

SPECIAL ARTICLE

# The ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): a tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development

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**Background:** Advances in precision oncology led to approval of tumour-agnostic molecularly guided treatment options (MGTOs). The minimum requirements for claiming tumour-agnostic potential remain elusive.

**Methods:** The European Society for Medical Oncology (ESMO) Precision Medicine Working Group (PMWG) coordinated a project to optimise tumour-agnostic drug development. International experts examined and summarised the publicly available data used for regulatory assessment of the tumour-agnostic indications approved by the US Food and Drug Administration and/or the European Medicines Agency as of December 2023. Different scenarios of minimum objective response rate (ORR), number of tumour types investigated, and number of evaluable patients per tumour type were assessed for developing a screening tool for tumour-agnostic potential. This tool was tested using the tumour-agnostic indications approved during the first half of 2024. A taxonomy for MGTOs and a framework for tumour-agnostic drug development were conceptualised.

**Results:** Each tumour-agnostic indication had data establishing objective response in at least one out of five patients (ORR  $\geq 20\%$ ) in two-thirds ( $\geq 4$ ) of the investigated tumour types, with at least five evaluable patients in each tumour type. These minimum requirements were met by tested indications and may serve as a screening tool for tumour-agnostic potential, requiring further validation. We propose a conceptual taxonomy classifying MGTOs based on the therapeutic effect obtained by targeting a driver molecular aberration across tumours and its modulation by tumour-specific biology: tumour-agnostic, tumour-modulated, or tumour-restricted. The presence of biology-

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informed mechanistic rationale, early regulatory advice, and adequate trial design demonstrating signs of biology-driven tumour-agnostic activity, followed by confirmatory evidence, should be the principles for tumour-agnostic drug development.

**Conclusion:** The ESMO Tumour-Agnostic Classifier (ETAC) focuses on the interplay of targeted driver molecular aberration and tumour-specific biology modulating the therapeutic effect of MGTs. We propose minimum requirements to screen for tumour-agnostic potential (ETAC-S) as part of tumour-agnostic drug development. Definition of ETAC cut-offs is warranted.

**Key words:** biomarkers, molecular targeted therapy, tumour-agnostic, classification, drug development

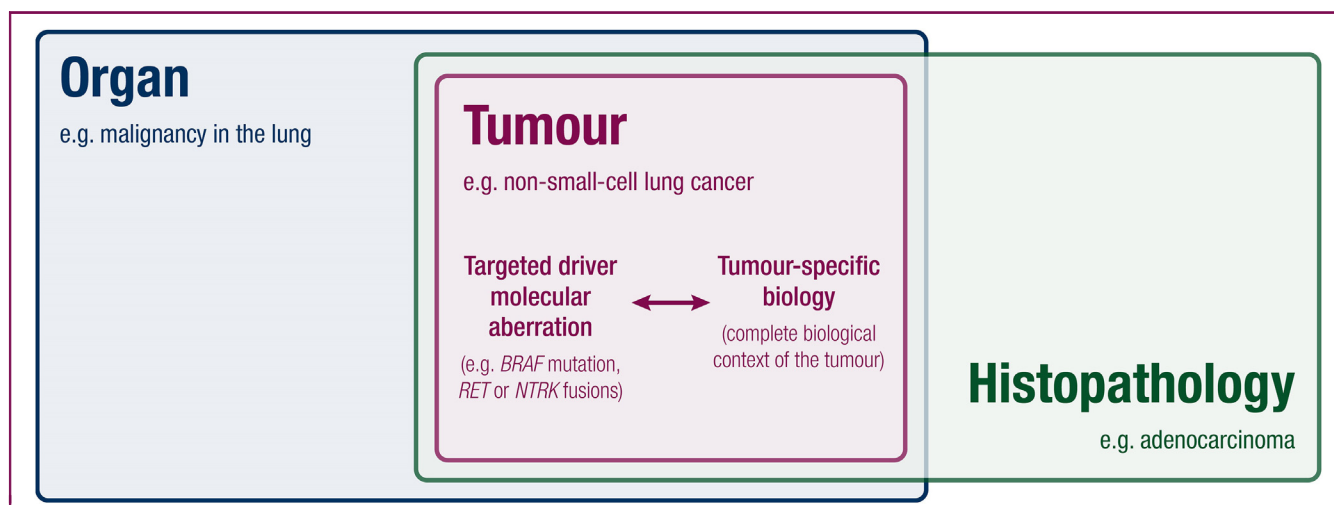
## INTRODUCTION

Advances in understanding the molecular foundations of cancer have been paralleled by technological advances in the field of cancer diagnostics. This has led to the discovery of molecular alterations as therapeutic targets. A variety of biomarkers have been investigated across cancers moving partly away from histology- or organ-driven treatment. Despite various examples of therapies with activity across different tumour types without targeting a specific biomarker, the promise of precision medicine is that of biology-informed activity. Effective molecularly guided treatment options (MGTs) targeting a shared driver molecular aberration may accelerate development of precision therapeutics across tumour types and ultimately make organ-based classification of limited use, replacing it with a biology-based definition of tumours (Figure 1). These developments have not only led to the approval of the first tumour-agnostic MGTs but have also highlighted the need to rethink drug development.<sup>1-4</sup>

