Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Exkivity

Active ingredient: Mobocertinib

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

April 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- 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.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (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. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ALT	Alanine aminotransferase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under concentration time curve from time zero to 24 hours
AUC_{∞}	Area under concentration time curve from time zero to infinity
AUC_{last}	Area under concentration time curve to the last measurable concentration
BCRP	Breast cancer resistance protein
CI	Confidence interval
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
cORR	Confirmed objective response
CR	Complete response
DLP	Data lock point
DOR	Duration of response
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
eGFR	Estimated glomerular filtration rate
EGFRm	Mutations of the *EGFR* oncogene
EU	European Union
ex20ins	Exon 20 insertion
FDA	Food and Drug Administration (United States)
GT	Grouped Term
IRC	Independent radiological review committee
MDR	Multidisciplinary review
NSCLC	Non-small cell lung cancer
ODxT	Oncomine Dx Target Test
ORR	Objective response rate
PBPK	Physiologically-based pharmacokinetics
PD-L1	Programmed death-ligand 1
PI	Product Information

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PPP	Pooled prior platinum
PR	Partial response
PT	Preferred Term
RMP	Risk management plan
SAE	Serious adverse event
TEAE	Treatment-emergent adverse events
TGA	Therapeutic Goods Administration
TKI	Tyrosine kinase inhibitors
T_{max}	Time to reach maximum concentration
UK	United Kingdom
ULN	Upper limit of normal
US(A)	United States (of America)

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Exkivity
Active ingredient:	Mobocertinib
Decision:	Approved for provisional registration
Date of decision:	14 July 2022
Date of entry onto ARTG:	19 July 2022
ARTG number:	370160
▼*Black Triangle Scheme*	Yes
for the current submission:	As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration
Sponsor's name and address:	Takeda Pharmaceuticals Australia Pty Ltd Level 39, 225 George Street Sydney NSW 2000
Dose form:	Capsule
Strength:	40 mg
Container:	Blister pack
Pack size:	112 capsules
Approved therapeutic use for the current submission:	*Exkivity has provisional approval in Australia for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has an exon 20 insertion mutation of the epidermal growth factor receptor (EGFR), who have received prior platinum-based chemotherapy.* *The decision to approve this indication has been made on the basis of objective response rate and duration of response in a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory study.*
Route of administration:	Oral
Dosage:	The recommended dosage of Exkivity is 160 mg orally once daily, continued until disease progression or unacceptable toxicity. Swallow Exkivity capsules whole. Do not open, chew or dissolve the contents of the capsules. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Takeda Pharmaceuticals Australia Pty Ltd (the sponsor) to register Exkivity (mobocertinib) 40 mg, capsule, blister pack, for the following proposed indication:[1]

> *Exkivity is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received prior platinum-based chemotherapy.*

Condition

This submission proposes the registration of a new chemical entity for the treatment of adult patients who have received prior platinum-based chemotherapy for locally advanced or metastatic non-small cell lung cancer (NSCLC) with tumours harbouring an exon 20 insertion (ex20ins) mutation in the epidermal growth factor receptor (EGFR) gene.

Lung cancer is the most deadly cancer, and after breast cancer, the second most common cancer worldwide, with an annual mortality of 1.8 million deaths (18% of global cancer deaths) and incidence of 2.2 million cases (or 11% of global cancers) in 2020.[2]

The Australian Institute of Health and Welfare estimates that lung cancer is the most deadly and fifth most commonly diagnosed in Australia, with an estimated age-standardised mortality rate in 2021 of 26.5 per 100,000 (8,693 deaths), and an age-standardised incidence of 42 per 100,000.[2,3]

Non-small cell lung cancer is the most common type of lung cancer (around 85%).[2] The two predominant histological types of NSCLC are adenocarcinoma (around half of all NSCLC) and squamous cell carcinoma (around 40%), while other less common types include large cell carcinoma.[4]

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered on the Australian Register of Therapeutic Goods.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249

[3] Estimates for 2021, based on actual mortality to 2019 and incidence to 2017.

[4] Chen Z, Fillmore CM, Hammerman PS, Kim CF, Wong KK. Non-small-cell lung cancers: a heterogeneous set of diseases. Nat Rev Cancer. 2014 Aug;14(8):535-46.

The mean age of diagnosis of NSCLC in Australia is at around 70 years, and almost half of patients present with *de novo* metastatic disease (or cancer that has already spread at the time it is diagnosed).[5] Although survival has improved over past decades,[6] the five-year relative overall survival rate remains very poor, at around 15%.[4,7]

The *EGFR* gene codes for the epidermal growth factor receptor, a transmembrane glycoprotein that functions a receptor on the surface of cells. Activating mutations of the *EGFR* oncogene (*EGFRm*) occur in a subset of NSCLC tumours, and are associated with tumours in patients of female sex, non-smoker status, and tumours with adenocarcinoma histology.[8] There is a higher incidence of *EGFRm* in Asian patient populations: the proportion of lung adenocarcinomas found to harbour an *EGFRm* was 46% in Southern Asia and 30% in Northern Asia, compared to 9% in North America and 13% in Europe.[11] In squamous cell tumours, *EGFRm* are much less common (2% to 10%) and their clinical significance (including predictiveness of response to targeted therapy) is less clear.[9,10]

Exon 20 insertion mutations are a rare subset of *EGFRm*. The most common, 'classical' *EGFRm* are in frame deletions in exon 19, and L858R substitutions in exon 21. In an approximate 1:1 ratio, in frame deletions in exon 19 and L858R mutations comprise around 85 to 90% of *EGFRm*.[11,12,13] The remainder of *EGFRm* are a highly heterogeneous group of molecular alterations but tend to occur within exons 18 to 21 (see Figure 1).[14,15] They include ex20ins mutations (3% to 12% of identified *EGFRm*)[16,17,18] and point mutations at G719X (that is, G719A,

[5] Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax. 2013;68(6):551-64.

[6] Lu T, Yang X, Huang Y, et al. Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. Cancer Manag Res. 2019;11:943-953. Published 2019 Jan 21.

[7] Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83(5):584-94.

[8] Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heeroma K, Itoh Y, Cornelio G, Yang PC. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol. 2014 Feb;9(2):154-62.

[9] Joshi A, Zanwar S, Noronha V, et al. EGFR mutation in squamous cell carcinoma of the lung: does it carry the same connotation as in adenocarcinomas?. Onco Targets Ther. 2017;10:1859-1863. Published 2017 Mar 28

[10] Jin R, Peng L, Shou J, Wang J, Jin Y, Liang F, Zhao J, Wu M, Li Q, Zhang B, Wu X, Lan F, Xia L, Yan J, Shao Y, Stebbing J, Shen H, Li W, Xia Y. EGFR-Mutated Squamous Cell Lung Cancer and Its Association With Outcomes. Front Oncol. 2021 Jun 14;11:680804

[11] Graham RP, Treece AL, Lindeman NI, Vasalos P, Shan M, Jennings LJ, Rimm DL. Worldwide Frequency of Commonly Detected EGFR Mutations. Arch Pathol Lab Med. 2018 Feb;142(2):163-167

[12] Shigematsu H and Gazdar AF, Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers, Int. J. Cancer 118 (2006) 257–262.

[13] Sharma, S., Bell, D., Settleman, J. et al. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 7, 169–181 (2007).

[14] Roengvoraphoj M, Tsongalis GJ, Dragnev KH, Rigas JR. Epidermal growth factor receptor tyrosine kinase inhibitors as initial therapy for non-small cell lung cancer: focus on epidermal growth factor receptor mutation testing and mutation-positive patients. Cancer Treat Rev. 2013 Dec;39(8):839-50.

[15] Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. Cancer Discov. 2017;7:596–609.

[16] Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. Cancer Res. 2004 Dec 15;64(24):8919-23.

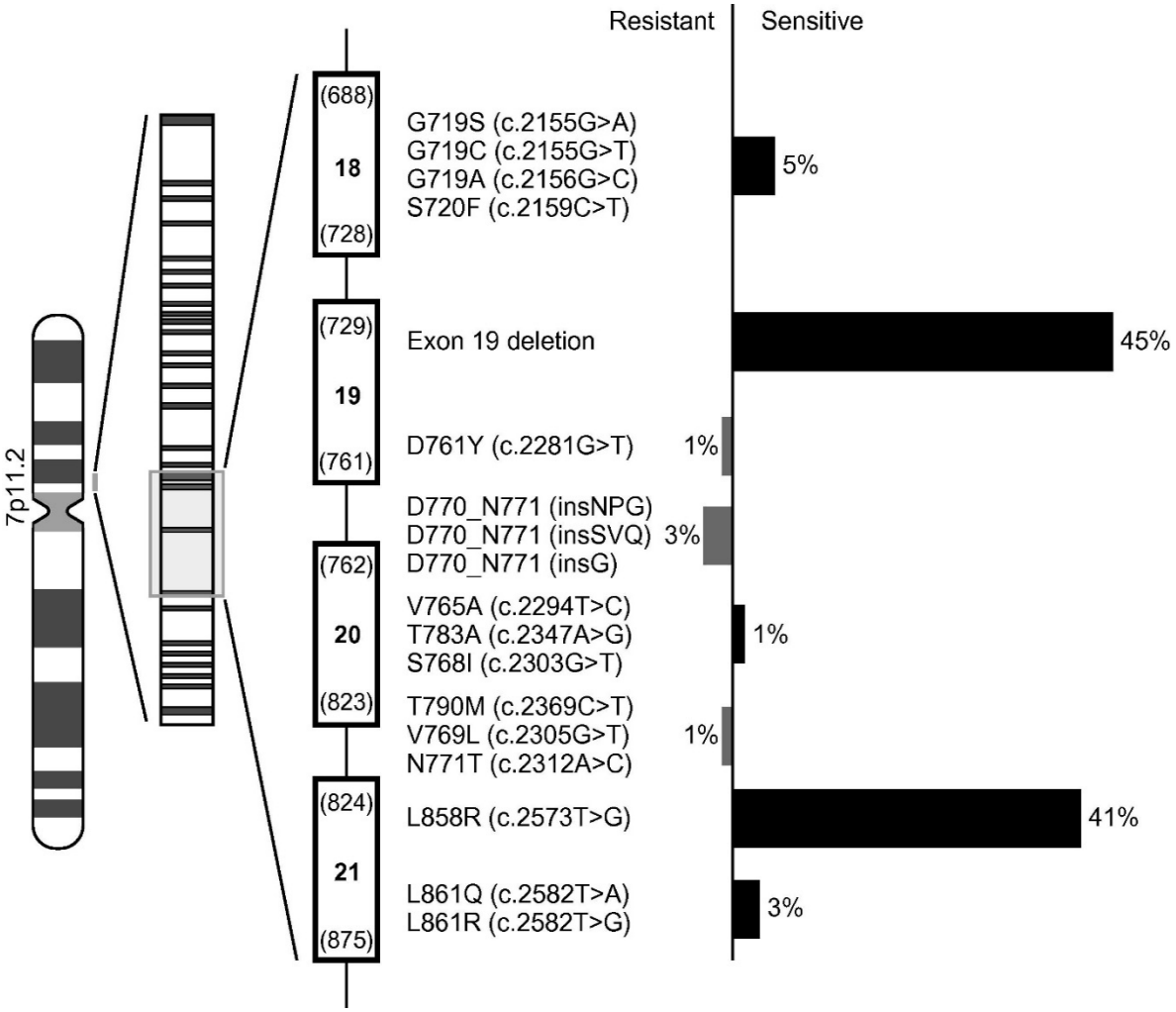
[17] Riess JW, Gandara DR, Frampton GM, Madison R, Peled N, Bufill JA, et al. Diverse EGFR Exon 20 insertions and co-occurring molecular alterations identified by comprehensive genomic profiling of NSCLC. J Thorac Oncol 2018;13:1560–8.

[18] Cheng L, Alexander RE, Maclennan GT et al. Molecular pathology of lung cancer: key to personalized medicine Mod Pathol, 25 (3) (2012), pp. 347-369

G719C, or G719S; exon 18; 3 to 5% of all *EGFRm*),[14],[19] at L861Q/L861R (exon 21; 2 to 3% of all *EGFRm*)[9],[20] and at S768I (exon 20; 1% of all *EGFRm*).[21]

Unlike other *EGFRm*, there does not appear to be a clear difference in frequency of ex20ins mutations in NSCSLC based on ethnicity.[21] They otherwise show similar demographic associations to other *EGFRm*, including the extreme rarity of co-occurrence with other oncogenic drivers (such as *KRAS*).[17]

Figure 1: The spectrum of described mutations in codons 18 to 21 of the *EGFR* gene (on chromosome 7), and their association with responsiveness to first generation *EGFR* tyrosine kinase inhibitors



Current treatment options

There are no therapeutic goods that are registered in Australia specifically for the treatment of patients with NSCLC whose tumours harbor *EGFR* ex20ins mutations.

[19] Li K, Yang M, Liang N, Li S. Determining EGFR-TKI sensitivity of G719X and other uncommon EGFR mutations in non-small cell lung cancer: Perplexity and solution (Review). Oncol Rep. 2017;37(3):1347-1358.
[20] O'Kane GM, Bradbury PA, Feld R, Leighl NB, Liu G, Pisters KM, Kamel-Reid S, Tsao MS, Shepherd FA. Uncommon EGFR mutations in advanced non-small cell lung cancer. Lung Cancer. 2017 Jul;109:137-144.
[21] Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. Cancer Treat Rev. 2020 Nov;90:102105.

