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RESEARCH ARTICLE

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Australian access to FDA-approved breakthrough therapy designation medicines: a 10-year review

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ABSTRACT

Background: Regulatory pathways adopted by the United States Food Drug and Administration (FDA) and Australian Therapeutic Goods Administration (TGA) enable expedited approval of medicines that are thought to offer significant clinical advantage over existing options for severe diseases.

Objectives: To review Australian accessibility to medicines approved through the FDA breakthrough therapy designation (BTD) process including timelines and approvals by the TGA and Pharmaceutical Benefits Advisory Committee (PBAC) for listing on the Pharmaceutical Benefits Scheme (PBS).

Methods: Retrospective review of published reports from the FDA, TGA, PBAC and PBS for BTDs from 1 January 2013–31 August 2023. Uniform data about BTD and milestone dates were collected. Analysis included all BTDs approved by FDA until 31-August-2022. Main outcome measures: Rates of approval by TGA and PBAC, and PBS-listing; and median (interquartile range, IQR) time from FDA submission to FDA approval, and FDA approval to TGA approval, PBAC approval and PBS listing for cancer and non-cancer medicines.

Results: Of 237 BTDs across 156 medicines, 68% were approved by the TGA, and 37% were listed on the PBS. Median (IQR) time from FDA submission to FDA approval was shorter for cancer compared to non-cancer; 179 days (140–210) vs 232 days (181–245), $p < 0.02$. Time from FDA approval to PBS listing was similar for cancer and non-cancer; median 744 days (IQR, 549–1136) and 733 days (IQR 440–960) respectively, with improvements for cancer BTDs noted for 2018–2022 compared to 2013–2017; 566 days (IQR 319–831) vs 880 days (IQR 620–1362), $p < 0.02$ but not for non-cancer BTDs.

Conclusion: BTD medicines are accessible in Australia approximately 2 years after FDA approval. Since 2018, time to PBS listing for cancer therapies improved,

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mirroring shorter FDA approval times for this category. Further understanding of clinical studies and context by therapeutic area may improve timely and safe access to life-saving medicines.

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KEYWORDS Drug approval; government regulation; humans; access

Introduction

Breakthrough Therapy designation (BTD) is a process designed to expedite the development and review of medicines that are intended to treat a serious condition and preliminary clinical evidence indicates that the medicine may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s) (USFDA(1), 2018). The United States Food and Drug Administration (FDA) confers a BTD specific for a medicine-indication pairing, which does not cover all indications that may be applied in the future. BTDs are invariably sought and granted some time before a registration dossier has been filed with the FDA. Previous evaluations of the impact of BTD on drug development have been conducted separately for cancer and non-cancer medicines (Poirier & Murphy, 2016; Shea et al., 2016).

In Australia, through 2017 and 2018, the Therapeutic Goods Administration (TGA) implemented the *priority reviews pathway* with the aim of reducing the time to registration of a medicine by three months, and the *provisional approval pathway* to reduce the time to registration by two years for those medicines that meet similar conditions for BTD by the FDA (TGA(1), 2023). In Australia, general access and affordable access to medicines occurs once these are listed on the Pharmaceutical Benefits Scheme (PBS).

The aim of the current study was to review accessibility in Australia of BTD medicines approved by the FDA, through examination of the timelines associated with review and approval by the Australian Therapeutics Goods Administration (TGA) for market release within Australia, and by the Pharmaceutical Benefits Advisory Committee (PBAC) for listing on the PBS.

Methods

Health technology assessment (HTA) setting for medicines in Australia

The Australian Government has an extensive history of utilising HTA within its decision-making processes in both regulatory and reimbursement settings. The TGA is responsible for approving and monitoring market authorisations within Australia. Approved medicines are listed within the public database

of the Australian Register of Therapeutic Goods (ARTG). The PBAC and its subcommittees evaluate cost-effectiveness before recommending the listing of new medicines on the PBS. Applications may be simultaneously considered by the TGA and the PBAC (PBS, 2021).