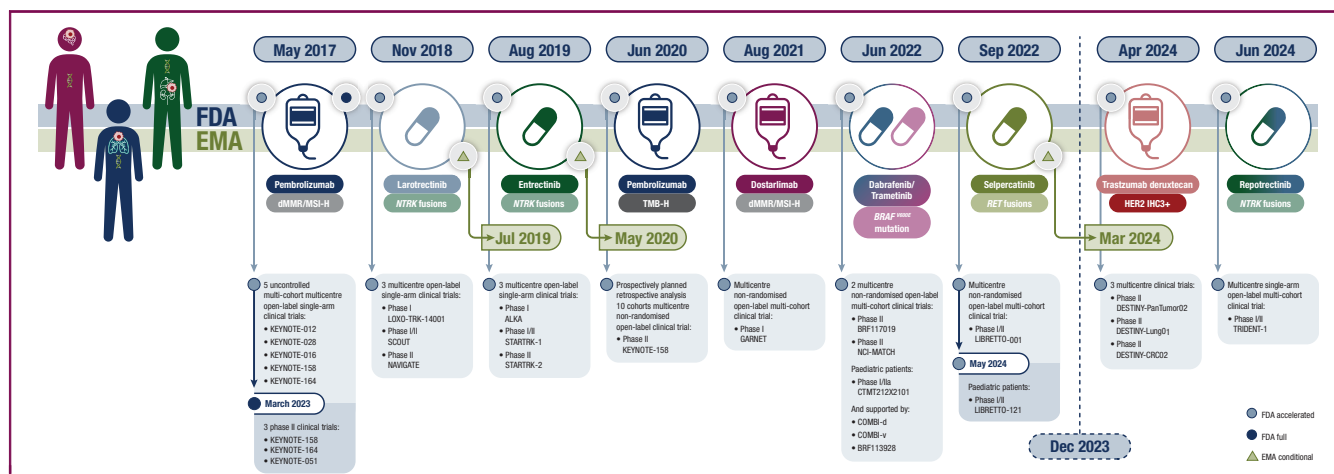
Precision oncology aims to integrate the results of molecular profiling into the management of patients with cancer. Most tumour-agnostic therapeutic targets are rare,<sup>5</sup> and their actionability may be modulated by the tumour-specific biological ecosystem resulting in varying efficacy across different cancers. Consequently, generating evidence

within clinical trials is particularly challenging requiring optimal implementation of tumour-agnostic and tumour-specific concepts in trial design based on robustly developed clinical and biological rationales. Furthermore, enrolment of patients into confirmatory clinical trials after conditional approval remains difficult.<sup>6,7</sup> It is crucial to learn from negative molecularly guided clinical trials,<sup>8-11</sup> and focus on learnings from successful cases for optimising tumour-agnostic drug development and consequently regulatory and health technology assessment (HTA) frameworks to facilitate accelerated access to innovative tumour-agnostic MGTs.<sup>12-15</sup>

In this context, we aim to outline the evidence supporting the approved tumour-agnostic indications as of December 2023 (Figure 2) and to propose a set of minimum eligibility requirements for screening tumour-agnostic potential. Subject to further validation, we tested this screening tool using the data supporting the two most recent tumour-agnostic indications approved during the first half of 2024 (Figure 2). We also propose a conceptual taxonomy for therapeutic effect of MGTs. Our vision is that these tools will contribute to standardising a proposed framework for the development of tumour-agnostic MGTs through a rethinking of the evidence generation paths implemented so far.



**Figure 1. Schematic representation of the concepts of organ, histopathology, and tumour.** The term ‘tumour’ captures the combination of factors related to organ, histopathology, and most importantly biology, the latter integrating a targetable driver molecular aberration modulated by the own tumour-specific biology. *NTRK*, neurotrophic tropomyosin receptor kinase genes; *RET*, rearranged during transfection genes.



**Figure 2.** Landscape of the tumour-agnostic authorised indications by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as of 31 December 2023, and during the first half of 2024. Dates in blue: FDA-accelerated (light) and full (dark) approvals with the respective clinical trials which provided the supportive evidence for the decision; dates in green: EMA conditional approvals.

dMMR, mismatch repair deficiency; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability-high; NTRK, neurotrophic tropomyosin receptor kinase genes; RET, rearranged during transfection genes; TMB-H, tumour mutational burden-high.

## METHODOLOGY

The US Food and Drug Administration (FDA) Prescribing Information Report, and the European Public Assessment Report were used as primary data sources for assessing the publicly available clinical data used to support the seven tumour-agnostic indications of six MGTs, targeting six different molecular alterations, approved as of 31 December 2023. We evaluated these data per tumour-agnostic targeted driver molecular aberration and a group of expert statisticians and clinicians reviewed and summarised the challenges and opportunities in clinical trial design in this setting. To investigate the minimum requirements shared between all the included approved tumour-agnostic MGTs, we used the data packages of these seven FDA-approved indications and explored different scenarios that would enable identification of a combination of three critical components—objective response rate (ORR), number of tumour types investigated, and number of evaluable patients per tumour type. Based on this approach, we propose minimum eligibility requirements needed for claiming tumour-agnostic potential, subject to further confirmatory evidence, which we tested using the data provided for the two most recent tumour-agnostic indications approved during the first half of 2024. This screening tool was developed with the aim of being used and tested in the future development of tumour-agnostic MGTs, consolidating a proposed conceptual taxonomy for classifying the therapeutic effect of MGTs, for which we suggest further methodological work to identify robust classification cut-offs of relevant efficacy metrics. Finally, we present a framework for optimising and accelerating tumour-agnostic drug development. This project was coordinated by the European Society for Medical Oncology (ESMO) Precision Medicine Working Group (PMWG) and details on methodology, semantics, and definitions considered are covered in the [Supplementary](#)

Material Section 1, Supplementary Tables S1 and S2, available at <https://doi.org/10.1016/j.annonc.2024.07.730>.