First line of therapy

Patients with early stage NSCLC can be treated with curative intent, however, only a small proportion of patients (30%) present with localised disease amenable to such approaches.[22] Five-year recurrence rates after resection are approximately 45% for Stage IB, 62% for Stage II and 76% for Stage III patients.[23] Systemic therapy is indicated for patients with advanced (locally advanced or metastatic) disease, including patients with recurrence following initial definitive treatment.[24]

Systemic treatment of metastatic NSCLC is guided by molecular testing.[25,26] In the absence of a 'driver' mutation for which a targeted therapy is available (such as activating mutations in *EGFR*, *ALK*, *ROS1* or *BRAF* genes), major international clinical guidelines recommend an anti-programmed death ligand 1 (PD-L1) antibody, with or without histology directed platinum doublet chemotherapy (depending on tumour PD-L1 expression level)[27,28,29,30] as standard of care first line treatment (Table 1).[31]

[22] Walters S, Maringe C, Coleman MP, Peake MD, Butler J, Young N, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. Thorax. 2013;68(6):551-64.

[23] Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D, Le Chevalier T; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008 Jul 20;26(21):3552-9.

[24] Lilenbaum RC (2020). Systemic chemotherapy for advanced non-small cell lung cancer. Last updated 4 Feb 2020.

[25] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. Version 1.2022. December 7, 2021. Fort Washington (PA): National Comprehensive Cancer Network; 2022. Accessed 28/02/2022

[26] Hanna NH, Robinson AG, Temin S, Baker S Jr, Brahmer JR, Ellis PM, Gaspar LE, Haddad RY, Hesketh PJ, Jain D, Jaiyesimi I, Johnson DH, Leighl NB, Moffitt PR, Phillips T, Riely GJ, Rosell R, Schiller JH, Schneider BJ, Singh N, Spigel DR, Tashbar J, Masters G. Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. J Clin Oncol. 2021 Mar 20;39(9):1040-1091. doi: 10.1200/JCO.20.03570. Epub 2021 Feb 16. Erratum in: J Clin Oncol. 2021 Aug 1;39(22):2520. PMID: 33591844.

[27] Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, Panwalkar A, Yang JC, Gubens M, Sequist LV, Awad MM, Fiore J, Ge Y, Raftopoulos H, Gandhi L; KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, Phase II cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Nov;17(11):1497-1508. doi: 10.1016/S1470-2045(16)30498-3. Epub 2016 Oct 10. PMID: 27745820; PMCID: PMC6886237.

[28] Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, Hermes B, Çay Şenler F, Csőszi T, Fülöp A, Rodríguez-Cid J, Wilson J, Sugawara S, Kato T, Lee KH, Cheng Y, Novello S, Halmos B, Li X, Lubiniecki GM, Piperdi B, Kowalski DM; KEYNOTE-407 Investigators. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2040-2051. doi: 10.1056/NEJMoa1810865. Epub 2018 Sep 25. PMID: 30280635.

[29] Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Apr 16. PMID: 29658856.

[30] Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G Jr, Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K, Lubiniecki GM, Zhang J, Kush D, Lopes G; KEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, Phase III trial. Lancet. 2019 May 4;393(10183):1819-1830. doi: 10.1016/S0140-6736(18)32409-7. Epub 2019 Apr 4. PMID: 30955977.

[31] Hanna NH, Schneider BJ, Temin S, Baker S Jr, Brahmer J, Ellis PM, Gaspar LE, Haddad RY, Hesketh PJ, Jain D, Jaiyesimi I, Johnson DH, Leighl NB, Phillips T, Riely GJ, Robinson AG, Rosell R, Schiller JH, Singh N, Spigel DR, Stabler JO, Tashbar J, Masters G. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. J Clin Oncol. 2020 May 10;38(14):1608-1632. doi: 10.1200/JCO.19.03022. Epub 2020 Jan 28. PMID: 31990617.

Table 1: Response rates, durations and survival seen in randomised studies of current standard of care first line treatments for non-small cell lung cancer in patients without driver mutations

Population	Subgroup	Treatment (n)	ORR % [95% CI]	Median DOR months range	Median OS months [95% CI]	OS rate % [95% CI]
PD-L1 positive (TPS≥1%) NSCLC[1] (histology-agnostic)	PD-L1 ≥50%[5]	Pembro[6] (n=299)	39.1 [33.6, 44.9]	28.1 2.1+ to 70.0+	20.0 [15.9, 24.2]	22 (5-year) [17.3, 26.9]
		Chemo[7] (n=300)	32.3 [27.1, 37.9]	10.8 1.8+ to 63.5+	12.2 [10.4, 14.6]	10 (5-year) [6.6, 13.7]
nsNSCLC[2]	PD-L1 agnostic	Pembro+chemo[8] (n=60)	58 [45, 71]	36.3 1.4+ to 49.3+	34.5 [24.0, NR]	50 (3-year) NS
		Chemo[9] (n=63)	33 [22, 46]	22.8 2.8+ to 47.2+	21.1 [14.9, 35.6]	37 (3-year) NS
nsNSCLC[3]	PD-L1 agnostic	Pembro+chemo[10] (n=410)	48.3 [43.4, 53.2]	12.5 1.1+ to 34.9+	22.0 [19.5, 24.5]	46 (2 year) NS
		Chemo[11] (n=205)	19.9 [14.7, 26.0]	7.1 2.4 to 27.8+	10.6 [8.7, 13.6]	27 (2 year) NS
sNSCLC[4]	PD-L1 agnostic	Pembro+chemo[12] (n=278)	62.6 [56.6, 68.3]	9.0 1.3+ to 45.0+	17.2 [14.4, 19.7]	30 (3-year) [24.5, 35.2]
		Chemo[13] (n=281)	38.8 [33.1, 44.8]	4.9 1.3+ to 44.8+	11.6 [10.1, 13.7]	18 (3-year) [13.8, 23.0]

CI = confidence interval; DOR = duration of response; NR = not reached; NS = not stated; nsNSCLC = non-squamous non small cell lung cancer; ORR = objective response rate; OS = overall survival; sNSCLC = squamous non small cell lung cancer; + = ongoing response

1) Updated findings from KEYNOTE-042;[32] 2) Updated findings from KEYNOTE-021;[33] 3) Updated findings from KEYNOTE-189;[34] 4) Updated findings from KEYNOTE-407;[35] 5) Subgroup congruent with a randomisation stratum; 6) Pembrolizumab monotherapy (200 mg every three weeks); 7) Investigator's choice of histology-directed, platinum-based chemotherapy for four to six cycles; 8) Pembrolizumab (200 mg pembrolizumab

[32] Castro GD, Kudaba I, Wu Y, et al. 363 KEYNOTE-042 5-year survival update: pembrolizumab versus chemotherapy in patients with previously untreated, PD-L1–positive, locally advanced or metastatic non–small-cell lung cancerJournal for ImmunoTherapy of Cancer 2021;9:

[33] Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JC, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Altan M, Jalal SI, Panwalkar A, Gubens M, Sequist LV, Saraf S, Zhao B, Piperdi B, Langer CJ. Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC. J Thorac Oncol. 2021 Jan;16(1):162-168.

[34] Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, Dómine M, Cheng SY, Bischoff HG, Peled N, Reck M, Hui R, Garon EB, Boyer M, Kurata T, Yang J, Pietanza MC, Souza F, Garassino MC. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Ann Oncol. 2021 Jul;32(7):881-895

[35] Robinson AG, Vicente D, Tafreshi A, Parra HS, Mazieres J, Cicin I, et al. 97o First-Line Pembrolizumab Plus Chemotherapy for Patients With Advanced Squamous NSCLC: 3-Year Follow-Up From KEYNOTE-407. J Thorac Oncol (2021) 16(4):S748–S9.

every three weeks [one cycle]) in combination with chemotherapy (4 cycles of carboplatin plus pemetrexed, then pemetrexed maintenance); 9) Chemotherapy alone (4 cycles of carboplatin plus pemetrexed, then pemetrexed maintenance): 70% of patients in this arm subsequently received anti–PD-(L)1 therapy; 10) Pembrolizumab (200 mg pembrolizumab every three weeks [one cycle]) in combination with chemotherapy (4 cycles of cisplatin or carboplatin plus pemetrexed, then pemetrexed maintenance); 11) Chemotherapy alone (4 cycles of cisplatin or carboplatin plus pemetrexed, then pemetrexed maintenance): 56% of patients in this arm subsequently received anti–PD-(L)1 therapy; 12) Pembrolizumab (200 mg pembrolizumab every three weeks [one cycle]) in combination with chemotherapy for 4 cycles (carboplatin plus either paclitaxel or nab–paclitaxel); 13) Chemotherapy alone for 4 cycles (carboplatin plus either paclitaxel or nab–paclitaxel).

Choice of systemic treatment for *EGFRm*-positive NSCLC depends on the specific *EGFRm* identified.[25] Four anti-EGFR tyrosine kinase inhibitors (TKIs) are currently registered in Australia for the treatment of NSCLC that harbours an *EGFRm*. These include 'first generation,' ATP competitive inhibitors erlotinib;[36] and gefitinib;[37] the 'second generation' covalently binding irreversible inhibitor, afatinib;[38] and the 'third generation' agent, osimertinib.[39] The latter has activity against tumours expressing a mutation (*T790m*) that confers resistance to earlier generation TKIs.[40] There is strong evidence to support these agents in the treatment of classical *EGFRm*, as the pivotal studies predominantly, or entirely, enrolled such patients. Treatment of tumours harbouring some uncommon mutations (particularly S768I, L861Q and/or G719X mutations) is also supported, based on analyses of the more limited data that is available for these rarer groups.[41],[42]

By contrast, ex20ins mutations are not generally associated with sensitivity to EGFR TKIs *in vitro* or *in vivo*, though there are exceptions such as p.A763_Y764insFQEA (and possibly p.A763_Y764insLQEA).[43,44] Therefore, although the registered indications for erlotinib, gefitinib, afatinib and osimertinib do not explicitly exclude treatment of ex20ins-positive tumours, such treatment would not generally be undertaken and they have been generally excluded from clinical trials of drugs targeting the classical *EGFRm*. For patients with ex20ins positive NSCLC, major clinical guidelines therefore recommend standard of care first-line treatment for tumours without a targetable mutation, although this effectiveness of these treatments have not been specifically studied in this subpopulation.[25]

[36] Erlotinib was first registered in Australia on 30 January 2006. ARTG number: 114714.
[37] Gefitinib was first registered in Australia on 28 April 2003. ARTG number: 90010.
[38] Afatinib was first registered in Australia on 7 November 2013. ARTG number: 201314.
[39] Osimertinib was first registered in Australia on 3 August 2016. ARTG number: 255492.
[40] John T, Akamatsu H, Delmonte A, et al. EGFR mutation analysis for prospective patient selection in AURA3 phase III trial of osimertinib versus platinum-pemetrexed in patients with EGFR T790M-positive advanced non-small-cell lung cancer. Lung Cancer 2018;126:133-138.
[41] Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, Yamamoto N, Yu CJ, Ou SH, Zhou C, Massey D, Zazulina V, Wu YL. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol. 2015 Jul;16(7):830-8.
[42] Cho JH, Lim SH, An HJ, et al. Osimertinib for Patients With Non-Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: A Multicenter, Open-Label, Phase II Trial (KCSG-LU15-09). J Clin Oncol. 2020;38(5):488-495.
[43] Oxnard GR, Lo PC, Nishino M, Dahlberg SE, Lindeman NI, Butaney M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. J Thorac Oncol 2013;8:179–84.
[44] Sousa AC, Silveira C, Janeiro A, Malveiro S, Oliveira AR, Felizardo M, Nogueira F, Teixeira E, Martins J, Carmo-Fonseca M. Detection of rare and novel EGFR mutations in NSCLC patients: Implications for treatment-decision. Lung Cancer. 2020 Jan;139:35-40..

Second line of therapy

For patients with ex20ins positive NSCLC with progression of disease following platinum-based chemotherapy, treatment options in Australia reflect those cited in the United States Food and Drug Administration (FDA) multidisciplinary review (MDR) document for mobocertinib:[45]

> '…treatment options include chemotherapy (single agent or docetaxel in combination with ramucirumab) associated with ORRs [objective response rates] of 6-23% with median DORs [duration of responses] in the range of 4 - 9 months, or single agent anti-PD-(L)1 antibodies if not received in the first-line setting, associated with ORRs of 14-20% and median DORs in the range of 16-17 months.'

Detailed tables summarising these standard of care options, including references, are contained in Table 1 of the FDA MDR.[45]

For patients with ex20ins positive NSCLC, the current NCCN guideline;[25] recommends consideration of an ex20ins specific molecule (amivantamab or mobocertinib) on progression, based on durable responses in early phase studies.[46,47] Neither of these agents is currently registered in Australia and the registration of mobocertinib is the subject of the current submission.

The pivotal trial enrolled patients who were second line or later: who had received prior platinum based chemotherapy. During the course of the study, the standard of care first line non-targeted treatment for NSCLC changed from (histology directed) platinum based chemotherapy alone to platinum based chemotherapy plus immunotherapy. A considerable proportion of patients (43%) received this new first line immunotherapy/chemotherapy combination, as is the current standard of care for ex20ins mutation positive NSCLC, and results in this subgroup were consistent with the primary analysis.

Rationale for product development

Structural differences between the mutant versions of the expressed EGFR protein underpin their differing responses to small molecule inhibitors.[48]

In the wild type receptor, a key structural element called the C-helix regulates receptor activity. When rotated from an outward to an inward position, the C-helix opens up the active site and allows stable dimerisation to occur (Figure 2).[49]

[45] US FDA multi-disciplinary review for Exkivity. Accessed 4 March 2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215310Orig1s000MultidisciplineR.pdf

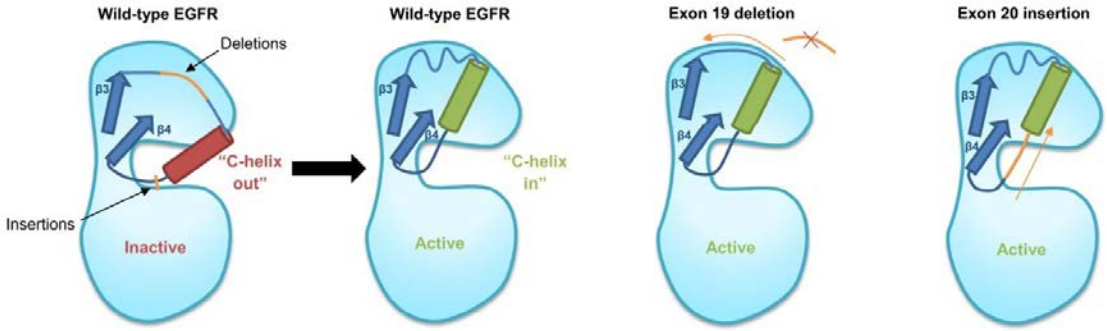
[46] Ramalingam SS, Zhou C, Kim TM, et al. . Mobocertinib (TAK-788) in EGFR exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): additional results from platinum-pretreated patients (pts) and EXCLAIM cohort of Phase 1/2 study [abstract]. J Clin Oncol. 2021;39(15)(suppl):9014.