Data collection

All US FDA approved BTDs from 1 July 2012–31 August 2023 were identified from the Drugs@FDA online database and Center for Drug Evaluation and Research publication of BTD approvals by A.M., C.P., M.S., E.M (USFDA(2), 2023). Vaccines and cellular therapies (e.g. chimeric antigen receptor T-cell therapy) were excluded from this review. Medicines and corresponding indication for each BTD were searched on the ARTG including the Prescription medicines registrations and Australian prescription medicine decision summaries webpages and Australian Public Assessment Reports (AusPAR) (TGA(2), 2024). These were matched with entries reported in the Pharmaceutical Benefits Advisory Committee (PBAC) outcome documents and decision summaries, and the PBS website (PBS, 2023). Uniform data were collected for BTDs including FDA orphan designation status, cancer or non-cancer indication, date of dossier submission, date of approval and FDA categorisation as new therapy, new indication, new dosage form or new combination. Any variations between PBS clinical criteria and FDA indications were recorded. Median time (and interquartile range), in calendar days, from FDA designation to FDA approval and from FDA approval to TGA approval, PBAC recommendation and PBS listing were calculated for all BTDs approved by the FDA up to 31st Aug 2022. Quantitative parameters were presented as medians and interquartile ranges (IQRs) and comparisons were made between the two time periods before and after the implementation of the TGA priority review pathway: 2013–2017 vs. 2018–2022. Categorical variables were compared using a $\chi 2$ or Fisher's exact test where appropriate. Continuous variables were compared using the Mann–Whitney U test. Statistical significance was demonstrated if $p < .05$. Statistical analysis was conducted using StatTools version 8.2.2 (Palisade Corporation, Ithaca, NY). Exploratory comparisons of cancer versus non-cancer medicines were performed using nonparametric tests with odds ratios (OR) and 95% confidence intervals calculated. Ethics approval was not required for this study.

Results

From 1 July 2012 to 31 August 2023, 164 medicines were approved by the FDA for 250 BTDs (see Supplemental Material Appendix for full list of medicines). The FDA reported these BTDs to be new medicines (51% overall; 45% cancer and 58% non-cancer), new indications (44% overall; 50% cancer and 37% non-cancer) or new dose form/formulation (5% overall).

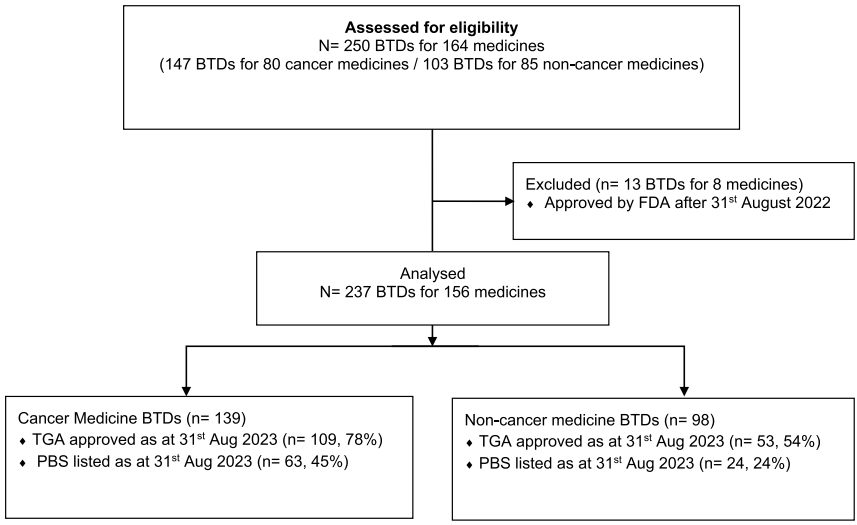

Figure 1. Flow diagram of FDA-approved Breakthrough Therapy Designation medicines analysed for accessibility in Australia.

Market access

As shown in Figure 1, as of 31 August 2023, the TGA had approved 162 of 237 (68%) BTDs included in this analysis (78% for cancer; 54% for non-cancer). TGA approval rates for all FDA approved BTDs in the period 2013–2017 vs 2018–2022 were 95% vs 67% (55 of 58 vs 54 of 81 for the two respective time periods, $p < 0.02$) for cancer and 76% vs 42% (26 of 34 vs 27 of 64; $p < 0.02$) for non-cancer. Overall, 87 of 237 BTDs (37%) were listed on the PBS; 63 of 139 BTDs (45%) for cancer and 24 of 98 BTDs (24%) for non-cancer with rates steadily declining over time, as outlined in Table 1.