## CLINICAL DATA SUPPORTING TUMOUR-AGNOSTIC APPROVALS (AS OF 31 DECEMBER 2023)

### Mismatch repair deficiency/microsatellite instability-high

Mismatch repair is a biological pathway that recognises and repairs DNA damage, maintaining genomic stability. Mismatch repair deficiency (dMMR) in cancer results in microsatellite instability-high (MSI-H), accumulation of genomic mutations, and the production of neoantigens recognisable by the immune system.<sup>16</sup>

In May 2017, pembrolizumab received accelerated FDA approval for adult and paediatric patients with unresectable or metastatic, dMMR, or MSI-H solid tumours that have progressed following prior treatment, as the first ever tumour-agnostic MGT.<sup>13</sup> The supportive evidence was based on data from 149 patients with dMMR or MSI-H cancers enrolled across five uncontrolled, open-label, multi-cohort, multicentre, single-arm clinical trials (Figure 2 and Table 1).<sup>17–22</sup> Ninety patients had colorectal cancer (CRC, ORR 36%) with the remaining 59 patients having one of 14 other tumour types. Among non-CRC tumours, endometrial ( $n = 14$ , ORR 36%), biliary ( $n = 11$ , ORR 27%), gastric or gastro-oesophageal junction ( $n = 9$ , ORR 56%), small intestine ( $n = 8$ , ORR 38%), and pancreatic ( $n = 6$ , ORR 83%) cancers were most frequent. In March 2023, the FDA converted the accelerated approval to full approval based on the data from three multicentre, non-randomised phase II clinical trials (Figure 2).<sup>19,20,23</sup> A pooled analysis of dMMR/MSI-H tumours ( $N = 504$ ) demonstrated an ORR of 33% [95% confidence interval (CI) 29% to 38%], 34% (95% CI 26% to 43%) in CRC, and 33% (95% CI 28% to 38%) in non-CRC.<sup>24</sup>

**Table 1.** Summary of the tumour-agnostic indications approved by FDA as of 31 December 2023 for the treatment of patients with unresectable/metastatic tumours previously treated and refractory to one or more systemic treatment lines or with no satisfactory standard treatment

| MGTO<br>Target<br><br>Variable                              | Pembrolizumab<br>dMMR/MSI-H <sup>a</sup>           | Larotrectinib<br>NTRK fusions <sup>b</sup> | Entrectinib<br>NTRK fusions <sup>c</sup>  | Pembrolizumab<br>TMB-H <sup>d,e</sup>            | Dostarlimab<br>dMMR/MSI-H <sup>f</sup>            | Dabrafenib/trametinib<br><i>BRAF</i> <sup>V600E</sup> mutation |                                     | Selpercatinib<br><i>RET</i> fusions |                                     | Summary statements<br>regarding the seven<br>approved indications                                                                                   |
|-------------------------------------------------------------|----------------------------------------------------|--------------------------------------------|-------------------------------------------|--------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                             |                                                    |                                            |                                           |                                                  |                                                   | With anchor<br>tumours <sup>g</sup>                            | Other solid<br>tumours <sup>h</sup> | With anchor<br>tumours <sup>i</sup> | Other solid<br>tumours <sup>j</sup> |                                                                                                                                                     |
| Total patients, <i>N</i>                                    | 149                                                | 55                                         | 54                                        | 102                                              | 209                                               | 823                                                            | 131                                 | 527                                 | 41                                  | The number of total and<br>evaluable patients was<br>>200 in 3/7 (43%)                                                                              |
| Evaluable patients, <i>n</i>                                | 147                                                | 54                                         | 54                                        | 102                                              | 209                                               | 823                                                            | 131                                 | 522                                 | 36                                  |                                                                                                                                                     |
| Prior systemic<br>treatment lines, <i>n</i> , %             | <b>0: 0, 0%</b><br>≥1: 149, 100%<br>(≥2: 107, 72%) | 0: 10, 18%<br>≥1: 45, 82%<br>(≥3: 19, 35%) | 0: 20, 37%<br>≥1: 34, 63%<br>(≥3: 9, 17%) | <b>0: 1, 1%</b><br>≥1: 101, 99%<br>(≥3: 14, 14%) | <b>0: 0, 0%</b><br>≥1: 209, 100%<br>(≥3: 44, 21%) | 0: 624, 76%<br>≥1: 199, 24%                                    | 0: 13, 10%<br>≥1: 118, 90%          | 0: 169, 32%<br>≥1: 358, 68%         | 0: 4, 10%<br>≥1: 37, 90%            | First-line patients not<br>represented in 3/7<br>(43%)                                                                                              |
| Paediatric patients,<br>yes/no (ORR, 95% CI)                | No                                                 | Yes (100%, 74-100) <sup>k</sup>            | No <sup>l</sup>                           | No                                               | No                                                | Yes (25%, 14-40) <sup>m</sup>                                  |                                     | Yes (NA) <sup>n</sup>               | No                                  | Efficacy demonstrated<br>in paediatric patients<br>in 3/7 (43%)                                                                                     |
| ORR, % (95% CI)                                             | 40% (32-48)                                        | 75% (61-85)                                | 57% (43-71)                               | 29% (21-39)                                      | 42% (35-49)                                       | 64% (61-68)                                                    | 41% (33-50)                         | 67% (63-71)                         | 44% (29-60)                         | <b>ORR was ≥40% in 6/7<br/>(86%)</b>                                                                                                                |
| ORR in evaluable<br>patients, % (95% CI)                    | 40% (32-49)                                        | 76% (62-87)                                | 57% (43-71)                               | 29% (21-39)                                      | 42% (35-49)                                       | 64% (61-68)                                                    | 41% (34-50)                         | 67% (63-71)                         | 50% (33-67)                         | No clinically relevant<br>differences by<br>restricting ORR to<br>evaluable patients                                                                |
| ORR in treatment-<br>naïve patients, %<br>(95% CI)          | Not included                                       | NA                                         | <b>65% (41-85)</b>                        | NA                                               | Not included                                      | <b>63% (59-67)<sup>o</sup></b>                                 | NA                                  | <b>79% (72-85)<sup>p</sup></b>      | NA                                  | When ORR is<br>available by prior<br>systemic treatment<br>exposure (3/7), ORR is<br>slightly lower in<br>previously treated<br>patients (Δ 2%-12%) |
| ORR in previously<br>treated patients, %<br>(95% CI)        | 40% (32-48)                                        | NA                                         | 53% (35-70)                               | NA                                               | 42% (35-49)                                       | 61% (48-74)                                                    | NA                                  | 72% (67-77) <sup>p</sup>            | NA                                  |                                                                                                                                                     |
| Lowest tumour-<br>specific ORR, %<br>(95% CI) <sup>q</sup>  | 27% (6-61)                                         | 25% (1-81)                                 | 20% (1-72)                                | 7% (0-34)                                        | 0% (0-60)                                         | 0% (0-71)                                                      | 0% (0-71)                           | 20% (3-56)                          | 20% (3-56)                          | The lowest tumour-<br>specific ORR was<br><20% in 3/7 (43%)                                                                                         |
| Highest tumour-<br>specific ORR, %<br>(95% CI) <sup>q</sup> | 83% (36-100)                                       | 100% (59-100)                              | 86% (42-100)                              | 47% (21-73)                                      | 45% (35-55)                                       | 80% (28-100)                                                   | 80% (28-100)                        | 85% (66-96)                         | 55% (23-83)                         | The highest tumour-<br>specific ORR was<br><80% in 2/7 (29%)                                                                                        |
| Tumour types, <i>n</i><br>evaluable/total                   | 13/15                                              | 12/12                                      | 10/10                                     | 9/9                                              | 15/15                                             | 16/16                                                          | 13/13                               | 13/17                               | 10/14                               | Tumour types ranged<br>from 9 to 17, and<br>were ≥10 in 6/7<br>(86%)                                                                                |