[47] Park K, Haura EB, Leighl NB, Mitchell P, Shu CA, Girard N, Viteri S, Han JY, Kim SW, Lee CK, Sabari JK, Spira AI, Yang TY, Kim DW, Lee KH, Sanborn RE, Trigo J, Goto K, Lee JS, Yang JC, Govindan R, Bauml JM, Garrido P, Krebs MG, Reckamp KL, Xie J, Curtin JC, Haddish-Berhane N, Roshak A, Millington D, Lorenzini P, Thayu M, Knoblauch RE, Cho BC. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol. 2021 Oct 20;39(30):3391-3402.

[48] Landau, M. & Ben-Tal, N. Dynamic equilibrium between multiple active and inactive conformations explains regulation and oncogenic mutations in ErbB receptors. Biochim. Biophys. Acta 1785, 12–31 (2008).

[49] Eck, M. J. & Yun, C. H. Structural and mechanistic underpinnings of the differential drug sensitivity of EGFR mutations in non-small cell lung cancer. Biochim. Et. Biophys. Acta 1804, 559–566 (2010).

Figure 2: Vyse et al. (2019) Illustration of the conformational change that occurs in wild-type EGFR between the active and inactive receptor state, and the effects of deletion mutations in exon 19 or insertion mutations in exon 20



Adapted from: Vyse, S., Huang, P.H. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Sig Transduct Target Ther 4, 5 (2019).[50]

The classical *EGFRm* cause destabilising conformational changes in the EGFR that allow ligand independent dimerisation, and constitutive activation of downstream signalling pathways.[50] Affected cells display sensitivity to EGFR inhibition consistent with an 'oncogene addiction' type dependency on such signalling for survival.[51] Deletions in exon 19, for example, shorten the N-terminal loop leading to the C-helix, and are hypothesised to 'pull' on it, restricting its ability to rotate outward, and promoting constitutive EGFR activation.[50] The classical *EGFRm* also cause reduced affinity for ATP at its binding site, where it would otherwise compete with the first generation TKIs.[52] A combination of these two effects is likely responsible for the sensitivity of classical *EGFRm* NSCLC to first generation EGFR TKIs.[50]

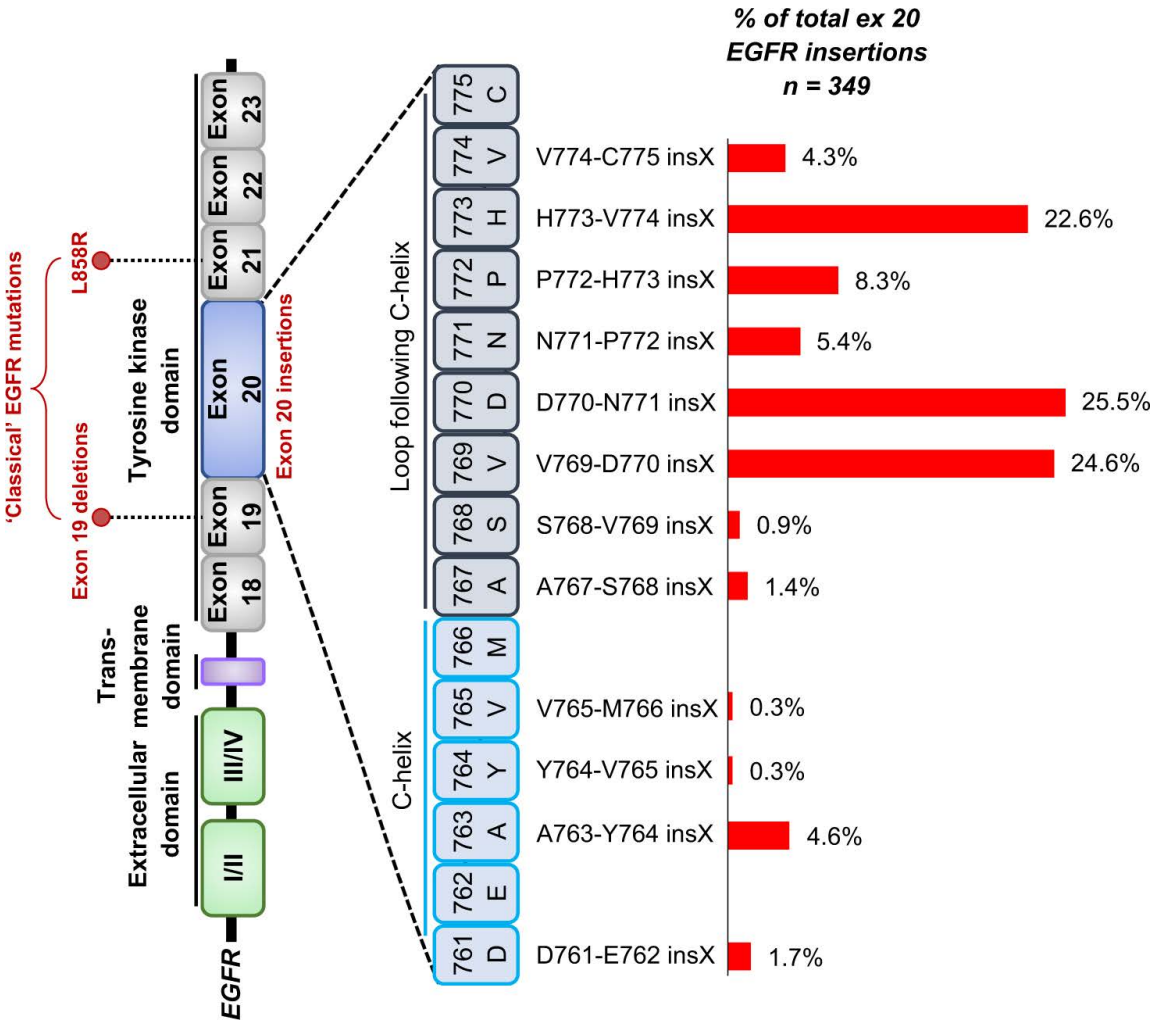
When T790M mutations occur in clones previously only expressing the classical *EGFRm*, they restore the ATP binding affinity of the mutant EGFR to almost wild-type receptor levels.[53] The restored binding site competition reduces the efficacy of reversible ATP competitive first generation EGFR inhibitors, and removes their specificity for mutant EGFR (over wild type).[50]

Exon 20 translates to the tyrosine kinase domain of the EGFR (Figure 3). Ex20ins mutations are a heterogeneous group of in frame insertions or duplications, clustered between residues 762 and 774, that is within the C-terminal of the C-helix or in the following loop. Studies of ex20ins mutation variant D770_N771insNPG revealed that, in contrast to Del19 mutations, ex20ins mutations 'push' the C-helix from the other direction, forcing it into an active conformation.[54] Unlike the classical *EGFRm*, D770_N771insNPG does not show reduced ATP affinity.[54] Further, it shows poor affinity for first-generation EGFR TKIs, attributed to steric hindrance by a prominent shift of the C-helix into the drug-binding pocket.[55] It is postulated that these are the reasons that ex20ins positive NSCLC is not responsive to registered TKIs.

[50] Vyse, S., Huang, P.H. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Sig Transduct Target Ther 4, 5 (2019).
[51] Weinstein, I. B. & Joe, A. Oncogene addiction. Cancer Res. 68, 3077–3080 (2008).
[52] Carey, K. D. et al. Kinetic analysis of epidermal growth factor receptor somatic mutant proteins shows increased sensitivity to the epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib. Cancer Res. 66, 8163–8171 (2006).
[53] Yun, C.-H. et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc. Natl Acad. Sci. 105, 2070–2075 (2008).
[54] Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer [published correction appears in Sci Transl Med. 2014 Feb 26;6(225):225er1]. Sci Transl Med. 2013;5(216):216ra177
[55] Robichaux, J. P. et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. Nat. Med. 24, 638–646 (2018).

Whilst most ex20ins mutant NSCLC is not responsive to registered TKIs, there are some exceptions, and it is postulated that the location of an ex20ins mutation is related to its sensitivity to registered TKIs (Figure 4).[50] In the case of the ex20ins variant A763_Y764insFQEA, the insertion occurs before residue 764, so it is located within the region that codes for the C-helix itself. Structural modelling suggests that this may confer an activation mechanism and structure that more closely resemble the classical *EGFRm* than other ex20ins mutations. This is congruent with multiple reports of partial responses to erlotinib in patients with tumours harbouring A763_Y764insFQEA insertions.[54,56,57,58]

Figure 3: Vyse et al. (2019) The spectrum of described insertion mutations in exon 20 of the EGFR gene, and their location with respect to the C-helix (in the C-helix itself, light blue; or in the loop following the C-helix, dark grey)[50]



Adapted from: Vyse, S., Huang, P.H. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Sig Transduct Target Ther 4, 5 (2019).

[56] Arcila, M. E. et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol. Cancer Ther. 12, 220–229 (2013).
[57] Voon, P. J., Tsui, D. W. Y., Rosenfeld, N. & Chin, T. M. Letter to Editor: EGFR Exon 20 Insertion A763-Y764insFQEA and response to Erlotinib. Mol. Cancer Ther. 12, 20–25 (2013).
[58] Wu J-Y, Yu C-J, Shih J-Y. Effectiveness of treatments for advanced non-small-cell lung cancer with exon 20 insertion epidermal growth factor receptor mutations. Clin Lung Cancer 2019;20:e620–30.

Figure 4: Ramon et al. (2020) A putative general association between the location of described insertion mutations in exon 20 of the EGFR gene, and responsiveness to first generation EGFR tyrosine kinase inhibitors

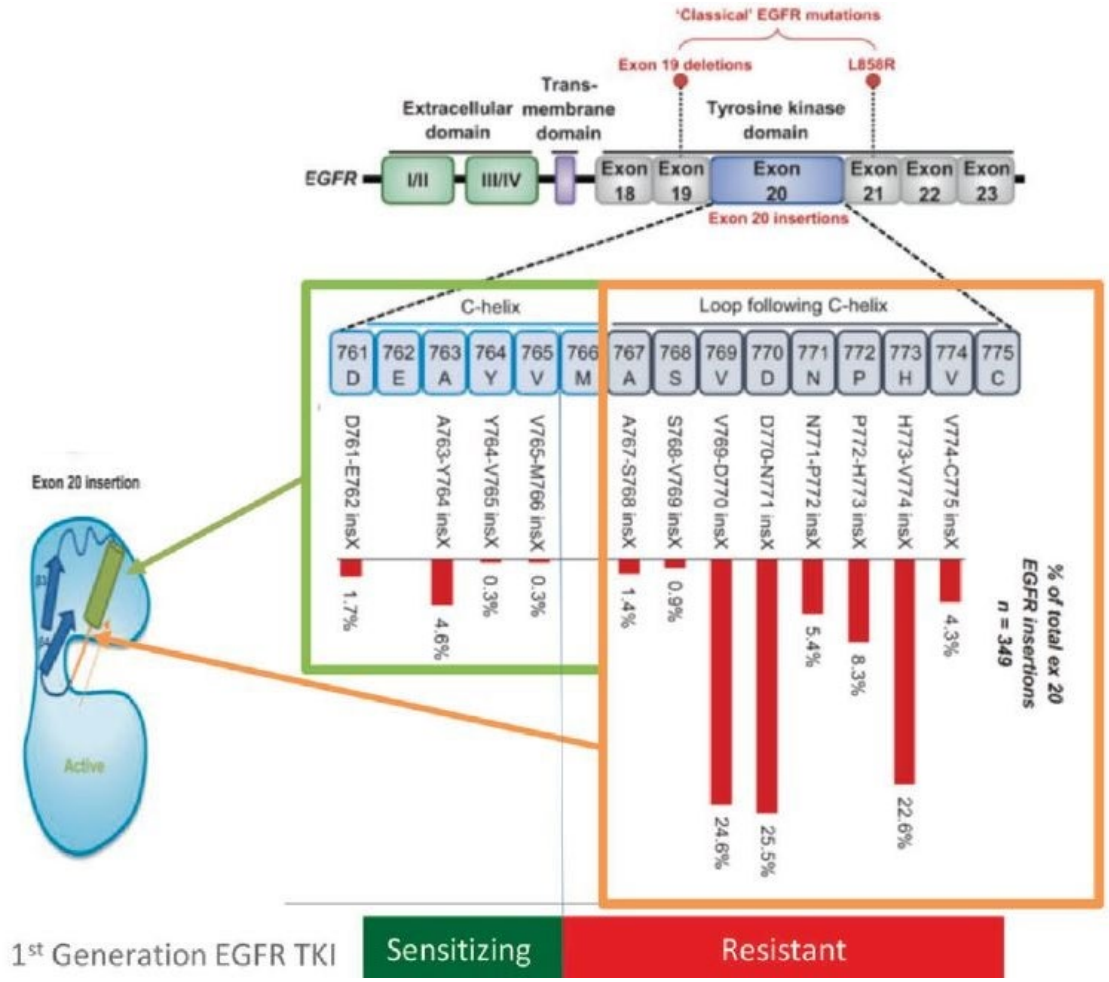


Diagram adapted from: Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. Cancer Treat Rev. 2020 Nov;90:102105

Whilst generalisations such as these may be of some use, the structural heterogeneity among ex20ins mutations suggests variable biology, and the specific sequence of ex20ins variant must be considered when assessing treatment options. For example, there are published reports of TKI response with the rare exon 20 insertion variant D770delinsGY, noting that this is in the loop region that would be assumed resistant according to the theory outlined in Figure 4, shown above.[59]

To complicate matters further, uncommon mutations are often identified as compound mutations, with further heterogeneity of sensitivity to TKIs, making effects on survival very difficult to understand due to rarity.[60]

[59] Yang GJ, Li J, Xu HY, Sun Y, Liu L, Li HS, Yang L, Zhang Y, Li GH, Wang Y. Osimertinib for Chinese advanced non-small cell lung cancer patients harboring diverse EGFR exon 20 insertion mutations. Lung Cancer. 2021 Feb;152:39-48. doi: 10.1016/j.lungcan.2020.11.027. Epub 2020 Dec 4. PMID: 33341538.