New medicines made up 48% and 64% of TGA approvals, and 41% and 67% of PBS listings for cancer and non-cancer therapies respectively. Rates of TGA approval for new medicines were significantly higher for cancer therapies compared to non-cancer therapies (83% vs 60%; OR = 3.2, 95% CI 1.38-7.56, $p = 0.006$). Of the BTDs that were PBS listed, new medicines accounted for 41% of cancer BTDs and 67% of non-cancer BTDs. There was a tendency for higher rates of PBS listing for new medicines for cancer compared to non-cancer, however this was not statistically significant (41% vs 28%; OR = 1.8, 95% CI 0.83-3.92, $p = 0.13$).

Approval timelines

Overall, the median time from FDA submission to PBS listing was 935 days (IQR: 664–1359 and range: 160-2796), with cancer BTDs associated with a longer median (IQR) overall time compared to non-cancer BTDs; 939 days

Table 1. TGA and PBS approvals, and timelines from FDA approval to TGA approval, PBAC first consideration and positive recommendation and final PBS listing for all breakthrough therapy designations.

	Cancer medicines								Non-cancer medicines							
	BTD, N (%)			Timelines: Days, median (IQR)[a]					BTD, N (%)			Timelines: Days, median (IQR)*				
Year of FDA approval	FDA approved at 31 Aug 2022	TGA-approved at 31 Aug 2023	PBS-listed at 31 Aug 2023	FDA approval to TGA approval	TGA Approval to first PBAC meeting	TGA approval to PBAC approval	PBAC approval to PBS listing	FDA approval to PBS listing	FDA approved at 31 Aug 2022	TGA-approved at 31 Aug 2023	PBS-listed at 31 Aug 2023	FDA approval to TGA approval	TGA Approval to first PBAC meeting	TGA approval to PBAC approval	PBAC approval to PBS listing	FDA approval to PBS listing
2013	2	2 (100%)	2 (100%)	355	308	703	92	1722	1	1 (100%)	1 (100%)	206	1	244	366	816
2014	7	7 (100%)	7 (100%)	266 (213-363)	72 (−13-225)	508 (225-1064)	184 (92-290)	1009 (688-1179)	7	6 (86%)	4 (57%)	389 (242-466)	−73 (−120 to −9)	119 (−25-291)	274 (227-320)	719 (506-944)
2015	10	10 (100%)	7 (70%)	410 (272-587)	202 (−66-649)	415 (106-651)	153 (138-184)	752 (640-1151)	10	8 (80%)	4 (40%)	245 (50-503)	554 (112-777)	408 (−45-899)	334 (198-350)	190 (168-689)
2016	14	13 (93%)	7 (50%)	378 (254-612)	85 (31-241)	665 (149-1368)	182 (152-184)	1054 (897-1541)	7	3 (43%)	3 (43%)	214 (194-449)	−48 (−54 to −46)	−48 (−54 to −30)	184 (123-229)	399 (369-566)
2017	25	23 (92%)	14 (56%)	364 (211-684)	53 (−69-264)	179 (145-572)	184 (153-244)	744 (582-1099)	9	8 (89%)	3 (33%)	240 (141-637)	−12 (−58-158)	470 (204-619)	244 (200-296)	801 (582-1118)
2018	23	15 (65%)	11 (48%)	249 (81-517)	107 (−8-388)	388 (245-566)	123 (122-184)	744 (550-1005)	15	11 (73%)	6 (40%)	336 (84-713)	80 (22-237)	201 (102-300)	153 (131-176)	927 (569-1282)
2019	16	14 (88%)	8 (50%)	213 (1-405)	11 (−66-260)	209 (79-406)	214 (176-434)	426 (275-967)	10	5 (50%)	1 (10%)	515 (462-574)	111	99	274	893
2020	21	12 (57%)	4 (19%)	552 (114-894)	27 (−54-208)	59 (−61-220)	123 (108-131)	361 (156-609)	14	4 (29%)	1 (7%)	340 (250-447)	55	239	242	783
2021	14	10 (71%)	3 (21%)	306 (269-408)	12 (−22-140)	203 (65-310)	304 (242-365)	304 (242-365)	15	5 (33%)	1 (7%)	234 (103-318)	54 (−7-181)	300	122	246
2022[b]	7	3 (43%)	0	129 (102-154)	129	226	N/A	N/A	10	2 (20%)	0	241	43	N/A	N/A	N/A
2013 −2017	58	55 (95%)	37 (64%)	351 (224-604)	85 (−46-320)	300 (137-690)	182 (151-243)	880 (620-1362)	34	26 (76%)	15 (44%)	248 (175-493)	−21 (−63-396)	−9 (−54-449)	273 (183-350)	621 (372-901)