Continued

Table 1. Continued

| MGTO<br>Target<br><br>Variable                        | Pembrolizumab<br>dMMR/MSI-H <sup>a</sup>                             | Larotrectinib<br>NTRK fusions <sup>b</sup>                                                                 | Entrectinib<br>NTRK fusions <sup>c</sup> | Pembrolizumab<br>TMB-H <sup>d,e</sup>      | Dostarlimab<br>dMMR/MSI-H <sup>f</sup>                                                         | Dabrafenib/trametinib<br>BRAF <sup>V600E</sup> mutation                                                                                                     |                                     | Selpercatinib<br>RET fusions        |                                     | Summary statements<br>regarding the seven<br>approved indications                                            |
|-------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|--------------------------------------------------------------------------------------------------------------|
|                                                       |                                                                      |                                                                                                            |                                          |                                            |                                                                                                | With anchor<br>tumours <sup>g</sup>                                                                                                                         | Other solid<br>tumours <sup>h</sup> | With anchor<br>tumours <sup>i</sup> | Other solid<br>tumours <sup>j</sup> |                                                                                                              |
| SCENARIO 1: considering tumour types with ≥5 patients |                                                                      |                                                                                                            |                                          |                                            |                                                                                                |                                                                                                                                                             |                                     |                                     |                                     |                                                                                                              |
| Tumour types, <i>n</i> (%)                            | 6 (6/15, 40%)                                                        | 4 (4/12, 33%)                                                                                              | 5 (5/10, 50%)                            | 6 (6/9, 67%)                               | 4 (4/15, 27%)                                                                                  | 7 (7/16, 44%)                                                                                                                                               |                                     | 5 (5/17, 29%)                       |                                     | ≥33% tumour types<br>had ≥5 patients in<br>5/7 (71%)                                                         |
| Tumour types with<br>ORR ≥ 30%, <i>n</i>              | 5 (5/6, 83%)                                                         | 4 (4/4, 100%)                                                                                              | 4 (4/5, 80%)                             | 3 (3/6, 50%)                               | 4 (4/4, 100%)                                                                                  | 7 (7/7, 100%)                                                                                                                                               |                                     | 4 (4/5, 80%)                        |                                     | ORR ≥30% in ≥67% (or<br>≥4) tumour types with<br>≥5 patients in 6/7<br>(86%)                                 |
| Tumour types with<br>ORR ≥ 20%, <i>n</i>              | 6 (6/6, 100%)                                                        | 4 (4/4, 100%)                                                                                              | 5 (5/5, 100%)                            | 4 (4/6, 67%)                               | 4 (4/4, 100%)                                                                                  | 7 (7/7, 100%)                                                                                                                                               |                                     | 5 (5/5, 100%)                       |                                     | ORR ≥20% in ≥67% (or<br>≥4) tumour types with<br>≥5 patients in 7/7 (100%)                                   |
| SCENARIO 2: considering tumour types with ≥4 patients |                                                                      |                                                                                                            |                                          |                                            |                                                                                                |                                                                                                                                                             |                                     |                                     |                                     |                                                                                                              |
| Tumour types, <i>n</i>                                | 6 (6/15, 40%)                                                        | 7 (7/12, 58%)                                                                                              | 6 (6/10, 60%)                            | 6 (6/9, 67%)                               | 5 (5/15, 33%)                                                                                  | 8 (8/16, 50%)                                                                                                                                               |                                     | 6 (6/17, 35%)                       |                                     | ≥33% tumour types had<br>≥4 patients in 7/7 (100%)                                                           |
| Tumour types with<br>ORR ≥ 30%, <i>n</i>              | 5 (5/6, 83%)                                                         | 6 (6/7, 86%)                                                                                               | 4 (4/6, 67%)                             | 3 (3/6, 50%)                               | 4 (4/5, 80%)                                                                                   | 8 (8/8, 100%)                                                                                                                                               |                                     | 5 (5/6, 83%)                        |                                     | ORR ≥30% in ≥67% (or<br>≥4) tumour types with<br>≥4 patients in 6/7 (86%)                                    |
| Tumour types with<br>ORR ≥ 20%, <i>n</i>              | 6 (6/6, 100%)                                                        | 7 (7/7, 100%)                                                                                              | 6 (6/6, 100%)                            | 4 (4/6, 67%)                               | 4 (4/5, 80%)                                                                                   | 8 (8/8, 100%)                                                                                                                                               |                                     | 6 (6/6, 100%)                       |                                     | ORR ≥20% in ≥67% (or<br>≥4) tumour types with<br>≥4 patients in 7/7 (100%)                                   |
| Additional criteria                                   |                                                                      |                                                                                                            |                                          |                                            |                                                                                                |                                                                                                                                                             |                                     |                                     |                                     |                                                                                                              |
| Non-responder<br>tumour types,<br><i>N</i> /total, %  | 2/15, 13%<br>(all with <2 patients,<br>renal cancer, and<br>sarcoma) | 4/12, 33%<br>(all with <3 patients,<br>cholangio carcinoma,<br>breast, appendix, and<br>pancreatic cancer) | None                                     | 1/9, 11%<br>(<2 patients,<br>mesothelioma) | 3/15, 20%<br>(pancreatic<br>4 patients,<br><2 patients:<br>renal and<br>oesophageal<br>cancer) | 5/16, 31%<br>(all with <4 patients,<br>GIST, pancreatic, anal,<br>neuroendocrine colon<br>cancer, and mixed<br>ductal/<br>adenoneuroendocrine<br>carcinoma) |                                     | None                                |                                     | Responses were<br>observed in all tumour<br>types in 2/7 (29%), and<br>in ≥67% tumour types<br>in 7/7 (100%) |
| mDoR, months<br>(range) and<br>% ≥6 months of DoR     | NR (1.6 <sup>+</sup> -22.7 <sup>+</sup> )                            | NR (1.6 <sup>+</sup> -33.2 <sup>+</sup> )                                                                  | NR (2.8-26.0 <sup>+</sup> )              | NR (2.2 <sup>+</sup> -34.8 <sup>+</sup> )  | 34.7 (2.6-35.8 <sup>+</sup> )                                                                  | NA                                                                                                                                                          |                                     | <sup>†</sup> 24.5 (9.2-NR)          |                                     | DoR ≥6 months in<br>≥67% of responders<br>in 6/6 (100%)                                                      |
| % ≥12 months of<br>DoR                                | ≥6 months: 78%<br>≥12 months: NA                                     | ≥6 months: 73%<br>≥12 months: 39%                                                                          | ≥6 months: 68%<br>≥12 months: 45%        | ≥6 months: NA<br>≥12 months: 57%           | ≥6 months: 95.4%<br>≥12 months: NA                                                             | ≥6 months: 68% (ATC),<br>77.8% (paediatric patients)<br>≥12 months: 53% (ATC)                                                                               |                                     | ≥6 months: 67%<br>≥12 months: NA    |                                     | DoR ≥12 months<br>in ≥33% of responders<br>in 4/4 (100%)                                                     |