[60] Cai Y, Wang Y, Sun J, et al. Successful treatment of a patient with NSCLC carrying uncommon compound EGFR G719X and S768I mutations using osimertinib: A case report. J Int Med Res. 2020;48(6):300060520928793. doi:10.1177/0300060520928793

As ex20ins mutations generally do not sensitise NSCLC to treatment with the available TKIs, they are mostly treated with therapies for NSCLC without a targetable mutation, and the prognosis for these patients is in line with that of the EGFR wild type population.[21]

There is therefore unmet medical need for targeted therapies for NSCLC with this type of molecular alteration.

Mechanism of action

Mobocertinib (also known as TAK-788 and AP32788) is an oral, irreversible EGFR TKI, which forms a covalent bond with cysteine 797 in EGFR and inhibits signalling. The sponsor states that a flexible monocyclic core in its structure may allow mobocertinib to bind and inhibit ex20ins-mutated EGFR despite the ex20ins induced conformation change distal to the ATP binding pocket which is thought to impede binding of approved EGFR TKIs. Based on its ability to inhibit ex20ins mutated EGFR more potently than wild type EGFR *in vitro*, mobocertinib was predicted to provide therapeutic benefit to patients with NSCLC harbouring *EGFR* ex20ins mutations.

This evaluation was facilitated through Project Orbis, an initiative of the United States Food and Drug Administration (FDA) Oncology Center of Excellence. Under this project, the FDA and the TGA collaboratively reviewed the submission. This evaluation process provided a framework for process alignment and management of evaluation issues in real time across jurisdictions. Each regulator made independent decisions regarding approval (market authorisation) of the new medicine.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this submission, a similar submission had been approved in United States of America (USA) on 15 September 2021. Similar submissions were under consideration in the United Kingdom (UK) (submitted on 4 June 2021); the European Union (EU) (submitted on 25 June 2021) and Switzerland (submitted on 31 August 2021).

The following table summarises these submissions and provides the indications where approved.

Table 2: International regulatory status

Region	Submission date	Status	Approved indications
United States of America	26 February 2021	Approved on 15 September 2021	*Exkivity is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have received prior platinum-based chemotherapy.*
United Kingdom	4 June 2021	Under consideration	Under consideration
European Union	25 June 2021	Under consideration	Under consideration
Switzerland	31 August 2021	Under consideration	Under consideration

Mobocertinib was granted accelerated approval by the US FDA on September 15, 2021, with the Oncomine Dx Target Test (Life Technologies Corporation) as a companion diagnostic device to select patients mobocertinib treatment.[61] FDA approval was based on Study AP32788-15-101 (abbreviated as Study 101) and the approval package is publicly available on the FDA website,[62] including the MDR which details the clinical review.[45] The FDA post-marketing requirements and commitments are outlined in the approval letter, and are summarised here in Table 3.[63]

Table 3: United States Food and Drug postmarketing requirements and commitments for Exkivity

Reference	Study	Expected availability
PMR 4148-1	Final PFS from a randomised control trial (RCT) of mobocertinib in patients with advanced *EGFR* ex20ins-positive NSCLC.	Final Protocol Submission: first quarter of 2021 Trial Completion: third quarter of 2023 Final Report Submission: first quarter of 2024
PMR 4148-2	Integrated safety analysis of RCT data on QT prolongation.	Draft Analysis Plan Submission: third quarter of 2022 Final Analysis Plan Submission: third quarter of 2023 Study Completion: third quarter of 2023 Final Report Submission: first quarter of 2024

[61] FDA approval announcement. Accessed 04/03/2022 at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mobocertinib-metastatic-non-small-cell-lung-cancer-egfr-exon-20
[62] FDA approval package for EXKIVITY. Accessed 04/03/2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215310Orig1s000TOC.cfm
[63] FDA approval letter for EXKIVITY. Accessed 04/03/2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/215310Orig1s000ltr.pdf

Reference	Study	Expected availability
PMR 4148-3	Integrated safety analysis of RCT data on cardiac failure.	Draft Analysis Plan Submission: third quarter of 2022 Final Analysis Plan Submission: third quarter of 2023 Study Completion: third quarter of 2023 Final Report Submission: first quarter of 2024
PMR 4148-4	Renal impairment clinical trial evaluating severe renal impairment.	Final Protocol Submission: fourth quarter of 2020 Trial Completion: third quarter of 2022 Final Report Submission: first quarter of 2023
PMR 4148-5	Hepatic impairment clinical trial evaluating moderate and severe hepatic impairment.	Final Protocol Submission: third quarter of 2020 Trial Completion: second quarter of 2022 Final Report Submission: fourth quarter of 2022
PMR 4148-6	Drug-drug interaction study for breast cancer resistance protein (BCRP) substrates.	Draft Analysis Plan Submission: fourth quarter of 2021 Final Analysis Plan Submission: fourth quarter of 2021 Study Completion: second quarter of 2022 Final Report Submission: second quarter of 2022
PMC 4148-7	Additional data to describe safety and efficacy in U.S. racial and ethnic minorities, including Black or African American patients.	Draft Analysis Plan Submission: third quarter of 2022 Final Analysis Plan Submission: third quarter of 2023 Study Completion: third quarter of 2023 Final Report Submission: first quarter of 2024

Abbreviations: PMC = post-marketing commitment; PMR = post-marketing requirement.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the Provisional review pathway.

Table 4: Timeline for Submission PM-2021-02546-1-4

Description	Date
Determination (Provisional)	27 May 2021
Submission dossier accepted and first round evaluation commenced	2 August 2021
First round evaluation completed	24 December 2021
Sponsor provides responses on questions raised in first round evaluation	23 February 2022
Second round evaluation completed	20 April 2022
Delegate's Overall benefit-risk assessment	28 July 2022
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	14 July 2022
Completion of administrative activities and registration on the ARTG	19 July 2022
Number of working days from submission dossier acceptance to registration decision*	199

*Statutory timeframe for standard submissions is 255 working days

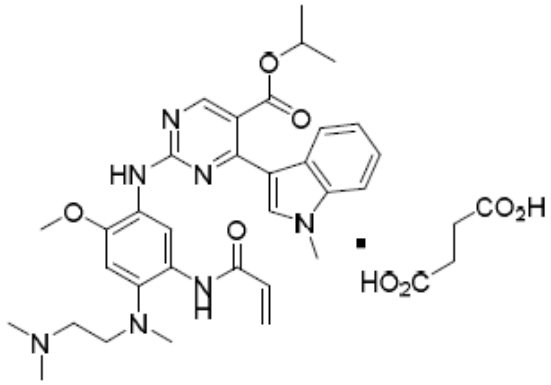
Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial-in-confidence.

Quality

Mobocertinib is an oral irreversible tyrosine kinase inhibitor, targeting epidermal growth factor receptor. It is synthesised as the succinate salt and is structurally related to other tyrosine kinase inhibitors such as imatinib and ceritinib (not registered in Australia).

Figure 5: Mobocertinib succinate skeletal structure



The proposed maximum daily dose is 160 mg (consisting of 4 x 40 mg capsules) taken orally once daily, taken with or without food. The capsules must be swallowed whole and the capsules must not be opened, chewed or dissolved before administration. The capsules will be packaged in blister strips in cartons of 28 capsules.

Nonclinical

The nonclinical evaluation came to the following conclusions outlined in this section.

The submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of pharmaceuticals (ICH M3(R2))[64] and anticancer pharmaceuticals (ICH S9).[65] The overall quality of the dossier was high with all pivotal safety studies conducted under Good Laboratory Practice (GLP) conditions. Although exposures achieved in the submitted toxicity studies were low, they were adequate to establish the safety profile of the drug.

The pharmacology studies support the proposed clinical indication. Key findings include:

- Mobocertinib binds EGFR and HER2 via covalent modification of EGFR Cys797 and HER2 Cys805.
- *In vitro*, it inhibits oncogenic mutant variants of EGFR (including exon 20 insertion mutants) more potently than wild-type EGFR. It also inhibits HER2, HER4, BLK, JAK3, TXK, BTK, BTK [E41K], BMX and ACK1.
- The major metabolites are AP32914 and AP32960.
- In murine EGFRm and HER2-mutant models, daily oral administration of mobocertinib induced dose dependent tumour regression/inhibition of growth.

No dedicated animal safety pharmacology studies were conducted with mobocertinib.

The pharmacokinetic profile in animals was qualitatively similar to that of humans.

Mobocertinib, AP32914 and AP32960 inhibited the cardiac hERG channel current at concentrations greater than 5 µM (equivalent to greater than 3700 times the free clinical maximum concentration (C_{max}) of mobocertinib at the maximum recommended human dose),

[64] CPMP/ICH/286/95: Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals - Scientific guideline

[65] EMA/CHMP/ICH/646107/2008: Non-clinical evaluation for anticancer pharmaceuticals - Scientific guideline

suggesting low potential for QT prolongation.[66] However, since QT prolongation and life-threatening arrhythmias have occurred in patients treated with mobocertinib, the warning in the proposed product information is warranted.

Repeat dose toxicity studies by the oral route were conducted in rats and dogs (up to three months). Mobocertinib related effects were observed at subclinical exposures. Most findings were dose and duration dependent, were fully or partially reversible and have been observed with other EGFR inhibitors. Target organs for toxicity included:

- Gastrointestinal tract: emesis, diarrhoea, fecal changes, decreased food intake and body weight loss, reversible microscopic lesions (epithelial atrophy single cell necrosis and mononuclear cell infiltration).
- Dermal effects: alopecia, scabbing, red or flaky skin, hair loss, histopathological findings of erosions, ulcerations, hair bulb atrophy, and/or inflammation in the skin and hair follicles, decreased thickness of squamous epithelium in the skin and oral cavity.
- Corneal effects: focal, multifocal, and diffuse superficial opacities, prominent nictitating membrane, discharge, injected sclera, redness, and partially and/or completely closed eyes.
- Lymphoid organs: lymph nodes (reactive hyperplasia), spleen (lymphoid depletion), thymus (lymphoid depletion) and bone marrow (increased myeloid progenitor cells, and decreased erythroid progenitor cells, red blood cell count, haemoglobin and haematocrit).

Reproductive organs: decreased organ weights, decreased epithelial thickness/inflammation of the cervix/vagina and atrophy of the uterus, prostate gland, mammary gland.

Mobocertinib was not mutagenic in an *in vitro* bacterial reverse mutation assay and was not clastogenic *in vitro* (in a chromosome aberration assay in human peripheral blood lymphocytes) or *in vivo* (in a bone marrow micronucleus test in rats).

Carcinogenicity studies were not conducted, which is acceptable as mobocertinib is intended to treat patients with advanced cancer.

Fertility/early embryonic development studies were not conducted with mobocerinib. Mobocertinib was not teratogenic but increased embryofetal loss (as increased post-implantation/early resorptions) and decreased fetal weights in pregnant rats. These effects were seen in the context of maternal toxicity (decreased food consumption and body weight).

Pregnancy Category D;[67] is considered appropriate for mobocertinib.

There are no objections on nonclinical grounds to the proposed registration of Exkivity for the proposed indication.

[66] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

[67] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Clinical

Pharmacology

Formulation

Three capsule formulations were used in the clinical pharmacology studies (formulations DiC-A, DiC-B, and DiC-C). Formulation DiC-C is the to-be-marketed formulation. A relative bioavailability clinical study was performed to bridge between formulations DiC-A and DiC-B (Study 1001 Part 3), and pharmacokinetic (PK) comparability between formulations DiC-A and DiC-C was confirmed by pooled PK analysis.

Pharmacokinetics

Mobocertinib has two major metabolites, AP32960 and AP32914, which show dose proportional PK and comprise around 62% and 7% of total parent 24 hour exposure (geometric mean molar area under concentration time curve for 24 hours ($AUC_{0\text{-}24h}$)), respectively, at the recommended mobocertinib dose. Both metabolites, AP32960 and AP32914 showed similar activity to mobocertinib in kinase and cellular assays.

Time to maximal plasma concentrations (T_{max}) for all three molecules is about 4 hours post-dose. They are highly (99%) protein bound *in vitro*, and do not show preferential binding for whole blood over plasma. The absolute bioavailability of mobocertinib is 37%, and the fraction absorbed is about 92%. The population PK model estimates a mobocertinib geometric mean apparent volume of distribution at steady state of 3510 L.

Clearance is mainly metabolic. Mobocertinib is predominantly (94%) metabolised by CYP3A4/5.[68] Both metabolites, AP32960 and AP32914 are almost exclusively metabolised by CYP3A4/5. Population PK analysis estimates the geometric mean effective half life of mobocertinib to be 17.6 hours, and the apparent oral clearance of mobocertinib to be 108 L/h.

Negligible accumulation of mobocertinib exposure at 160 mg daily (geometric mean accumulation ratio of 1.03) along with less than dose proportional increases in mobocertinib exposure from 120 to 160 mg daily suggest autoinduction of the apparent oral clearance of mobocertinib, likely via induction of CYP3A.