(*Continued*)

Table 1. Continued.

	Cancer medicines								Non-cancer medicines							
	BTD, N (%)			Timelines: Days, median (IQR)[a]					BTD, N (%)			Timelines: Days, median (IQR)*				
Year of FDA approval	FDA approved at 31 Aug 2022	TGA-approved at 31 Aug 2023	PBS-listed at 31 Aug 2023	FDA approval to TGA approval	TGA Approval to first PBAC meeting	TGA approval to PBAC approval	PBAC approval to PBS listing	FDA approval to PBS listing	FDA approved at 31 Aug 2022	TGA-approved at 31 Aug 2023	PBS-listed at 31 Aug 2023	FDA approval to TGA approval	TGA Approval to first PBAC meeting	TGA approval to PBAC approval	PBAC approval to PBS listing	FDA approval to PBS listing
2018	–2022[b]	81	54 (67%)	26 (32%)	274 (94-545)	24 (−26-269)	262 (100-415)	181 (123-228)	566 (319-831)	64	27 (42%)	9 (14%)	327 (120-494)	68 (−4-124)	233 (99-300)	153 (123-242)
783 (539-1196)																
All years	139	109 (78%)	63 (45%)	299 (128-593)	62 (−45-290)	298 (109-591)	182 (123-243)	744 (549-1136)	98	53 (54%)	24 (24%)	310 (150-497)	22 (−44-199)	201 (−16-348)	229 (153-283)	733 (440-960)

FDA = Food and Drug Administration; TGA = Therapeutics Goods Administration; PBS = Pharmaceutical Benefits Scheme; BTD = Breakthrough Therapy Designation
[a]IQR = interquartile range, calculated if more than four breakthrough therapy designations in the category
[b]to 31 August 2022

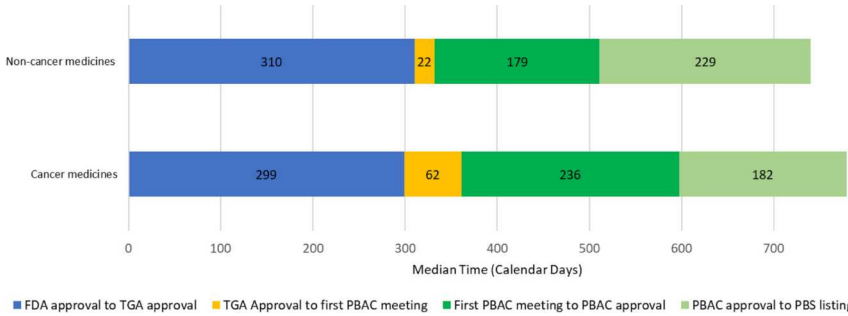

Figure 2. Component median times from FDA approval to TGA approval, to PBAC first consideration, to PBAC positive recommendation and to PBS listing for breakthrough therapy designations.

(676–1353) vs 886 days (619–1266), not statistically significant. This is despite a shorter median time (IQR) to FDA approval for cancer BTDs compared to non-cancer BTDs; 179 days (140–210) vs 232 days (181–245), $p < 0.02$. There was no difference in time from FDA approval to TGA approval for cancer and non-cancer BTDs with median (IQR) time calculated as 299 days (128–593) for cancer BTDs and 310 (150–497) for non-cancer BTDs (Figure 2).