Data source: FDA Prescribing Information Reports of accelerated approvals to reflect the available data when FDA granted accelerated approval.

Data were mostly generated from multicentre non-randomised, open-label, phase I-II trials, recruiting patients with unresectable or metastatic tumours previously treated with one or more systemic treatment lines or with no satisfactory standard treatment, ranging from 41 to 209 patients per data package. Primary endpoint was ORR (range 29%-75%) and in most cases follow-up is not mature for estimating mDoR or survival endpoints. The heterogeneity of response per tumour type—lowest tumour-specific ORR (7%) to highest tumour-specific ORR (100%)—illustrates a spectrum of tumour-agnostic therapeutic effects, with a remaining level of uncertainty as to their efficacy across all tumour types, and no effect seen in some underrepresented cancers. Detailed information in [Supplementary Material Section 2, Table S3](https://doi.org/10.1016/j.annonc.2024.07.730), available at <https://doi.org/10.1016/j.annonc.2024.07.730>.

ATC, anaplastic thyroid cancer; CRC, colorectal cancer; dMMR, mismatch repair deficiency; DoR, duration of response; FDA, US Food and Drug Administration; GIST, gastrointestinal stromal tumour; mDoR, median duration of response; MGTO, molecularly guided treatment option; MSI-H, microsatellite instability-high; NA, not available; NR, not reached; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic tropomyosin receptor kinase gene; ORR, objective response rate; RET, rearranged during transfection genes; TMB-H, tumour mutational burden-high.

In August 2021, dostarlimab received accelerated FDA approval for the same indication.<sup>25</sup> The non-randomised, open-label, multi-cohort GARNET trial<sup>26</sup> enrolled 209 dMMR patients and demonstrated an ORR of 42% (95% CI 35% to 49%), 45% (95% CI 35% to 55%) in endometrial cancer ( $n = 103$ ), and 39% (95% CI 29% to 49%) in non-endometrial cancers ( $n = 106$ ). Out of the 14 non-endometrial cancer types, CRC ( $n = 69$ , ORR 36%), small intestinal ( $n = 12$ , ORR 33%), and gastric ( $n = 8$ , ORR 38%) cancers were the most common.<sup>27</sup>

### Neurotrophic tropomyosin receptor kinase genes fusions

Oncogenic fusions encompassing neurotrophic tropomyosin receptor kinase genes (*NTRK1*, *NTRK2*, and *NTRK3*) are observed in fewer than 1% of all cancers, but in over 90% of specific rare cancers.<sup>28,29</sup>

In November 2018, the FDA granted accelerated approval to larotrectinib, a selective inhibitor of tropomyosin receptor kinase (TRK), for the treatment of adult and paediatric patients with metastatic or inoperable solid tumours, who have either received prior treatment or have no valid treatment options, and with an *NTRK* gene fusion without known acquired resistance mutation, based on the analysis of data from 55 patients enrolled in three multicentre, open-label, single-arm clinical trials (Figure 2 and Table 1) with an ORR of 75% (95% CI 61% to 85%).<sup>30,31</sup> Among the 12 tumour types reported, salivary gland tumours ( $n = 12$ , ORR 83%), soft-tissue sarcomas ( $n = 11$ , ORR 91%), infantile fibrosarcomas ( $n = 7$ , ORR 100%), and thyroid cancers ( $n = 5$ , ORR 100%) were the most frequent.<sup>32</sup> In July 2019, the European Medicines Agency (EMA) issued a conditional approval to larotrectinib for the same indication based on an update including 93 patients, reporting an ORR of 72% (95% CI 62% to 81%).<sup>33</sup>