Excretion of mobocertinib is mainly fecal (76%), with 4% of radiolabelled dose recovered in the urine (unchanged mobocertinib, AP32960, and AP32914 making up 1%, combined).

Food effect

Food effect studies demonstrated that a meal (regardless of low or high fat content) had no clinically meaningful effect on the combined molar exposure (maximum concentration (C_{max}) and area under concentration time curve from time zero to infinity ($AUC_{0\text{-}\infty}$)) of mobocertinib and its major metabolites.

[68] **Cytochrome P450** (**CYP**) **enzymes** are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds. Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

Gastrointestinal toxicity (mainly diarrhoea) is predominant in the toxicity profile for mobocertinib, however, trends across toxicity metrics suggest correlation between diarrhoea and systemic exposure. As dosing with food would not meaningfully change systemic exposure, it would not be expected to reduce gastrointestinal toxicity. Limited clinical data from a cohort of patients in Study 101 supports this.

Dose and exposure-response relationships

The proposed dose is 160 mg orally once daily, regardless of timing relative to food intake. The proposed dose of 160 mg daily was the maximum tolerated dose in the dose finding portion of the pivotal efficacy and safety study, Study 101. This dose was deemed adequately justified by the regulatory clinical pharmacology review, based on demonstration of efficacy and adequate tolerability for most patients, evidence of exposure-response relationships for both efficacy and toxicity, and adequate management of toxicities with the proposed dose reduction schedule for most patients.[45]

Exposure-response analyses indicated trends of increased toxicity whether exposure included only mobocertinib, only AP32960 and AP32914, or the sum of molar concentration for all three (combined molar exposure).

Population pharmacokinetic

The following parameters, age (18 to 86 years), sex (183 male, 244 female), race (283 White, 19 Black, 115 Asian participants), body weight (37 to 132 kg), mild or moderate renal impairment (178 mild, 30 moderate) and mild hepatic impairment (54 mild) did not demonstrate clinically significant effects on the PK of mobocertinib.

Renal function

Patients with mild and moderate renal impairment were included in the clinical studies of mobocertinib. In the population PK analysis, creatinine clearance (26 to 251 mL/min) and estimated glomerular filtration rate (eGFR: 34 to 304 mL/min/1.73 m^2) were not identified as significant covariates. Therefore, no dose adjustment is required for renal impairment that is mild or moderate (creatinine clearance at least 30 mL/min; eGFR ≥ 30 mL/min/1.73 m^2). The effect of severe renal impairment is being evaluated in an ongoing study (Study TAK-788-1007).

Hepatic function

Study eligibility criteria allowed enrolment of patients with total bilirubin less than or equal to 1.5 times the upper limit of normal (ULN) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than or equal to 2.5 times the ULN. Accordingly, patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (that is, total bilirubin less than or equal to ULN and AST or ALT greater than ULN or total bilirubin greater than 1 to 1.5 times ULN and any AST or ALT), were included in the clinical studies of mobocertinib. Bilirubin, ALT, and AST were not significant co-variates in the population PK model. Therefore, no dose adjustment is required for mild hepatic impairment.

The effect of moderate and severe hepatic impairment is being evaluated in an ongoing study (Study TAK-788-1008). Top line results for C_{max} and area under concentration time curve to last measurable concentration ($AUC_{0\text{-}last}$) in patients with moderate hepatic impairment (n = 6) indicate combined molar exposure (mobocertinib, AP32960, and AP32914) is not meaningfully different from patients with normal hepatic function, and no dose adjustment is required for moderate hepatic impairment.

Interactions

Mobocertinib as a substrate

Mobocertinib and its two major active metabolites (AP32960 and AP32914) are predominantly metabolised by CYP3A.[68] Results of interaction studies related to dose recommendations are summarised in Table 5.

In vitro, mobocertinib is not a substrate of BCRP, OATP1B1 or OATP1B3, but is a substrate of P-glycoprotein (P-gp). Nevertheless, as it demonstrates high permeability and solubility, there is low risk of P-gp inhibitors or inducers affecting mobocertinib PK.

Mobocertinib as a perpetrator

Mobocertinib and its two major active metabolites (AP32960 and AP32914) are time dependent inhibitors and inducers of CYP3A. Results of interaction studies related to dose recommendations are summarised in Table 5.

In vitro data also demonstrate that mobocertinib inhibits P-gp, and the breast cancer resistance protein (BCRP) transporter. Physiologically-based PK (PBPK) modelling (of probe substrates digoxin and dabigatran etexilate in presence of mobocertinib at the recommended dose) was adequate to predict lack of a clinically meaningful effect on P-gp substrates. However, the physiological based PK model used in the submission to simulate interactions between mobocertinib and a BCRP substrate was found to be inadequate by the regulatory review.[45]

> 'The sulfasalazine model was developed using results from a pharmacogenetic study to quantify the contribution of BCRP to its disposition. Whether the model can detect a positive DDI is unknown, and the *in vitro* to *in vivo* extrapolation on the Ki (inhibition constant) has not been established for the BCRP-mediated DDIs [drug-drug interactions]. As such, it is not known if mobocertinib and its active metabolites may increase BCRP substrate plasma concentrations *in vivo*, which may increase the incidence and severity of adverse reactions.'

A study into the effect of mobocertinib of a BRCP substrate is the subject of an FDA post-marketing requirement (see Table 3, above).

Mobocertinib and its two major active metabolites do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, or OCT1 at clinically relevant concentrations *in vitro*.

Table 5: Interaction studies submitted for mobocertinib that support regulatory dosing advice [1]

Reference	Study	Results	Regulatory dosing advice
TAK-788-1006 (Part 1)	PK in healthy adult subjects: single dose mobocertinib 20 mg orally and multiple doses itraconazole 200 mg orally	CME after a single 20 mg dose of mobocertinib was much higher (about 6-fold), in the presence of itraconazole. PBPK modelling predicted that steady state CME with 160 mg daily dosing of mobocertinib would increase by about 5-fold and about 2-fold with strong and moderate CYP3A inhibitors, respectively, and by 16% with weak CYP3A inhibitors.	Avoid coadministration of mobocertinib with strong or moderate CYP3A inhibitors. Reduce mobocertinib dose by 50% if coadministration with a moderate CYP3A inhibitor is necessary, and conduct additional ECG monitoring.
TAK-788-1006 (Part 2)	PK in healthy adult subjects: single dose mobocertinib 160 mg orally and multiple doses rifampin 600 mg orally	CME after a single 20 mg dose of mobocertinib was reduced by about 95% in the presence of rifampin. PBPK modelling predicted that steady state CME with 160 mg daily dosing of mobocertinib would decrease by more than 90% and about 60% with strong and moderate CYP3A inducers, respectively.	Avoid coadministration of mobocertinib with strong or moderate CYP3A inducers.[2] (see Cardiac safety)
TAK-788-1004	PK in patients with advanced NSCLC: single dose mobocertinib 160 mg orally and single dose midazolam 3 mg orally	The AUC of 3 mg oral midazolam decreased by 32% when coadministered with a single dose of 160 mg mobocertinib, but the C_{max} was unchanged.	Avoid concomitant use of mobocertinib with hormonal contraceptives, and other CYP3A substrates for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, consider increasing the CYP3A substrate dose in accordance with accepted clinical practice.

Abbreviations: AUC = area under the curve; CME = combined molar exposure (area under the curve) of mobocertinib, AP32960, and AP32914; ECG = electrocardiogram; PBPK = physiologically based pharmacokinetic; IV = intravenous

[1] More detail is published in the United States (US) Food and Drug Administration (FDA) Multidisciplinary review (MDR) for Exkivity. Available as of 4 March 2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215310Orig1s000MultidisciplineR.pdf

[2] The sponsor proposes that coadministration with moderate CYP3A inducers could be undertaken, with weekly up-titration of mobocertinib by 40 mg increments, as tolerated, to a maximum of twice the mobocertinib dose that was tolerated prior to the initiation of the moderate CYP3A inducer. The regulatory clinical review did not agree with this approach, as mobocertinib auto-induces its own metabolism by CYP3A. The PBPK model used by the sponsor has not been validated by clinical data for doses higher than 180 mg, where the auto-induction effect of mobocertinib is unquantified and may not be linear. Safety or efficacy may be compromised by such an approach.

Pharmacodynamics

Mobocertinib treatment is associated with concentration-dependent QTc prolongation. The FDA undertook an independent review of electrocardiogram (ECG) and exposure data from Study 101. At the recommended dose, the mean increase in the QTc interval was 23 msec (upper 95% confidence interval limit: 26 msec).[69]

The FDA safety review also included a review of ECGs that were taken in triplicate during Study 101.[45]

> 'ECGs from a subset of 250 patients who had at least one baseline ECG and one subsequent scheduled or unscheduled ECG were analyzed to further characterise the risk of QTc prolongation. Of these 250 patients, 1.2% had a QTc interval > 500 msec and 11% of patients had a change-from-baseline QTc interval > 60 msec.'

For more information see section: *Cardiac safety*, below.

Efficacy

Study AP32788-15-101 (Study 101)

The pivotal data supporting efficacy come from Study AP32788-15-101 (abbreviated here as Study 101).

Design

Study 101 was a global, Phase I/II, single arm, three part study of mobocertinib.[70] The study design is summarised in Table 6 and is described in the publicly available FDA label.[71]

The primary efficacy analysis for this submission was performed in the pooled prior platinum (PPP) analysis set from Study 101 (n = 114), with a data cut-off date of 1 November 2020. The PPP analysis set includes patients from all parts of Study 101 who had advanced NSCLC harbouring *EGFR* ex20ins mutations, who had previously been treated with platinum-based chemotherapy, and who received mobocertinib at the recommended dose. There were six such patients in Part 1, 22 patients in Part 2 and 86 patients in Part 3 of the study. The main inclusion and exclusion criteria of Study 101 relevant to the PPP population are summarised in Table 7.

Enrolment was based on exon20ins *EGFR* mutation status determined by local testing. The sample size for Part 3 (n = 91) was chosen to give adequate (greater than 91%) power to detect a true objective response rate (ORR) of 36% with a minimally important response rate threshold of 20%, based on real world/external data (see Study TAK-788-5002); and assuming a 20% discrepancy between the documented mutation status by local testing results and central testing using an analytically validated central test (Oncomine Dx Target Test (ODxT)).

[69] US FDA Interdisciplinary Review Team for Cardiac Safety Studies. QT Study Review. Page 26 of 'Other Review(s) (PDF).' Accessed 2 May 2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215310Orig1s000OtherR.pdf

[70] Zhou C, Ramalingam SS, Kim TM, et al. Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With EGFR Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer: A Phase 1/2 Open-label Nonrandomized Clinical Trial [published correction appears in JAMA Oncol. 2022 Feb 24;:]. JAMA Oncol. 2021;7(12):e214761

[71] US FDA approved label for Exkivity. Accessed 7 March 2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215310s000lbl.pdf

Plasma cell-free DNA testing was recorded as the methodology used to identify *EGFR* ex20ins mutation for six patients (5%). Mutation status was centrally confirmed for 63 patients (53% of the PPP population), and this population was described as the centrally confirmed analysis set.

Patients in the PPP analysis set received treatment with mobocertinib 160 mg daily orally, until unacceptable toxicity or disease progression per RECIST v1.1 criteria.[72],[73] Treatment beyond radiological progression was allowed at the discretion of the investigator, if they opined that the patient was still deriving clinical benefit.

The primary efficacy outcome was the rate of confirmed;[74] objective response (cORR) according to independent radiological review committee (IRC) review, to be assessed when all ongoing patients had completed their Cycle 6 disease assessment. IRC assessments were not disclosed to investigators. Disease status was assessed every 8 weeks after the initial dose of mobocertinib through Cycle 14 (28 day cycles) then every 12 weeks thereafter until end of treatment. Descriptive statistics were used to present results, with two-sided exact 95% binomial confidence intervals (CIs) for all binary endpoints. Kaplan Meier estimates and exploratory landmark rates were generated for response duration (DOR).[75] Other outcomes such as time-to-event outcomes and patient-reported outcomes were included in the clinical study report but are considered exploratory in this study setting.

Protocol amendments and deviations underwent regulatory review and are considered unlikely to have altered study conclusions. Compliance with Good Clinical Practice was considered adequate by the regulatory review.

Table 6: Study AP32788-15-101 Summary of the three-part design

Part	Primary objective(s)	Design and population	Mobocertinib treatment	Size (treated)
Part 1: dose escalation	RP2D, safety, PK	3+3 design, refractory advanced NSCLC	Daily doses of 5, 10, 20, 40, 80, 120, 160 and 180mg PO	N = 73
Part 2: expansion	Anti-tumour activity	7 cohorts, advanced EGFR or HER2-mutant solid tumours*	160 mg daily PO	N = 136
Part 3: extension	Efficacy (confirmed ORR per IRC)	2L+ ex20ins-positive advanced NSCLC	160 mg daily PO	N = 96

2L+ = second-line plus; EGFR = epidermal growth factor receptor; ex20ins = exon 20 insertion mutation; HER2 = human epidermal growth factor receptor 2; IRC = independent radiological review committee; NSCLC = non-small cell lung cancer; ORR = objective response rate using RECIST v1.1 criteria; PK = pharmacokinetics; PO = oral; RP2D = recommended Phase 2 dose.

[72] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

[73] The Response Evaluation Criteria In Solid Tumours (RECIST) is a voluntary international standard with unified and easily applicable criteria to define when a patient's tumour has improved ('respond'), stayed the same ('stabilise'), or worsened ('progress') during treatment. The criteria were published in February 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group. Today, the majority of clinical trials evaluating cancer treatments for objective response in solid tumours use RECIST. These criteria were developed and published in February 2000, and subsequently updated in 2009.

[74] Confirmed responses are those that persist on repeat imaging 4 weeks (allowing a minus 3-day time window) or more after initial response.