Cancer therapies were associated with slower time to reach PBAC consideration and positive recommendation compared to non-cancer therapies with median (IQR) time from TGA approval to first PBAC meeting calculated as 62 days (−45–290) vs 22 days (−44–199); and TGA approval to PBAC positive recommendation calculated as 298 days (109–591) vs 201 days (−16–348). These differences for the 2013–2017 period were more marked, as shown in Table 1.

Where TGA application dates were reported (83% of cancer therapies and 67% of non-cancer therapies), the median (IQR) time from FDA approval to TGA submission was similar; 3 (−88–313) days for cancer therapies (n = 95) and 4 (−126–253) days for non-cancer therapies (n = 38). There was a TGA application date for only 4 of the 75 BTDs not approved by the TGA but these submission dates were not consistently published on the TGA website or in AusPAR reports. Five of 110 cancer therapies and 3 of 52 non-cancer therapies were approved by the TGA more than one month before approval by the FDA.

PBAC decisions

Eight of 65 cancer therapies and 6 of 23 cancer therapies received PBAC positive recommendations at least one month before TGA approval. Overall, there were 68 instances of 'not-recommend' decisions by the PBAC (56 for cancer and 12 for non-cancer) and 97 reasons (46 reasons associated with clinical study outcomes and 51 reasons associated with economic outcomes) for

these decisions. The most common clinical study concerns reported were uncertain clinical benefit (42%) e.g. inappropriate clinical endpoint; appropriateness of comparator or study design (40%); and safety concerns (18%). The most common economic concerns were cost-effectiveness not demonstrated (85%); and uncertainty around the economic modelling (15%).

Cancer therapies

FDA approved cancer BTDs were most common for lymphoma (19%), lung (17%), breast (12%), skin and melanoma (7%). The most common cancer medicines were pembrolizumab (8%), nivolumab (7%), ibrutinib (4%) and trastuzumab deruxtecan (4%). For cancer therapies, the median (IQR) time from FDA approval to TGA approval improved from 351 days (224–604) for 2013–2017 to 274 days (94–545) for 2018–2022. Similar improvements are seen in time from TGA approval to first PBAC meeting and PBAC positive recommendation, ultimately resulting in a shorter time from FDA approval to PBS listing of 566 (319–834) days for 2018–2022 (n = 27) compared to 880 (620–1362) days for 2013–2017 (n = 35), $p < 0.02$. Albeit the rate of PBS listing is lower (32% for period 2018–2022 vs 64% for 2013-2017). Whilst lower rates of PBS listing were similarly observed for non-cancer therapies, trends for non-cancer therapies were otherwise different, as outlined in Table 1.

Review of the 10th percentile of BTDs with longest timelines for approval, identified 10 cancer therapies and 6 non-cancer therapies with longest time to TGA approval; and 7 cancer therapies and 2 non-cancer therapies with longest times to PBS listing. Of the cancer therapies associated with late PBS listing, these were generally associated with delays in first submission to PBAC after TGA approval (n = 4) or these were previously approved medicines for new indications in an earlier line of cancer therapy where there was a medicine of the same class already on the PBS (n = 2)

Discussion

To our knowledge, this is the first Australian study to report on accessibility to medicines that have been fast tracked in the US through the FDA breakthrough therapy process, over the 10-year period since establishment of this expedited approvals process. Overall, it took approximately 2 years (median 744 days for cancer, and 733 days for non-cancer) after FDA approval for a BTD to be accessible on the Australian PBS. At the time of this review, two-thirds of all FDA approved BTDs had a corresponding TGA approval and less than half were PBS listed. From 2018, the time from FDA approval to PBS listing for cancer therapies had improved to 1.6 years (median 566 days) compared to the prior 5-year period, albeit a smaller proportion (but similar absolute number) of BTDs were approved by the TGA and listed on the PBS.

Since program inception in 2013, the number of FDA-approved BTDs per year has steadily increased to 2018 after which the yearly average has settled at about 30–35 approved BTDs per year. Although our review identified slightly more cancer BTDs approved by the US FDA compared to non-cancer BTDs (59% cancer; 41% non-cancer), Poddar et.*al.* reported that requests for BTD for non-cancer indications was two-fold higher than cancer indications, with 61% of non-cancer requests denied for BTD (Poddar et al., 2024).