In August 2019, the FDA granted accelerated approval to entrectinib, an oral kinase inhibitor of TRK, ROS1, and ALK, for the same indication, based on pooled data from adult patients enrolled in one of three multicentre, open-label, single-arm clinical trials (Figure 2 and Table 1), showing an ORR of 57% (95% CI 43% to 71%).<sup>34,35</sup> A total of 54 patients with 10 tumour types were included, and patients with soft-tissue sarcoma ( $n = 13$ , ORR 46%), non-small-cell lung cancer (NSCLC,  $n = 10$ , ORR 70%), mammary analogue secretory carcinoma ( $n = 7$ , ORR 86%), breast cancer ( $n = 6$ , ORR 83%), and thyroid cancer ( $n = 5$ , ORR 20%) were the most frequent.<sup>36</sup> In May 2020, the EMA authorised the conditional approval to the same indication, based on data from 74 patients, with an ORR of 64% (95% CI 52% to 74%).<sup>37</sup>

### Tumour mutational burden-high

Tumour mutational burden (TMB) is a measure of the number of mutations present within the tumour DNA.<sup>38</sup>

In June 2020, pembrolizumab received accelerated FDA approval for the treatment of patients with TMB-high (TMB-H) solid tumours (Figure 2 and Table 1).<sup>39,40</sup> The data used for this approval derived from a prospectively planned

<sup>a</sup>Data package from patients enrolled in five uncontrolled, open-label, multi-cohort, multicentre, single-arm clinical trials: KEYNOTE-012 (NCT01848834—gastric, bladder, or triple-negative breast cancers), -028 (NCT02054806—oesophageal, biliary, breast, endometrial, or CRC), -016 (NCT01876511—CRC and non-CRC), -158 (NCT02628067—non-CRC), and -164 (NCT02460198—CRC).<sup>17</sup>

<sup>b</sup>Data package from patients enrolled in three multicentre, open-label, single-arm clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)—all patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease.<sup>32</sup>

<sup>c</sup>Data package from patients enrolled in three multicentre, single-arm, open-label clinical trials: ALKA -372-001 (EudraCT 2012—000148—88), STARTRK-1 (NCT02097810), and STARTRK-2 (NCT02568267)—all patients have progressed following systemic therapy for their disease, if available, or would have required surgery causing significant morbidity for locally advanced disease.<sup>36</sup>

<sup>d</sup> $\geq 10$  mutations per megabase, mut/Mb.

<sup>e</sup>Data package from patients included in a prospectively planned retrospective analysis of a 10-cohort multicentre, non-randomised, open-label trial: KEYNOTE-158 (NCT02628067)—all patients with previously treated unresectable or metastatic solid tumours.<sup>42</sup>

<sup>f</sup>Data package from patients enrolled in a non-randomised, multicentre, open-label, multi-cohort trial: GARNET (NCT02715284)—all patients with dMMR recurrent or advanced solid tumours who progressed following systemic therapy and had no satisfactory alternative treatment options.<sup>27</sup>

<sup>g</sup>Data package including patients with anchor tumours: (i) first-line *BRAF*<sup>V600E/V600K</sup> mutation-positive unresectable or metastatic cutaneous melanoma patients enrolled in COMBI-d (NCT01584648,  $N = 211$ ) and COMBI-v (NCT01597908,  $N = 352$ ) trials; (ii) first-line ( $n = 36$ ) or previously treated ( $n = 57$ ) *BRAF*<sup>V600E</sup> mutation-positive metastatic NSCLC patients enrolled in BRF113928 (NCT01336634); and (iii) previously treated *BRAF*<sup>V600E</sup> mutation-positive locally advanced or metastatic anaplastic thyroid cancer enrolled in BRF117019 (NCT02034110,  $n = 36$ ); and the cohort of other *BRAF*<sup>V600E</sup> mutation-positive unresectable or metastatic solid tumours (NCT02465060,  $n = 131$ ).<sup>45</sup>

<sup>h</sup>Data package from patients enrolled in a multi-cohort, multicentre, non-randomised, open-label trial: BRF117019 (NCT02034110), and in the arm H of a single-arm, open-label study: NCI-MATCH (NCT02465060)—all patients had previously treated *BRAF*<sup>V600E</sup> mutation-positive unresectable or metastatic solid tumours or with no satisfactory standard treatment.<sup>45</sup>

<sup>i</sup>Data package from patients enrolled in a multicentre, open-label, multi-cohort clinical trial: LIBRETTO-001 (NCT03157128)—all patients had locally advanced or metastatic *RET* fusion-positive solid tumours or with no satisfactory standard treatment (NSCLC patients  $n = 316$ , medullary thyroid cancer  $n = 143$ , thyroid cancer  $n = 27$ , other solid tumours  $n = 41$ ).<sup>59</sup>

<sup>j</sup>*RET* fusion-positive tumours other than NSCLC patients and thyroid cancer with disease progression on or following prior systemic treatment or who had no satisfactory alternative treatment options, enrolled in the LIBRETTO-001 trial.<sup>59</sup>

<sup>k</sup>From Drilon et al.<sup>64</sup>

<sup>l</sup>Only the safety population includes paediatric patients from STARTRK-NG (NCT02650401).<sup>36</sup>

<sup>m</sup>Data from CTMT212X2101 (NCT02124772).<sup>45</sup>

<sup>n</sup>Only available for thyroid cancer patients.<sup>59</sup>

<sup>o</sup>Only melanoma and NSCLC patients, subgroup analyses not available for anaplastic thyroid cancer and other solid tumours.<sup>45</sup>

<sup>p</sup>Only thyroid cancer and NSCLC patients, not available for other solid tumours.<sup>59</sup>

<sup>q</sup>From tumour types with  $\geq 3$  patients.