[75] Kaplan, E. L., and Paul Meier. "Nonparametric Estimation from Incomplete Observations." Journal of the American Statistical Association, vol. 53, no. 282, [American Statistical Association, Taylor & Francis, Ltd.], 1958, pp. 457–81,

Table 7: Study AP32788-15-101 Key eligibility criteria for the pooled prior platinum population

Included	Excluded
• Consenting, non-reproducing adults with local advanced, unresectable or metastatic NSCLC (histology or cytology-confirmed) • Measurable disease by RECIST v1.1 • ECOG performance status score < 2 and life expectancy at least 3 months • Adequate organ function • Normal QTcF interval • At least one prior systemic therapy in the advanced setting • In-frame ex20ins EGFR mutation by local testing	• Active CNS metastases • Inadequate cardiac health, uncontrolled hypertension • Concurrent QT prolonging medication • Significant infection • Interstitial lung disease, pneumonitis requiring corticosteroids or any drug-related pneumonitis • Pregnancy • GI disruption that could affect absorption

Population

Patients were enrolled across 70 sites in 10 countries (USA, Germany, Spain, Great Britain, Italy, China, Japan, South Korea, Taiwan), and dosing was commenced between June 2016 (first patient) and March 2019 (last patient).

Demographics and baseline disease characteristics were generally in keeping with what would be expected for the intended recipient patient population in Australia, that is patients with locally advanced or metastatic NSCLC with *EGFR* ex20ins mutations whose disease has progressed on or after platinum based chemotherapy. *EGFR* ex20ins mutation testing is summarised in Table 8.

Amongst the PPP group, the median age was 60 years (range 27 to 84); 7% were over 75 years of age; 66% were female; 60% were Asian and 37% were White; baseline ECOG PS;[76] was 0 in 25% and 1 in 75%; 99% had metastatic disease at diagnosis, and 35% had a history of prior brain metastases. In addition to prior platinum-based chemotherapy, 43% of patients in the PPP population had received prior immunotherapy, and 25% had received prior tyrosine kinase inhibitor therapy.

[76] Eastern Cooperative Oncology Group Performance Status (ECOG PS): The 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, for example, 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

Table 8. Study AP32788-15-101 *EGFR* mutation testing and status in the pooled prior platinum population (data cut-off date of 1 November 2020)

		Mobocertinib 160 mg daily (n = 114)
Method of assessment	Sanger sequencing or NGS, n (%)	55 (48%)
	PCR, n (%)	25 (22%)
	Other, n (%)	32 (28%)
Ex20ins mutation present	A767_V769insASV, n (%)	20 (18%)
	S768_D770insSVD, n (%)	10 (9%)
	N771_H773insNPH, n (%)	8 (7%)
	Other, n (%)	48 (42%)
	Specific insertion unknown, n (%)	29 (25%)

Abbreviations: DCO = data cut-off date; NGS = next-generation sequencing; PCR = polymerase chain reaction; PPP = pooled prior platinum analysis set

Disposition

At the data cut-off (1 November 2020), the median duration of follow up for all patients was 14.2 months (95% CI 13.2 to 14.6). Some key patient disposition information for the PPP population is summarised in Table 9.

Table 9. Study AP32788-15-101 Patient disposition in the pooled prior platinum population (data cut-off of 1 November 2020)

		Mobocertinib 160 mg daily (n = 114)
Ongoing on study, n (%)		55 (48%)
Discontinued study		59 (52%)
Reason for study discontinuation	*Death, n (%)*	*45 (76%)*
	Lost to follow-up, n (%)	*3 (5%)*
	Withdrawal by patient, n (%)	*10 (17%)*
	Other, n (%)	*1 (2%)*
Ongoing on treatment, n (%)		26 (23%)
Discontinued treatment, n (%)		88 (77%)
Reason for treatment discontinuation	*Adverse event, n (%)*	*14 (16%)*
	Withdrawal by patient, n (%)	*8 (9%)*
	Started a new anti-cancer therapy, n (%)	*3 (3%)*
	Clinical progressive disease, n (%)	*28 (32%)*
	Radiological progressive disease, n (%)	*32 (36%)*
	Other, n (%)	*3 (3%)*

Abbreviations: DCO = data cut-off date; PPP = pooled prior platinum analysis set

Outcomes

Key results for the PPP population in Study 101 are summarised in Table 10. At the data cut-off, the response was ongoing for 16 responders.

Table 10. Study AP32788-15-101 Results per independent radiological review committee in the pooled prior platinum population (data cut-off of 1 November 2020)

	Mobocertinib 160 mg daily (n = 114)
ORR	
cORR, % (95% CI)[a]	28 [20, 37]
Complete response (CR), n (%)	0
Partial response (PR), n (%)	32 (28%)
Stable disease (SD), n (%)	57 (50%)
Progressive disease (PD), n (%)	13 (11%)
Not evaluable (NE), n (%)	12 (11%)
DOR	
Median duration of responses,[b] months [95% CI]	17.5 [7.4, 20.3]
Responses ≥ 6 months, n (%)[c]	19 (59%)
Responses ≥ 12 months, n (%)[c]	6 (19%)

Abbreviations: CI = confidence interval; cORR = confirmed objective response rate; DCO = data cut-off date; DOR = duration of confirmed responses by; IRC = independent radiological review committee; ORR = objective response rate (per RECIST v1.1); PPP = pooled prior platinum analysis set

[a] Exact Clopper-Pearson CI

[b] Kaplan-Meier estimate

[c] Descriptive analysis

Sensitivity and subgroup analyses

Subgroup analyses (ORR by race, age, gender, ECOG status, and prior anti-PD (L)1 treatment status) were consistent with the primary efficacy results. The ORR was 25% (14, 40) in patients who have previously received a prior anti-PD ligand 1 agent (43% of the PPP population) and 30% (20, 43) in those who had not, with similar durability of responses.

Efficacy in patients with a confirmed mutation per central analysis (the centrally confirmed analysis set; n = 63) were also consistent:

- Confirmed ORR (95% CI) = 27% (16, 40)
- Median DOR (95% CI) = 17.5 months (3.7, not reached)

Study TAK-788-5002

Study TAK-788-5002 was considered as a supportive study for this submission.

Due to the rarity of ex20ins mutation positive NSCLC and the lack of a specific standard of care for these patients, an analysis of real world data was submitted as historical benchmark data to support interpretation of the pivotal evidence.

Study TAK-788-5002 was a retrospective, observational cohort study of patients with NSCLC harbouring *EGFR* ex20ins mutations. This study used longitudinal data (data cut off 29 February 2020) from the Flatiron Health Research Database: a de-identified database of United States electronic health records.

The analysis included two cohorts of relevance to the patients in the PPP population of Study 101:

- A cohort of study-aligned patients, defined as patients whose baseline characteristics were aligned with the key eligibility criteria of Part 3 of Study 101, who initiated the next treatment after a confirmed diagnosis of advanced NSCLC, had documented *EGFR* ex20ins mutations, and had at least one prior line of therapy in the advanced setting (n = 63).

- A cohort of study aligned patients (as defined above) who had previously received platinum based chemotherapy (n = 50).

The primary endpoint was confirmed real world ORR, defined as the proportion of patients that had a partial response (PR) or complete response (CR) followed by a subsequent assessment of, PR, CR or stable disease during the course of a single line of therapy.

For study aligned patients and prior platinum study aligned patients who received any treatment type in the second line or greater setting in Study TAK-788-5002, confirmed real world ORR was 11% and 14%, respectively. For those who received immunotherapy agents as monotherapy, confirmed real world ORR was 5% in study aligned patients (n = 21) and also 5% in prior-platinum study aligned patients (n = 20).

Other real world data analyses made similar findings.

Whilst the submitted real world data are exploratory, they support the selection of 20% as a lower bound for response rate in choosing a sample size for the pivotal efficacy analysis.

Safety

Safety database

Data to describe the safety of mobocertinib in NSCLC was submitted from two ongoing studies: the Phase I/II pivotal efficacy study (Study 101), and an open label, multicentre, dose escalation study in Japanese patients with locally advanced or metastatic NSCLC (Study 1003).

Across these clinical studies, 325 patients with cancer, including 320 patients with NSCLC, have been exposed to mobocertinib.

The regulatory safety review focussed primarily on an analysis of data with a cut-off date of 29 May 2020. Data were submitted for three populations:

- All patients in the PPP analysis set who received at least one dose of mobocertinib (the primary safety population) (n = 114)
- All patients with cancer who received at least one dose of mobocertinib at 160 mg in Study 101 (the pooled safety population) (n = 256)
- All patients with cancer who received at least 1 dose of mobocertinib at any strength across Study 101 (the overall safety population) (n = 325).

A 90 day safety update with a data cut off date of 1 November 2020 was also reviewed, which did not reveal any new or worsening safety signals.

The FDA's 'Warnings and Precautions' label content is based on safety data for the pooled safety population. All of these patients received at least one dose at 160 mg daily, but approximately one-third of patients either started at a different dose or had dose reductions, so adverse events in this group may have occurred at doses other than 160 mg daily.

The FDA's 'Adverse Reactions' label content is based on safety data for the primary safety population.

Protocol for dose modification in case of adverse events

The Study 101 protocol (amendment 6 version) specified that the mobocertinib dose should be modified for adverse events as outlined in Table 11. The protocol also specified the following dose reduction schedule:

- Starting dose: 160 mg daily

- First dose reduction: to 120 mg daily
- Second dose reduction: 80 mg daily

Table 11. Study AP32788-15-101 Dose modifications specified by the protocol (version 6) for patients receiving mobocertinib

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Confirmed pneumonitis	Permanently discontinue.			
Other non-haematological toxicities	No change to dose	If intolerable, recurrent, or uncontrolled by supportive measures: • Withhold until resolved • Resume at reduced dose	• Withhold until ≤ Grade 1 or baseline • Resume at reduced dose, or same dose, based on clinical judgement	• Withhold until ≤ Grade 1 or baseline • Resume at reduced dose, or discontinue, based on clinical judgement
Haematological toxicities	No change to dose	No change to dose	• Withhold until ≤ Grade 2 or baseline • Resume at reduced dose, or same dose, based on clinical judgement	• Withhold until ≤ Grade 2 or baseline • Resume at reduced dose, or discontinue, based on clinical judgement

Exposure

Disposition and exposure to study treatment for the primary and pooled safety populations are summarised in Table 12.

Table 12. Disposition and exposure in the primary and pooled safety populations (data cut off: 29 May 2020)

		Primary safety population (n=114)	Pooled safety population (n=256)
Disposition			
Patients ongoing on treatment, n (%)		38 (33)	75 (29)
Patients who discontinued treatment, n (%)		76 (67)	181 (71)
Reason treatment discontinued*	Adverse event	14 (18)	28 (11)
	Clinical progression	25 (33)	82 (32)
	Radiographic progression	24 (32)	25 (11)
	Withdrawal by patient	8 (11)	15 (6)
	New treatment	2 (3)	2 (<1)
	Other[77]	3 (4)	26 (10)
Patients ongoing on study, n (%)			
Patients who exited the study, n (%)		44 (39)	117 (46)
Reason treatment discontinued*	Death	30 (68)	71 (28)
	Adverse event	2 (5)	2 (<1)
	Lost to follow-up	2 (5)	2 (<1)
	Patient withdrawal	6 (14)	17 (7)
	Completed	N/A	9 (4)
	Other	4 (9)	16 (6)
Exposure			
Mean treatment duration, months (SD)		7.6 (5.8)	6.6 (5.4)
Median treatment duration, months [range]		7.0 [0, 30.9]	5.6 [0, 30.9]
Mean relative dose intensity, % (SD)		92 (12)	92 (21)
Duration of exposure <3 months		25 (22)	73 (29)
Duration of exposure at least 12 months		16 (14)	30 (12)

Abbreviations: DCO = data cut-off date, SD = standard deviation

* Denominator for percentages is discontinued portion of the population

Deaths

At the primary data cut off (29 May 2020), 27 fatal adverse events had occurred in the pooled safety population (n = 256). Fourteen were disease progression events, and the remainder were: respiratory failure (n = 3), pneumonia (n = 3), dyspnoea (n = 1), hypoxia (n = 1), multiple organ dysfunction syndrome (n = 2), cardiac failure (n = 1), cardiac arrest (n = 1) and cerebrovascular accident (n = 1). Based on review of case narratives, attribution to mobocertinib could not be ruled out for three cases of respiratory failure in context of pneumonitis, and one case of cardiac failure. Two of these fatal events (cardiac failure [n = 1], and pneumonitis [n = 1]) occurred in the primary safety population (n = 114).

There were 14 additional fatal adverse events that occurred in the broader, 'overall safety population' that is patients treated at doses other than the recommended dose. All were attributable to disease progression except for one fatal case of pneumonitis.

A further six fatal adverse events occurred outside the 30 day window for being defined as 'treatment-emergent'. These were: respiratory failure, subdural haemorrhage, pneumonia, dyspnoea, disease progression and renal failure. The case of renal failure occurred in the setting

[77] 30 patients across the overall safety population discontinued treatment due to "Other" reasons - these included death (n=10), physician decision (n=13) and not reported (n=7).

of incomplete intestinal obstruction and abdominal metastases that occurred 32 days after mobocertinib was discontinued due to disease progression, with attribution to mobocertinib possible.

Dose modifications and permanent discontinuations

Adverse events that led to dose modification or permanent discontinuation in at least 2% of the primary safety population (n = 114) as at the 29 May 2020 data cut off are summarised in Table 13. Gastrointestinal events accounted for the majority.

In addition to those included in the table, events that led to permanent discontinuation for less than 1% of patients in the primary safety population (one patient each) were abdominal pain, alopecia, cardiomyopathy, clostridium test positive, increased amylase, muscular weakness, pericardial effusion, pleural effusion, pneumonitis, ventricular arrhythmia, vision blurred, and weight decreased.

