FROM THE ANALYST'S COUCH

Tumour-agnostic therapies

Ann-Marie Looney, Khurram Nawaz and Rachel M. Webster

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In an era of increased focus on precision medicine, tumour-agnostic therapies have emerged as a revolutionary new approach to cancer treatment. Tumour-agnostic therapies target specific genomic anomalies or molecular features regardless of tumour site of origin. Pan-tumour approaches signal an important new paradigm in clinical management, whereby tumour genomic signature supersedes histology in informing treatment decisions. In recent years, tumour-agnostic therapies have become a key focus area for an increasing number of small and large pharmaceutical companies.

Approved therapies

To date, three tumour-agnostic therapies have received regulatory approval.

In May 2017, the PD-1 inhibitor pembrolizumab (Keytruda; Merck & Co.) became the first drug to receive tumour-agnostic approval in oncology — a watershed in the history of precision medicine. The FDA granted accelerated approval for pembrolizumab as treatment for adult and paediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours that have progressed following prior treatment and who have no suitable alternative treatment options. This approval was based on tumour response rate and durability of response across five distinct, single-arm phase I or II trials. Among 149 evaluable patients across 15 tumour types, pembrolizumab demonstrated an overall response rate (ORR) of 40% (including a complete response (CR) rate of 7%). In addition, 78% of responses lasted 6 months or longer, and no additional safety concerns were identified outside of those previously reported. In January 2019, pembrolizumab received regulatory approval by the Ministry of Health, Labour and Welfare (MHLW) in Japan for the treatment of advanced or recurrent MSI-H solid tumours that have progressed after chemotherapy and are refractory or intolerant to standard therapies, based on results of the phase II KEYNOTE-164 and KEYNOTE-158 trials.

Larotrectinib (Vitrakvi; Bayer), a tropomyosin receptor kinase (TRK) inhibitor, was the second tumour-agnostic therapy to enter the market. The agent was granted FDA approval in November 2018, and European Medicines Agency (EMA) approval in September 2019, for the treatment of adult and paediatric patients with solid tumours that have a neurotrophic tyrosine/tropomyosin receptor kinase (NTRK) gene fusion (without a known acquired resistance mutation), whose disease is metastatic or for whom surgical resection would lead to severe morbidity, and who have no satisfactory treatment alternatives. These approvals were based on three distinct, single-arm trials that collectively demonstrated clinical efficacy of larotrectinib in patients with NTRK fusion-positive tumours.

A third tumour-agnostic therapy, entrectinib (Rozlytrek; Roche/Chugai), another TRK inhibitor, received regulatory approval from Japan's MHLW in June 2019 for the treatment of adult and paediatric patients with NTRK fusion-positive, advanced recurrent solid tumours. In August 2019, entrectinib was approved by the FDA for the same patient population (patients with solid tumours with NTRK gene fusion who have progressed following treatment or have no satisfactory alternative therapy). Similar to pembrolizumab and larotrectinib, entrectinib received regulatory approval based on pooled data from four single-arm trials that evaluated entrectinib in patients with previously treated, unresectable or metastatic solid tumours with NTRK gene fusions. In addition to its tumour-agnostic label, entrectinib has also received tumour-specific FDA approval for *ROS1*-positive metastatic non-small-cell lung cancer (NSCLC).

The successful tumour-agnostic approvals of pembrolizumab, larotrectinib and entrectinib epitomize the growing importance of 'basket' trials in oncology drug development. By focusing on specific molecular features regardless of tumour type, basket trials can broaden the target patient population and include niche and rare cancers that are often underrepresented in clinical trials; for example, salivary gland cancer and sarcoma were among the most common cancer types in the basket trials that led to the tumour-agnostic approvals of larotrectinib and entrectinib. Basket trials benefit from relatively small sample sizes and can offer early evidence of clinical activity by focusing on tumour response end points. However, they are typically early phase, single-arm studies, owing in part to the challenge in defining appropriate controls across disparate tumour types.