<sup>r</sup>Data only from *RET* fusion-positive other solid tumours from LIBRETTO-001.<sup>59</sup>

<sup>+</sup>Denotes ongoing response.

retrospective analysis of 102 patients with previously treated unresectable or metastatic solid tumours deemed TMB-H ( $\geq 10$  somatic mutations per megabase of genomic sequence, 10 mut/Mb) enrolled in the multicentre, non-randomised, open-label, phase II trial KEYNOTE-158.<sup>41</sup> ORR was 29% (95% CI 21% to 39%) across nine distinct tumour types. The most frequent malignancies were small-cell lung cancer ( $n = 34$ , ORR 29%), and cervical ( $n = 16$ , ORR 31%), endometrial ( $n = 15$ , ORR 47%), anal ( $n = 14$ , ORR 7%), vulvar ( $n = 15$ , ORR 17%), and neuroendocrine ( $n = 5$ , ORR 40%) cancers.<sup>42</sup>

### **BRAF<sup>V600E</sup> mutation**

Activating BRAF<sup>V600E</sup> mutation occurs across tumour types, with the highest incidence in melanoma and thyroid cancer.<sup>5,43,44</sup>

In June 2022, the combination of dabrafenib and trametinib was granted accelerated FDA approval for patients 6 years or older with BRAF<sup>V600E</sup>-mutated unresectable or metastatic solid tumours who have progressed following prior treatment, excluding CRC.<sup>15</sup> This followed several disease-specific approvals for BRAF<sup>V600E</sup>-mutated melanoma, NSCLC, and anaplastic thyroid cancer.<sup>45</sup> The tumour-agnostic approval was based on two multi-cohort, multicentre, non-randomised, open-label clinical trials and one phase I/IIa trial with paediatric patients (Figure 2 and Table 1).<sup>46,47</sup> Among the 131 adult patients with 13 different tumour types, the ORR was 41% (95% CI 33% to 50%). The most frequent tumour types were biliary tract cancer ( $n = 48$ , ORR 46%), high-grade glioma ( $n = 48$ , ORR 33%), low-grade glioma ( $n = 14$ , ORR 50%), and low-grade serous ovarian carcinoma ( $n = 5$ , ORR 80%).<sup>45</sup> For the 36 paediatric patients, the ORR was 25% (95% CI 12% to 40%).<sup>48-50</sup> Supporting studies included COMBI-d ( $N = 211$ , ORR 68%) and COMBI-v ( $N = 352$ , ORR 64%) in melanoma, and BRF113928 in previously treated ( $n = 57$ , ORR 61%) and treatment-naïve NSCLC ( $n = 36$ , ORR 61%).<sup>51,52</sup>

### **Rearranged during transfection gene fusions**

Rearranged during transfection (RET) gene fusions leading to constitutive activation of the RET kinase activity are strong oncogenic drivers across a spectrum of cancers.<sup>53-55</sup>

In September 2022, the FDA provided accelerated approval to selpercatinib for the treatment of adult patients diagnosed with advanced or metastatic solid tumours carrying a RET gene fusion that have progressed on or following prior systemic treatment, based on results from the multicentre open-label, multi-cohort phase I/II clinical trial LIBRETTO-001 (Figure 2 and Table 1).<sup>56-58</sup> The data package included 41 individuals across 14 types of RET fusion-positive solid tumours with an ORR of 44% (95% CI 29% to 60%). In this trial, the most frequent malignancies were pancreatic adenocarcinoma ( $n = 11$ , ORR 55%) and CRC ( $n = 10$ , ORR 20%). This approval was further supported by outcomes of patients with NSCLC ( $n = 316$ , previously treated with platinum,  $n = 247$  and ORR 61%, or treatment-naïve,  $n = 69$  and ORR 84%), medullary thyroid

cancer ( $n = 143$ , previously treated with cabozantinib/vandetanib,  $n = 55$  and ORR 69%, or cabozantinib/vandetanib-naïve,  $n = 88$  and ORR 73%), and thyroid cancer ( $n = 27$ , previously treated,  $n = 19$  and ORR 79%, or treatment-naïve,  $n = 8$  and ORR 100%) with RET gene fusions in the LIBRETTO-001 trial, which had previously led to tumour-specific approvals.<sup>59-61</sup> In March 2024, the EMA authorised the conditional approval to the same indication, supported by an update including 52 patients, reporting an ORR of 44% (95% CI 31% to 59%),<sup>62</sup> followed by the extension of the accelerated FDA approval for paediatric patients 2 years of age and older in May 2024, based on data from the clinical trial LIBRETTO-121.<sup>63</sup>

## **CLINICAL TRIAL DESIGN AND MINIMUM ELIGIBILITY REQUIREMENTS FOR TUMOUR-AGNOSTIC POTENTIAL: A PROPOSED TAXONOMY FOR MOLECULARLY GUIDED TREATMENT OPTIONS**

### **Basket and platform trials**

Early phase clinical trials offer an opportunity to assess the therapy's safety and optimal dosing, and explore early signals of activity across various tumour types. In recent years, standard phase I, II, and III trials have been evolving, giving way to novel trial designs, including basket, umbrella, platform, and seamless trials served by master protocols,<sup>65-68</sup> ultimately leading to accelerated drug evaluation processes and approvals of MGTs. In essence, the concept of tumour-agnostic drug development is inspired by the classic phase I dose-escalation design, which enrolled patients with advanced, refractory disease irrespective of tumour type to establish a recommended dose for the subsequent tumour-specific expansion cohorts or phase II trial.<sup>69</sup> Recently, optimised recommendations for novel phase I endpoints and methodologies have been published.<sup>70-72</sup>

Basket trials investigate MGTs, such as a drug or a drug combination, targeting a specific molecular aberration across tumour types.<sup>73,74</sup> The study may include multiple cohorts by histopathology and/or organ of origin or pool several cancers in a single cohort, based on clinical, biological, and prevalence-based considerations. This design facilitates investigation of the efficacy of therapies in patients with rare molecular alterations<sup>75</sup> and allows pooling data from subgroups.<sup>76</sup> Basket trials have been instrumental in the assessment of efficacy in both tumour-specific and tumour-agnostic contexts<sup>60,77-79</sup> and may enable experimental biomarker-driven repurposing of therapies with market authorisation.<sup>80,81</sup>