Table 13. Study AP32788-15-101 Adverse events that led to dose modification or permanent discontinuation in at least 2% of patients (primary safety population, total n = 114; data cut off: 29 May 2020)

	Primary safety population (n=114)		
Adverse event	**Dose interruptions n (%)**	**Dose reductions n (%)**	**Permanent discontinuations n (%)**
Any	58 (51)	28 (25)	19 (17)
Diarrhoea	24 (21)	11 (10)	5 (4.4)
Nausea	8 (7)	6 (5)	4 (3.5)
Vomiting	7 (6)	3 (2.6)	2 (1.8)
Stomatitis	6 (5)	3 (2.6)	2 (1.8)
Increased blood creatinine	5 (4.4)	2 (1.8)	0
Decreased appetite	4 (3.5)	2 (1.8)	2 (1.8)
Paronychia	4 (3.5)	3 (2.6)	0
Pyrexia	4 (3.5)	0	0
Increased amylase	3 (2.6)	0	0
Dyspnoea	3 (2.6)	0	0 [pneumonitis: 1 (0.9)]
Increased lipase	3 (2.6)	2 (1.8)	0 [increased amylase: 1 (0.9)]
Musculoskeletal pain	3 (2.6)	0	0
Pruritis	3 (2.6)	1 (0.9)	0
Rash	3 (2.6)	4 (3.5)	1 (0.9)
Fatigue	2 (1.8)	3 (2.6)	1 (0.9)

DCO = data cut-off date

Common and high-grade adverse events

The approved FDA label contains the following description of common adverse events and laboratory abnormalities with mobocertinib in the pooled safety population (n = 256):[71]

> 'The most common (> 20%) adverse reactions are diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.'

An overview of the most common treatment emergent adverse events and Grade 3 to 4 common treatment emergent adverse events in Study 101 is provided in Table 14, using clinically rational groupings of MedDRA Preferred Terms (PT) defined as Grouped Terms (GT) for the regulatory clinical safety review. Diarrhoea and rash are extremely common.

Common laboratory abnormalities in patients who received mobocertinib are summarised in Table 15.

Table 14. Study AP32788-15-101 Most common (in ≥ 10%) treatment-emergent adverse events (primary safety population; data cut off 29 May 2020)

Treatment-emergent adverse events	Primary safety population (n=114)	
CTCAE grade[78]	All grades (%)	Grade 3-4 (%)
Gastrointestinal disorders		
Diarrhoea	92	22
Stomatitis*	46	4.4**
Vomiting	40	2.6**
Decreased appetite	39	0.9**
Nausea	37	4.4**
Decreased weight	21	0
Abdominal pain*	18	1.8**
Gastroesophageal reflux disease	15	0
Dyspepsia	11	0
Skin and subcutaneous tissue disorders		
Rash*	78	1.8**
Paronychia*	39	0.9**
Dry skin	32	0
Pruritus	24	0.9**
Alopecia	19	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	34	2.6**
General disorders and administration site conditions		
Fatigue*	29	3.5**
Respiratory, thoracic and mediastinal disorders		
Cough*	24	0
Upper respiratory tract infection*	16	0
Dyspnoea*	15	4.4
Rhinorrhoea	13	0
Eye disorders		
Ocular toxicity*	11	0
Cardiac disorders		
QTc interval prolongation*	10	3.5
Hypertension*	10	4.4**
Nervous system disorders		
Headache	10	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off date.

* Grouped MedDRA Preferred Terms

** Grade 3 only (no Grade 4 occurred)

Table 15. Study AP32788-15-101 Select laboratory abnormalities worsening from Baseline in ≥ 20% (primary safety population; data cut off 29 May 2020)

Laboratory abnormality	Primary safety population (n=114)	
	All grades (%)*	Grade 3-4 (%)
Haematology		
Decreased red blood cells	59	3.5
Decreased lymphocytes	52	15
Decreased platelets	26	0.9
Decreased leukocytes	25	0
Chemistry		
Increased creatinine	52	2.7
Increased amylase	40	13
Increased lipase	35	10
Decreased potassium	29	5.3
Increased alkaline phosphatase	25	1.8
Decreased albumin	23	1.8
Decreased magnesium	23	2.7
Increased alanine aminotransferase	22	2.7
Increased aspartate aminotransferase	21	1.8
Decreased sodium	20	0.9

* The denominator used to calculate the rate varied from 93 to 113 based on the number of patients with a baseline and at least one post-treatment value. The laboratory abnormalities are values that reflect worsening from Baseline.

Serious adverse events

Serious adverse events were defined in the protocol as AEs that fulfil any of these critera:

- Fatal or life threatening
- Results in persistent or significant disability or incapacity
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Congenital anomalies/birth defects
- New primary cancer
- Important medical event

Serious adverse events occurred in 41% of patients in the pooled safety population, and Serious adverse events that occurred in greater or equal to 2% of patients (according to the term groupings used for the regulatory safety review) included diarrhoea (GT), dyspnoea, vomiting, pyrexia, acute kidney injury (GT), nausea, pleural effusion (GT), and cardiac failure (GT). The most common SAE was diarrhoea, occurring in 8% of patients.

Adverse event of special interest

The mechanism of action of mobocertinib is similar to other EGFR TKIs. The adverse events of special interest nominated by the sponsor in designing the trial were therefore based on the known toxicities of other EGFR TKIs, including pneumonitis/interstitial lung disease, cardiac disorders (cardiac failure, cardiomyopathy, decrease in left ventricular ejection fraction), gastrointestinal toxicities (diarrhoea, nausea, and vomiting), stomatitis, amylase/lipase increases, and skin toxicities. The FDA conducted an independent assessment of these adverse

events of special interest and other treatment emergent adverse events of clinical interest. The sponsor's and the FDA reviewer's findings regarding adverse event of special interest are described in detail in section 8.2.4.5 of the publicly available review document.[45] A summary of each is outlined below.

QT prolongation

Study 101 excluded patients with or at risk of QT prolongation/torsades de pointes.

Treatment-emergent adverse events of QTc prolongation were recorded for 10% of patients in the primary safety population (Grade 3 for 3%). With further follow up (90 day safety update; data cut off :1 November 2020) the all grade rate rose to 12%.

Torsades de pointes with QT prolongation (confirmed on ECG) occurred in one patient (1%): a 74 year old female who was admitted to a cardiac intensive care unit due to life threatening ventricular arrhythmias, in context of hypomagnesaemia (Grade 2 (1.73 mmol/L)) and hypokalaemia (Grade 2 [3 mmol/L]). She experienced multiple bouts of loss of consciousness due to ventricular tachycardia during her admission, required cardioversion multiple times and received a temporary venous pacemaker, but recovered and was discharged after about a week in hospital. Mobocertinib was permanently discontinued.

In context of the pharmacodynamic findings, the clinical data are clearly suggestive of a mobocertinib attributable risk of clinically meaningful QT prolongation and life threatening arrhythmia.

This risk warrants warning/precautionary text for QTc prolongation and torsades de pointes in the Australian Product Information. A post-market integrated analysis of QTc prolongation and related events from randomised clinical trials is expected to be available in 2024 and its submission should be a condition of registration.

Non-QT cardiac conduction abnormalities

In addition to QT prolongation and torsades de pointes, other conduction abnormalities occurred in patients receiving mobocertinib. In the pooled safety population (n = 256), there were single events of ventricular tachycardia, first degree atrioventricular block, second degree atrioventricular block left bundle branch block, supraventricular extrasystoles and ventricular extrasystoles (each 0.4%), and 4 patients (1.6%) with atrial fibrillation.

> 'One serious event of Grade 3 ventricular tachycardia occurred in a 64-year-old woman who was seen in the emergency department for a seizure approximately 3.5 months after starting treatment and a screening ECG showed non-sustained ventricular tachycardia. She was treated with amiodarone, and mobocertinib was held for 2 days at which time the event grade was decreased to Grade 2. The event was attributed as possibly related to mobocertinib, although concomitant medications, tiotropium bromide or fluticasone which possess arrhythmic effects, could have contributed to the event.'[45]

Cardiac conduction abnormalities other than QTc prolongation were generally mild, but a contributory effect of mobocertinib can't be ruled out. The '*Warnings and Precautions*' section of the FDA label for mobocertinib describes these events of cardiac conduction abnormalities in concert with the QT prolongation information. Similar information should be included in the Australian PI, in section 4.8.

Interstitial lung disease

Drug induced interstitial lung disease is known to be associated with other agents in this class. In the pooled safety population (n = 256), according to the regulatory safety review, interstitial

lung disease/pneumonitis occurred in 10 patients (4.3%), of which half were at least Grade 3 and three (30%) were fatal. Mobocertinib was either interrupted or discontinued in all cases. Two patients recovered. One additional patient in the overall safety population (n = 325) who received mobocertinib 120 mg once daily had a fatal adverse event of pneumonitis.

The Australian PI should contain warning or precaution text reflecting this risk and recommendations for discontinuation of mobocertinib for confirmed cases of interstitial lung disease.

Congestive heart failure

The regulatory safety review identified eight patients with an adverse event consistent with cardiac failure in the overall safety population (n = 325), six of which were at least Grade 3 and two that were fatal. A summary narrative for the first fatal case is provided by the sponsor in the FDA multidisciplinary review:[45]

> 'A 68-year-old male patient (former smoker) experienced serious cardiac failure (Grade 4) on Study Day 90 (study dosing was discontinued the day before this event). Cardiac failure was considered related to the study drug by the investigator and was ultimately fatal. The patient had a concurrent medical history of coronary artery disease without angina pectoris and a previous echocardiogram demonstrating an ejection fraction of 55% to 60%. On Study Day 90 the patient had nonserious Grade 3 tachycardia, deemed not related to study dosing; nonserious Grade 2 nausea and vomiting deemed related to study dosing; nonserious Grade 3 pneumonia and Grade 1 wheezing, both deemed not related to study dosing; nonserious creatinine increase, initially a Grade 1 on Study Day 16, progressing to Grade 2 on Study Day 90, and Grade 3 on Study Day 96. Grade 1 dehydration was noted on Study Day 29, advancing to Grade 2 on Study Day 90.
>
> At the time the patient presented with cardiac failure, an echocardiogram revealed a cardiomyopathy with an ejection fraction of 20%, borderline left ventricular dilation, and pulmonary hypertension. Troponin levels were 118. An electrocardiogram was fairly unremarkable and showed sinus tachycardia with a leftward axis and occasional premature ventricular contractions. The patient progressed to renal failure approximately 2 days after presenting with cardiac failure and dialysis treatment was initiated. The patient was treated with symptomatic measures for heart failure including but not limited to B1-agonist agent, anti-diuretics, IVF, and analgesics. The patient died on Study Day 97 due to worsening cardiac failure.'

The second fatal case was an event of respiratory failure, in which the narrative was consistent of cardiac failure:

> 'A 63-year-old woman who developed dyspnea two weeks after starting treatment and was hospitalised for tachycardia, hypoxia and lethargy. CXR showed unchanged pleural effusion and atelectasis; diagnosed with Klebsiella UTI; treated with antibiotics and steroids including empiric treatment for pneumocystis pneumonia. An ECHO the day of admission showed stress induced cardiomyopathy and decreased EF (no value reported) with worsening hypoxia. CT did not show any parenchymal process to explain acute hypoxia. Repeat echocardiograms showed worsening ventricular dysfunction with elevated BNP and troponin. The patient developed worsening hypotension requiring blood pressure support and she died due to Grade 5 respiratory failure 5 days after admission.'

The regulatory safety review notes:[45]

> 'In the mobocertinib once daily population (n = 256), cardiac failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of cardiac failure.
>
> While the original protocol did not include screening assessments with ECHO or MUGA scans, all ongoing studies with mobocertinib include left ventricular ejection fraction monitoring given the identified risk of cardiac failure; this recommendation is also included in product labeling.'

The Australian PI should contain warning or precaution text reflecting this risk and recommendations for discontinuation of mobocertinib for ≥ Grade 2 heart failure or Grade 3 or 4 decreased ejection fraction. A post-market integrated analysis of cardiac failure and related events from randomised clinical trials is expected to be available in 2024 and its submission should be a condition of registration.

Gastrointestinal toxicity

Diarrhoea was the most common (and most common high grade) treatment-emergent adverse events, and resulted in the most drug interruptions (44%), reductions (20%) and discontinuations (8%) in the primary safety population (n = 114). Grade 3 diarrhoea occurred in 21% of patients and Grade 4 in 1 patient (1%). The median time to onset was five days, and resolution was recorded in half of cases, with median time to resolution three days. Introduction of loperamide at first sign of diarrhoea to the study protocol appears to have reduced the need for dose reduction.

Stomatitis, vomiting, nausea, decreased appetite, weight decreased, abdominal pain and weight decreased were also very common in the primary safety population (see Table 16).

Table 16: Gastrointestinal toxicities in the primary safety population according to the regulatory safety analysis (n = 114)

Primary safety population (n=114)	All grade TEAE (%)	≥ Grade 3 TEAE (%)	SAE (%)	Dose modifications (%)			All grade TEAEs resolved (%)
				Interruption	Reduction	Discontinuation	
Diarrhoea	92	22	8	21	10	4.4	89
Stomatitis	46	4.4	0	5	2.6	1.8	78
Vomiting	40	2.6	4.4	6	2.6	1.8	86
Nausea	37	4.4	2.6	7	5	3.5	63
Decreased appetite	39	0.9	0.9	3.5	1.8	1.8	57
Weight decreased	21	0	0	0	0.9	0.9	37
Abdominal pain	18	1.8	1.8	0.9	0	0.9	68
Gastroesophageal reflux disease	15	0	0	0	0	0	47

Acute kidney injury

Treatment emergent adverse events of acute kidney injury occurred in 7% of patients in the pooled safety population (n = 256), and were serious or Grade 3 and higher in around 3% of patients. Dose interruption for acute kidney injury occurred in 2% of patients, dose reduction in one patient and no discontinuations. In addition to events reported as treatment emergent

adverse events, according to serum biochemistry measurements, 52% of patients had worsening serum creatinine compared to baseline; 3% of these events were of Grade 3 or greater severity. acute kidney injury events were not strongly associated with diarrhoea and dehydration: 20% of acute kidney injury events occurred within 7 days of the onset of diarrhoea events.