Pan-tumour pipeline

The pipeline for tumour-agnostic therapies is expanding and encompasses multiple agents directed at both existing and novel targets (TABLE 1).

Selitrectinib (Bayer) is a TRK inhibitor under phase I/II development for advanced solid tumours that harbour NTRK gene fusions (approximately 1% of solid tumours). Interestingly, the trial is designed to enrol patients with relapse, no response or

Table 1 | **Select pan-tumour therapies in development**

Product	Companies	Target	Development phase
Selitrectinib	Bayer	TRK	I/II
Repotrectinib	Turning Point Therapeutics	ALK, ROS1 and TRK	I/II
Debio1347	Debiopharm Group	FGFR	II[a]
Pralsetinib	Blueprint Medicines Corporation	RET	I/II[a]
Selpercatinib	Eli Lilly	RET	I/II[a]
TPX-0046	Turning Point Therapeutics	RET and SRC	I/II
Dubermatinib	Tolero Pharmaceuticals	AXL kinase	I/II[a]
PLX8394	Plexxikon	BRAF	I/II

[a]Indication-specific development is ongoing for specified agents. ALK, anaplastic lymphoma kinase; FGFR, fibroblast growth factor receptor; TRK, tropomyosin receptor kinase.

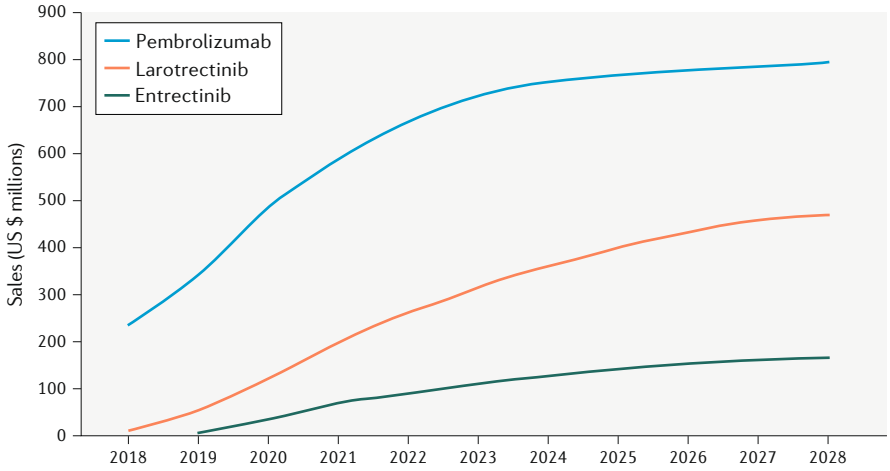

Fig. 1 | **Forecast US sales of currently approved tumour-agnostic therapies.** Sales of pembrolizumab reflect its use for advanced MSI-high/dMMR colorectal cancer, gastric and gastro-oesophageal junction (GEJ) adenocarcinoma, and endometrial carcinoma. Sales of larotrectinib and entrectinib reflect use for advanced NTRK fusion-positive tumours. dMMR, mismatch repair deficient; MSI, microsatellite instability.

intolerance to prior TRK inhibitor therapy. Repotrectinib (Turning Point Therapeutics) is a multitargeting inhibitor directed against the kinases TRKA, TRKB, TRKC, ROS1 and ALK. The multi-cohort phase I/II TRIDENT-1 trial for repotrectinib includes registrational cohorts of patients with NTRK fusion-positive advanced solid tumours who are TRK inhibitor-naive or TRK inhibitor-pretreated. If the results are positive, these trials could help position selitrectinib and repotrectinib as suitable therapies for patients who develop resistance to existing TRK inhibitors, such as larotrectinib or entrectinib.

Debio1347 (Debiopharm Group) is a pan-fibroblast growth factor receptor (FGFR) inhibitor currently being evaluated in the basket phase II FUZE trial in patients with solid tumours that harbour *FGFR1*, *FGFR2* or *FGFR3* gene rearrangements. Debio1347 is also under indication-specific development in a phase I/II trial for metastatic breast cancer.

