Hepatitis led to discontinuation of Tecentriq in 2 (0.1%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.2% (3/1636) of patients receiving Tecentriq. Grade 3 - 4 events of ALT increased, AST increased and blood bilirubin increased occurred in 14 (0.9%), 16 (1.0%) and 2 (0.1%) patients, respectively.

Immune-related colitis

Colitis occurred in 0.9% (15/1636) of patients who received Tecentriq. The median time to onset was 3 months (range 15 days to 12.7 months). The median duration was 1.2 months (range: 6 days to 8.3* months; where * denotes a censored value). Colitis led to discontinuation of Tecentriq in 2 (0.1%) patients. Colitis requiring the use of corticosteroids occurred in 0.3% (5/1636) of patients receiving Tecentriq. As per Table 5, diarrhoea occurred in 17.5% (287/1636) of patients.

Immune-related endocrinopathies

Hypothyroidism occurred in 4.6% (76/1636) of patients who received Tecentriq. The median time to onset was 4.6 months (range: 15 days to 31.3 months). Hyperthyroidism occurred in 1.8% (30/1636) of patients who received Tecentriq. The median time to onset was 3.2 months (range: 21 days to 31.3 months).

Adrenal insufficiency occurred in 0.4% (6/1636) of patients who received Tecentriq for. The median time to onset was 5.5 months (range: 3 days to 19 months). Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (5/1636) of patients receiving Tecentriq.

Hypophysitis occurred in < 0.1% (1/1636) of patients who received Tecentriq. The time to onset for this patient was 13.7 months.

Diabetes mellitus occurred in 0.3% (5/1636) of patients who received Tecentriq. The time to onset ranged from 3 days to 6.5 months. Diabetes mellitus led to the discontinuation of Tecentriq in 1 (< 0.1%) patient.

Immune-related meningoencephalitis

Meningitis occurred in 0.2% (3/1636) of patients who received Tecentriq. The time to onset ranged from 15 to 16 days. All three patients required the use of corticosteroids and discontinued Tecentriq. Encephalitis occurred in 0.1% (2/1636) of patients. The time to onset was 14 and 16 days. One of these patients required the use of corticosteroids. Encephalitis led to the discontinuation of Tecentriq in 1 (< 0.1%) patient.

Immune-related neuropathies

Neuropathies, including Guillain-Barré syndrome and demyelinating polyneuropathy, occurred in 0.3% (5/1636) of patients who received Tecentriq. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 4.6 months (1 day to 8.3* months; * denotes a censored value). Guillain-Barré syndrome led to the discontinuation of Tecentriq in 1 (< 0.1%) patient. Guillain-Barré syndrome requiring the use of corticosteroids occurred in 0.1% (2/1636) of patients.

Immune-related pancreatitis

Pancreatitis, including amylase increased and lipase increased, occurred in 0.5% (8/1636) of patients who received Tecentriq. The median time to onset was 7.5 months (range: 9 days to 16.9 months). The median duration was 10 days (range 3 days to 11.2* months; where * denotes a censored value). Pancreatitis requiring the use of corticosteroids occurred in 0.1% (2/1636) of patients receiving Tecentriq.

Laboratory Abnormalities

All identified laboratory abnormalities were reported as ADRs, refer to Table 5.

DOSAGE AND ADMINISTRATION

General

Tecentriq must be administered as an IV infusion under the supervision of a qualified healthcare professional. Do not administer as an IV push or bolus.

The recommended dose is 1200 mg administered by IV infusion every three weeks. The initial dose of Tecentriq must be administered over 60 minutes. If the first infusion is tolerated all subsequent infusions may be administered over 30 minutes.

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded in the patient medical record.

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Duration of Treatment

Patients are treated with Tecentriq until loss of clinical benefit (see *CLINICAL TRIALS*) or unmanageable toxicity.

Delayed or Missed Doses

If a planned dose of Tecentriq is missed, it should be administered as soon as possible; do not wait until the next planned dose. The schedule of administration should be adjusted to maintain a 3-week interval between doses.

Dose Modifications

No dose reductions of Tecentriq are recommended.

Table 8. Dose modification advice for specified Adverse Drug Reactions

Adverse reaction	Severity	Treatment modification
Infusion-related reactions (see also *PRECAUTIONS*)	Grade 1 or 2	Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved.
	Grade 3 or 4	Permanently discontinue Tecentriq.
Rash (see also *ADVERSE EFFECTS*)	Grade 3	Withhold Tecentriq. Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day.
	Grade 4	Permanently discontinue Tecentriq.
Pneumonitis (see also *PRECAUTIONS*)	Grade 2	Withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg oral prednisone equivalent per day.
	Grade 3 or 4	Permanently discontinue Tecentriq.
Hepatitis (see also *PRECAUTIONS*)	Grade 2: (ALT or AST > 3 x ULN *or* blood bilirubin > 1.5 x ULN)	If persists > 5 - 7 days, withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day.
	Grade 3 or 4: (ALT or AST > 5 x ULN *or* blood bilirubin > 3 x ULN)	Permanently discontinue Tecentriq.