There was one fatal event of renal insufficiency that occurred 32 days after mobocertinib was discontinued due to disease progression in a 72 year old male with a history of hypertension and diabetes mellitus (see page 190 of the multi-disciplinary review):[45]

> '[the patient] had a normal creatinine at Baseline and on Day 12 of treatment, he developed Grade 1 increased serum creatinine which worsened to Grade 2 on Day 113 of treatment and did not resolve; he also had intermittent Grade 1 TEAEs of increased BUN. He was on treatment for approximately 6.5 months, then discontinued mobocertinib due to disease progression. Two days after discontinuation of treatment, he developed incomplete intestinal obstruction with nausea, vomiting and no bowel movements. Four days later he developed Grade 4 renal insufficiency and he started dialysis. Evaluation of his ascites fluid showed evidence of adenocarcinoma cells, and he transitioned to hospice and died 13 days after admission. The investigator attributed the cause of death to Grade 5 renal insufficiency and discontinuation of treatment; however, it is possible that treatment with mobocertinib contributed to his renal insufficiency.'

Acute kidney injury is included minimally in the FDA product labelling: as a clinically relevant adverse reaction occurring in less than 10% of patients in the primary safety population. This information should be included in the Australian PI in a similar manner.

Amylase/lipase increase

Elevations of amylase and lipase from Baseline occurred in around a third of patients, based on laboratory assessments, but were not serious, generally resolved without dose modification and were not associated with reported events of pancreatitis. Of 17 patients with Grade 3 or 4 events of elevated amylase or lipase, three patients had elevated lipase alone, three patients had elevated amylase alone, and 11 patients had both elevated simultaneously (at least one patient to Grade 3 or 4). Treatment emergent adverse events during the two week period around the event of high grade elevated amylase and/or lipase were reviewed: 3 of 17 had preceding events of abdominal pain; none were serious.

The following three patients had Grade 4 events of increased amylase or lipase:[45]

> 'A 53-year-old female with baseline Grade 3 amylase elevation of salivary source that remained elevated throughout treatment; on Study Day 220 she developed asymptomatic Grade 4 increased amylase and on the same day she came off treatment due to disease progression; she had other ongoing AEs of dry mouth, dysgeusia and diarrhea; there were no other symptoms related to increased amylase; the lipase levels throughout were low or normal; the outcome of the event was 'unknown'.
>
> A 66-year-old female with normal baseline amylase and lipase who developed intermittent events of elevated amylase and lipase throughout treatment. Starting on Study Day 57, she developed Grade 4 increased lipase with Grade 3 increased amylase; mobocertinib was held until approximately one week later when the events improved to Grade 2 severity and mobocertinib was restarted at a reduced dose of 120 mg. On Study Day 113, she experienced a second episode of asymptomatic Grade 4 increased lipase with Grade 1 increased amylase. There was no evidence of pancreatitis on CT imaging. Mobocertinib was held for one week, then restarted at the same dose when the increased lipase improved to Grade 3 severity. She had ongoing intermittent events of increased amylase and lipase between Study Days 120 to 295, ranging from Grades 1 to 3, which

were unresolved as of the last data cut-off date. As of the data cut- off date, treatment was ongoing with a partial tumor response.

63-year-old male with baseline Grade 1 amylase and lipase elevations who developed Grade 4 increased lipase and Grade 3 increased amylase on Study Day 15. Mobocertinib was held for 1 week until the events resolved, and mobocertinib was restarted at a reduced dose of 120 mg. On Study Day 29, he had recurrent Grade 3 increased lipase and Grade 1 increased amylase, and the dose was held until the lipase elevation improved to Grade 1; he then resumed mobocertinib at the same dose. On Study Day 71, he had recurrent Grade 3 increased lipase; the dose was held until resolution one week later, and he restarted mobocertinib at a reduced dose of 80 mg with no further events. He stopped treatment on Study Day 134 due to progressive disease.'

Skin toxicities

Rash was very common, occurring in 73% of patients in the pooled safety population (n = 256).

Palmar plantar erythrodysaesthesia is a known risk of TKIs, and occurred in 3 to 4% of patients across safety populations. Around 90% were Grades 1 to 2 and none were serious. Palmar-plantar erythrodysaesthesia is included in the FDA label as a clinically relevant adverse reaction occurring in less than 10% of patients in the primary safety population and should be included in the Australian PI.

Paronychia is also a known risk of EGFR TKIs. All grade treatment emergent adverse events of the grouped term paronychia (including preferred terms paronychia, onychoclasis, nail disorder, onycholysis, onychalgia, nail infection, onychomycosis, onychomadesis, nail bed tenderness, nail discoloration and ingrowing nail) occurred in 32% of patients in the pooled safety population (n = 256). All events except for one were Grade 1 or 2.

Other skin disorders were common, including dry skin in 30% of patients, pruritis in 18% and alopecia in 14%. All treatment emergent adverse events were low grade and non-serious except one Grade 3 event of pruritis; none required discontinuation except one Grade 1 event of alopecia.

Ocular toxicities

FDA performed a detailed review of eye disorders because ocular events, including conjunctival hyperemia, corneal opacity, discharge, thinning and/or atrophy of the corneal epithelium, were observed in non-clinical studies of mobocertinib. Eye disorders occurred in 15% of patients and were all low grade, however one patient discontinued for an eye disorder:

'A71-year-old female who developed Grade 1 events of increased lacrimation, eye discharge and blurry vision starting approximately 2 weeks after initiating mobocertinib. The investigator assessed the events as probably related to mobocertinib and mobocertinib was discontinued. The events did not resolve.'

Whilst ocular toxicities were low grade, due to the evidence of ocular toxicity in non-clinical studies and the presence of ocular toxicities for other EGFR TKIs, FDA considered ocular toxicity a clinically relevant adverse event and included the grouped term their label. The Australian PI adverse event table should include this grouped term.

Cardiac safety

The sponsor conducted a concentration-QTc model analysis, in which the estimated weighted sum of mobocertinib, AP32960, and AP32914 plasma concentration was a statistically

significant predictor of QTcF and JTpeak.[79] The model based prediction of QTcF interval change from Baseline at the steady state C_{max} following 160 mg once daily mobocertinib was 12.7 msec (90% CI: 8.69, 16.8). The corresponding prediction for the JTpeak interval change from Baseline was 11.1 msec (90% CI: 3.12, 18.9). The sponsor concluded that:

> 'No statistically significant relationship was identified between concentration and the RR interval, supporting the lack of a clinically meaningful effect on heart rate.'

The regulatory safety reviewer did not agree with the concentration QTc analysis method used, however, because the effect of time on the QTc interval cannot be estimated with confidence in the absence of a placebo control. The reviewer's analysis suggested that mobocertinib treatment is associated with a concentration dependent QTc prolongation effect. At therapeutic doses (160 mg once daily) of mobocertinib, mean increases in the QTc interval of 23 msec (UCL: 26 msec) were detected in the QT assessment by the FDA. For additional details, see the FDA Interdisciplinary Review Team for Cardiac Safety Studies: QT Study Review.[80]

Companion diagnostic considerations

In Study 101, central determination of *EGFR* exon 20 insertion mutations was performed with local laboratory tests, using PCR and next generation sequencing approaches. The ODxTT has been approved by FDA as a companion diagnostic, based on a dataset including results from a bridging study from the LLTs to the ODxTT and analytical validation studies.[81]

Confirmatory data plan

Study TAK-788-3001 is a Phase III, open label, multicentre, randomised, controlled study to evaluate the efficacy and safety of mobocertinib, compared with platinum doublet chemotherapy, as first line systemic therapy for patients with locally advanced or metastatic NSCLC harbouring an *EGFR* exon20ins mutation.[82] The enrolment of Study 3001 is ongoing, and the last patient is anticipated to be enrolled by the end of 2022. Patient accrual is consistent with planned projections, however, accrual of progression free survival events is occurring slower than projections. The data cut off for interim analysis is anticipated to be in the first half of 2023, with it becoming the final analysis for progression free survival if reaching statistical significance at that time. If not, a final analysis of progression free survival is planned in the second half of 2023. These projected milestones may change with more mature data, as the study is event driven.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 0.1 (dated 19 March 2021; data lock point (DLP) 4 September 2020) and Australia specific annex (ASA) version 1.0 (dated 8 April 2021) in support of this application. In response to TGA questions, the sponsor

[79] The J-Tpeak interval is the time from the end of the QRS complex to the peak of the T-wave, corresponding to early repolarization.

[80] FDA Interdisciplinary Review Team for Cardiac Safety Studies. QT Study Review. Page 26 of "Other Review(s) (PDF)." Accessed 02/05/2022 at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215310Orig1s000OtherR.pdf

[81] Premarket approval details for Oncomine Dx Target Test (ODxT Test). PMA number: P160045 Supplement Number: S029. Accessed 02/05/2022 at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160045S029

[82] https://clinicaltrials.gov/ct2/show/NCT04129502

submitted EU-RMP version 0.3 (dated 11 February 2022; DLP 23 December 2020) and ASA version 2.0 (dated 14 February 2022) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 17. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach.

Table 17: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Pneumonitis/ Interstitial Lung Disease	✓	✓*	✓	–
	Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation	✓	✓*	✓	–
	Cardiac failure	✓	✓*	✓	–
Important potential risks	Reproductive and developmental toxicity	✓	–	✓	–
Missing information	Use in patients with severe renal impairment	✓	–	✓	–
	Use in patients with moderate or severe hepatic impairment	✓	–	✓	–
	Long-term use	✓	✓*	–	–

*Study TAK-788-3001

The summary of safety concerns is adequate at second round of RMP evaluation. The Important Identified Risk 'QTc interval prolongation' has been changed to 'Ventricular arrhythmias, including Torsades de pointes, due to QTc interval prolongation.' In addition, Missing Information 'Drug-drug interactions with substrates of CYP3A' has been removed following completion of Study TAK-788-1004.

Both routine and additional pharmacovigilance activities are proposed. Additional pharmacovigilance includes ongoing Study TAK-788-3001, which will be used to further characterise all the important identified risks as well as Missing Information of long term use.

Routine risk minimisation activities only are proposed. This is acceptable as mobocertinib is given orally and prescribed by specialists who are familiar with this class of medicines and their side effects.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> 'The Exkivity EU-RMP (version 0.3, dated 11 February 2022, DLP 23 December 2020), with ASA (version 2.0, dated 14 February 2022), included with submission PM-2021-02546-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.'

The following wording is recommended for the PSUR requirement:

> 'An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
>
> Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.'

As Exkivity is being considered for a provisional registration it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> 'Exkivity (mobocertinib) is to be included in the Black Triangle Scheme. The PI and CMI for Exkivity must include the black triangle symbol and mandatory accompanying text for 5 years, or for the product's entire period of provisional registration, whichever is longer.'

As Exkivity is being considered for a provisional registration the following wording regarding confirmatory trial data is recommended for the condition of registration:

> 'Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.
>
> Specifically the sponsor must conduct studies as described in the clinical study plan in version 2.0 (dated 14 February 2022) of the ASA. The following study report should be submitted to TGA:
>
> - Study TAK-788-3001, fourth quarter of 2024'

Risk-benefit analysis

Delegate's considerations

Proposed action

Overall, mobocertinib has demonstrated a clinically meaningful response rate and durability of responses when used to treat a condition for which there is unmet clinical need in Australia. The

toxicity profile is acceptable, given the clinical setting, that is for patients with a dire prognosis who have no other registered treatment option and for whom standard of care therapies are very limited. The benefit risk balance of provisional registration of mobocertinib for the proposed usage, taking into account the uncertainties, is positive.

Advisory Committee considerations

The Delegate did not refer this submission to the Advisory Committee on Medicines for advice.

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Exkivity (mobocertinib) 40 mg, capsule, blister pack, indicated for:

> *Exkivity has provisional approval in Australia for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has an exon 20 insertion mutation of the epidermal growth factor receptor (EGFR), who have received prior platinum-based chemotherapy.*
>
> *The decision to approve this indication has been made on the basis of objective response rate and duration of response in a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory study.*

Specific conditions of registration applying to these goods

- Exkivity (mobocertinib) is to be included in the Black Triangle Scheme. The PI and CMI for Exkivity must include the black triangle symbol and mandatory accompanying text for 5 years, or for the product's entire period of provisional registration, whichever is longer.
- The Exkivity EU-RMP (version 0.3, dated 11 February 2022, DLP 23 December 2020), with ASA (version 2.0, dated 14 February 2022), included with submission PM-2021-02546-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs). Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of the approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of the approval letter, or the entire period of provisional registration, whichever is longer.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided.

Specifically, the sponsor must conduct studies as described in the clinical study plan inversion 2.0 (dated 14 February 2022) of the ASA. The following should be submitted to TGA:

  - All interim and final clinical study reports for Study TAK-788-3001 (interim and final), with the next analysis expected to be performed in 2023.

    Further guidance for sponsors is available on the TGA website.

- Submit post-market assessments to better characterise the risks of QTc prolongation/Torsades de Pointes and cardiac failure. Expected availability first quarter of 2024.
- Submit the results of Study TAK-788-1007 with regard to the effect of severe renal impairment on mobocertinib pharmacokinetics. Expected availability first quarter of 2023.
- Submit the results of Study TAK-788-1008 with regard to the effect of moderate to severe hepatic impairment on mobocertinib pharmacokinetics. Expected availability fourth quarter of 2022.
- Submit the results of a clinical study with regard to the effects of concurrent administration of mobocertinib on the pharmacokinetics of a BRCP substrates. Expected availability fourth quarter of 2022.

Attachment 1. Product Information

The PI for Exkivity approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

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Reference/Publication #