Pralsetinib (Blueprint Medicines Corporation) and selpercatinib (Eli Lilly) are small-molecule inhibitors of RET kinase under phase I/II development for advanced, RET-altered solid tumours in the ARROW and LIBRETTO-001 trials. RET aberrations are present in approximately 2% of all solid tumours, primarily medullary thyroid cancer and lung cancer (*Clin. Cancer Res.* **15**, 1988–1997; 2017). Both agents are in phase III trials for NSCLC, based on which the two developers have declared their intention to file for approval. Selpercatinib is also under phase III development for medullary thyroid cancer. A third RET inhibitor, TPX-0046 (Turning Point Therapeutics), which also targets SRC, is under phase I/II development for advanced solid tumours harbouring *RET* fusions or mutations.

Other notable agents under pan-tumour development include the AXL kinase inhibitor dubermatinib (Tolero Pharmaceuticals), which is currently being evaluated in two phase I/II trials focused on advanced solid tumours and chronic lymphocytic leukaemia, and PLX8394 (Plexxikon), a BRAF inhibitor in phase I/II development for advanced, unresectable *BRAF*-mutated solid tumours.

Market indicators

Pembrolizumab. MSI occurs most commonly in colorectal, endometrial and gastric cancers; the prevalence of MSI-H varies from 0% to 31% across 39 tumour types (*JCO Precis. Oncol.* 10.1200/PO.17.00073; 2017). In the USA, we forecast sales of pembrolizumab to reach nearly US$800 million in 2028 for advanced MSI-H or dMMR colorectal, endometrial and gastric cancers (FIG. 1). In advanced colorectal cancer, pembrolizumab is facing competition from other immune checkpoint inhibitors in the second-line and later-line metastatic setting; nivolumab (Opdivo; Bristol-Myers Squibb) received accelerated approval for colorectal cancer shortly after pembrolizumab (in July 2017), followed by the combination of nivolumab and ipilimumab (Yervoy; Bristol-Myers Squibb) in June 2018. However, if successful, results from the phase III KEYNOTE-177 trial, which evaluates pembrolizumab versus standard-of-care chemotherapy as a first-line therapy would boost overall forecasted sales of this agent in MSI-H or dMMR advanced colorectal cancer to approximately $260 million in 2028. In advanced endometrial cancer, sales of pembrolizumab are expected to exceed $510 million by 2028, boosted by the relatively high frequency of MSI (approximately 25% of endometrial cancers) and the dearth of effective treatment options for patients who fail standard first-line chemotherapy. Conversely, in advanced gastric cancer, sales of pembrolizumab for MSI-H or dMMR tumours are forecast to reach only $25 million because these aberrations have a low prevalence and this drug is also approved for another subset of patients with this tumour type (PD-L1-positive, previously treated with at least two prior therapies).

Larotrectinib and entrectinib. We forecast that US sales of larotrectinib and entrectinib will reach approximately $470 million and $165 million, respectively, for NTRK fusion-positive tumours in 2028 (FIG. 1). The positioning of both TRK inhibitors as later-line therapies will constrain sales, as will the rarity of NTRK gene fusions in solid tumours. More importantly, the commercial potential of TRK inhibitors will likely be tied to adoption of NTRK gene fusion testing as part of standard diagnostic protocols. Suitable detection techniques include next-generation sequencing, immunohistochemistry, fluorescence in situ hybridization, and reverse transcription–polymerase chain reaction, each of which offers different logistical and technical advantages and disadvantages that must be balanced against the variable prevalence of NTRK gene fusions in solid tumours, particularly in rare cancers. Optimized diagnostic algorithms for NTRK fusion-positive tumours will be required for larotectinib and entrectinib to fully reach their target population.

Ann-Marie Looney, Khurram Nawaz and Rachel M. Webster✉

Decision Resources Group, London, UK.

✉*e-mail: rwebster@TeamDRG.com*

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Competing interests
The authors declare no competing interests.

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