Adverse reaction	Severity	Treatment modification
Colitis (see also *PRECAUTIONS*)	Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) *or* Symptomatic colitis	Withhold Tecentriq. Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day.
	Grade 4 (life threatening; urgent intervention indicated) diarrhoea *or* colitis	Permanently discontinue Tecentriq.
Hypothyroidism or hyperthyroidism (see also *PRECAUTIONS*)	Symptomatic	Withhold Tecentriq. *Hypothyroidism:* Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and thyroid function is improving. *Hyperthyroidism:* Treatment may be resumed when symptoms are controlled by an anti-thyroid drug and thyroid function is improving.
Adrenal insufficiency (see also *PRECAUTIONS*)	Symptomatic	Withhold Tecentriq. Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of ≤ 10 mg oral prednisone or equivalent per day and patient is stable on replacement therapy (if required).
Hypophysitis *(see also PRECAUTIONS)*	Grade 2 or 3	Withhold Tecentriq. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg per day of oral prednisone or equivalent and patient is stable on replacement therapy (if required).
	Grade 4	Permanently discontinue Tecentriq.
Type 1 diabetes mellitus (see also *PRECAUTIONS*)	Grade 3 or 4 hyperglycaemia (fasting glucose greater than 13.9 mmol/L)	Withhold Tecentriq. Treatment may be resumed when metabolic control is achieved on insulin replacement therapy.
Myasthenic Syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis (see also	Any grade	Permanently discontinue Tecentriq.

Adverse reaction	Severity	Treatment modification
PRECAUTIONS)		
Myocarditis (see also *PRECAUTIONS*)	Grade 2	Withhold Tecentriq. Consider initiation of treatment with systemic corticosteroids.
	Grade 3 or 4	Permanently discontinue Tecentriq.
Pancreatitis (see also *PRECAUTIONS*)	Grade 3 or 4 serum amylase or lipase levels increased (> 2.0 x ULN) or Grade 2 or 3 pancreatitis	Withhold Tecentriq. Treatment with Tecentriq may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg oral prednisone or equivalent per day.
	Grade 4 or any grade of recurrent pancreatitis	Permanently discontinue Tecentriq.

Special Dosage Instructions

Children

The safety and efficacy of Tecentriq in children and adolescents below 18 years of age have not been established.

Elderly

Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see *PRECAUTIONS* and *PHARMACOLOGY*).

Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with renal impairment (see *PRECAUTIONS* and *PHARMACOLOGY*).

Hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment. There are no data in patients with moderate or severe hepatic impairment (see *PRECAUTIONS* and *PHARMACOLOGY*).

Instructions for dilution

Tecentriq does not contain any antimicrobial preservative and should be prepared by a healthcare professional using aseptic technique.

Withdraw 20 mL of Tecentriq concentrate from the vial and dilute into a 250 mL PVC, polyethylene (PE) or polyolefin infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. After dilution, one mL of solution should contain approximately 4.4 mg of Tecentriq (1200 mg/270 mL). The bag should be gently inverted to mix the solution in order to avoid foaming.

Instructions for administration

Parenteral medicinal products should be inspected visually for particulates and discolouration prior to administration. If particulates or discoloration are observed, the solution should not be used.

The product is for single use in one patient only. Discard any residue.

Incompatibilities

No incompatibilities have been observed between Tecentriq and IV bags with product-contacting surfaces of polyvinyl chloride (PVC), polyethylene (PE) or polyolefin. In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane.

OVERDOSAGE

There is no information on overdose with Tecentriq.

For information on the management of overdose, contact the Poisons Information Centre (call 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

Available in a single-use glass vial containing 1200 mg of Tecentriq in a 20 mL concentrated solution for intravenous infusion.

Store the vials at 2 °C to 8 °C. Do not freeze.

Tecentriq should be protected from light. Do not shake.

This medicine should not be used after the expiry date (EXP) shown on the pack.

The diluted solution for infusion should be used immediately. If the solution is not used immediately, it can be stored for up to 24 hours at 2 °C to 8 °C, or 8 hours at ambient temperature (≤ 30 °C).

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

NAME AND ADDRESS OF THE SPONSOR

Distributed by:
Roche Products Pty Limited
ABN 70 000 132 865
4-10 Inman Road
Dee Why NSW 2099
AUSTRALIA
Medical enquiries: 1800 233 950

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

27 July 2017