New medicines made up half of FDA-approved BTDs for both cancer and non-cancer and were more commonly approved by the TGA for cancer (83%). However, there was no correlation between new medicine status and TGA approval for non-cancer indications or PBS listing (for cancer and non-cancer indications). This may align with observations that trial characteristics of successful BTD approvals were not likely attributable to the designation, but to cancer disease category driving trial design (Pregelj et al., 2021). In a report by Pham et al., FDA approvals were rarely associated with refusals for marketing authorisations by other HTA agencies for non-cancer medicines, but never for cancer medicines; two non-cancer FDA approved BTDs were subsequently rejected by the European Medicines Agency due to inadequate demonstration of efficacy and unjustifiable increased risk of hepatic toxicity (Pham et al., 2023). The TGA currently does not publish reasons for non-approval, and it is not possible to systematically determine if the one-third of BTDs not approved by the TGA are because Sponsors have not submitted applications or if these applications have failed efficacy/safety assessments, or if applications are under active consideration by the TGA. Similarly, there is sparse information in the public domain, and no systematically reported information on the FDA and TGA websites about which BTDs were subsequently not approved or approved and then rescinded.

To date, limited number of cancer reviews have reported that BTDs were associated with better survival outcomes compared to therapies that did not have a BTD, and that BTD criteria accurately identified medicines that improved long-term outcomes for patients with non-small cell lung cancer (Collins et al., 2023), with no greater risk of adverse events (Hwang et al., 2018). Collins et al. showed that BTD drugs for non-small cell lung cancer reduced the risk of death by a median of 31% while drugs never receiving BTD reduced the risk of death by 15% (Collins et al., 2023). However, these findings cannot be generalised to all BTDs, as similar research has not been conducted in other oncology and non-oncology therapeutic areas, and there are conflicting views of the overall safety and value of BTD cancer therapies with some suggesting that the quality of clinical evidence is lacking (Molto et al., 2020; Mulder et al., 2020). The FDA has reiterated that BTDs are held to the same approval standards as for non-BTDs but that it shows flexibility, especially for rare diseases or cancers, where it may not be feasible or ethical to conduct a randomised trial. In such contexts, single cohort trials or historical controls still provide

acceptable evidence of effectiveness for the Regulator to make a determination on overall safety and efficacy (Corrigan-Curay et al., 2018).

In contrast, BTD medicines that are granted approval on the basis of unblinded, or non-randomised trials may have different experiences with the PBAC. This review highlighted that although the most common reasons for PBAC rejection were associated with economic factors, just under half of the rejections were due to clinical study outcomes, where uncertainty around clinical trial design and measures of clinical benefit with use of surrogate primary clinical endpoints featured amongst the more prominent concerns in the PBAC assessment.

Conclusion

Australians get general access to BTD medicines approximately two years after approval by the FDA. For cancer therapies, these timelines have improved over the last five years in line with shorter time frames for FDA processing of cancer BTDs. Further understanding of clinical trial design, clinical endpoints and health economic evidence within a therapeutic area is needed to improve opportunities in Australia for timely and safe access to life-saving medicines.

Disclosure statement

SL is the secretary of the Pharmacy & Therapeutics Advisory Committee at the Peter MacCallum Cancer Centre and has oversight of the hospital medicines formulary. JZ holds leadership positions in ICON Group and Lipotek; has pecuniary interests in Biomarin, Ophthea, Amarin, Frequency Therapeutics, Gilead, UniQure, Orphazyme and Moderna Therapeutics; is on Advisory Boards for Merck Sharp & Dohme, Specialized Therapeutics, Deciphera, Revolution Medicine, FivePHusion, Genorbio, 1Global, Novotech and Alloplex Biotherapeutics Inc; and has received research funding from Bristol-Myers Squibb, AstraZeneca, Pfizer, IQvia, Mylan, Ipsen, Eisai, Medtronic, MSD Oncology, Servier and Astellas Pharma. All other authors declare no conflicts of interest.

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