Platform trials feature flexible designs that allow the addition or removal of new treatment arms or patient subgroups within a single master trial protocol and can be perpetual, according to *a priori* defined criteria.<sup>4,6,82-84</sup> They may also take a form of basket trials in which tumour type cohorts can be added or stopped dynamically.<sup>6</sup> Platform trials enhance operational efficiency, reduce white space between set-up of independent trials, and reduce cost and efforts.<sup>85,86</sup>

The increased use of these designs with comparator arms highlights the importance of making a distinction between

exploratory and confirmatory basket trials. In an exploratory basket trial, the hypothesis investigated (though not formally confirmed or rejected) is that the targeted driver molecular aberration determines treatment response, though it also acknowledges the possibility of heterogeneous results. Thus, these trials aim to evaluate the potential benefit of a single MGTO across different cancer types sharing a specific molecular aberration. On the other hand, confirmatory basket trials formally test the efficacy of a targeted therapy in biomarker-defined populations based on *a priori* defined criteria and may employ randomisation against standard of care.<sup>87</sup> Regarding confirmatory basket trials, the sharing of data across subpopulations/cohorts may require a preplanned biological/clinical rationale and special statistical methods. Also, the assessment of the benefit/risk profile in pooled target populations can be complicated.<sup>6</sup> Combining components of basket and platform trials may offer a flexible framework (platform) that will accommodate both exploratory and confirmatory studies, but this will need to be tested in real-life oncology trials.

#### **Statistical and methodological considerations: challenges and opportunities**

Because of their unique design, basket and platform trials present several statistical and methodological challenges distinct from the classical clinical trial designs (Supplementary Material Section 2, Table S4, available at <https://doi.org/10.1016/j.annonc.2024.07.730>).

**Number and type of study cohorts.** The challenging balance between limited statistical power in multiple small tumour-specific cohorts and optimal scientific inference of tumour type heterogeneity in a pan-tumour cohort warrants the definition of a minimal number of tumour types and patients per tumour type. A basket trial analysis can be carried out in a frequentist or in a Bayesian framework,<sup>88</sup> and the cohort may be treated independently, or information can be shared across (all or some) cohorts.<sup>89-91</sup> Bayesian adaptive hierarchical modelling and the multisource exchangeability model may offer valuable approaches to determine the operating characteristics of basket designs with such information sharing.<sup>92,93</sup> They can accommodate for early stopping for futile treatments.

**Sample size and type I error.** The statistical design of a trial should be guided by its primary scientific question. For exploratory trials, the sample size can be determined based on the desired level of precision required to achieve a meaningful estimate of the effect of the treatment (e.g. based on the width of the CI). Several exploratory basket trials have been designed utilising the Simon two-stage approach.<sup>94</sup> For complex basket trial design, simulations may be required to determine sample sizes and power.<sup>95</sup> In confirmatory basket trials where the primary purpose is to test a single MGTO across several tumour types, there is a risk of two types of false-positive conclusions. The first is the marginal type I error rate, related to each treatment in a

subpopulation/cohort, while the second is the family-wise type I error.<sup>96</sup> The concept of family-wise error rate in a basket trial aims at providing control of an MGTO being deemed efficacious in at least one of the subpopulations/cohorts when there is no treatment effect in any. In a confirmatory platform basket trial intended for successive regulatory submissions, regulators may require the control of the master protocol family-wise error rate, in a similar vein as subgroup analyses, and multiplicity adjustment may be needed when the data are pooled from different sub-studies. However, if these sub-studies can be considered independent for supporting separate regulatory claims, no multiplicity adjustment would be necessary for each benefit/risk assessment.<sup>6</sup> Interestingly, the concept of false discovery rate has been proposed in this setting which can be defined as the expected proportion of false positives among the rejected basket-specific null hypotheses.<sup>97</sup> Basket trials often incorporate interim monitoring and stopping rules to assess treatment efficacy and safety throughout the trial's duration. Bayesian monitoring techniques, group sequential methods, and adaptive sample size re-estimation approaches enable efficient decision making based on accumulating data while controlling error rates.<sup>98</sup>

**Comparator.** Exploratory basket trials are mostly designed as single-arm trials. Although confirmatory trials are typically randomised, single-arm trials may be considered as well. This is particularly relevant for treating patients with rare tumours and/or rare molecular aberrations, where the natural history of the disease is well understood, and there is a robust clinical endpoint demonstrating large treatment effect. In these circumstances the use of external controls based on real-world data (RWD) is increasing, particularly when randomisation is considered unethical or not feasible.<sup>99,100</sup> The accelerated use of RWD to produce evidence in oncology<sup>101</sup> and its increased use to support regulatory decisions<sup>102</sup> highlights the need for proper guidance for reporting RWD studies,<sup>103</sup> as well as effective tools to assess data quality. Methodological challenges, such as prospective standardised primary data collection to minimise missing data, robust description of baseline characteristics to reduce selection bias and to allow matched comparisons, and rigorous endpoint assessments to mitigate outcome measurement biases, need to be addressed for the optimal use of RWD external comparators.<sup>104</sup> Alternatively, inpatient comparisons of efficacy, using each patient as its own control, might provide additional insight into drug efficacy as compared to previous standard therapies.<sup>105</sup> Whenever possible and applicable, clinical trialists should seek the design of basket/platform trials that allow for randomisation to produce the highest level of evidence.

Owing to the heterogeneity of patient's and disease's characteristics across different tumour types, a pan-tumour randomised controlled trial (RCT) poses considerable statistical and methodological challenges. Quotas for tumour types may be set up in the protocol to avoid over-representation of most frequent and no >20% of the randomised patients allowed to be enrolled for a given

tumour type.<sup>8,106</sup> While randomisation may guarantee that the two groups of patients have comparable characteristics and the same overall prognosis, heterogeneity may still dilute the expected benefit. Stratification of the randomisation by prognosis could help to overcome this issue. In the setting of modern therapies, cross-over between arms and comparison of progression-free survival between standard of care and experimental treatment could also be applied to generate data on the efficacy of the intervention tested.

**Endpoints.** Early phase trials conducted in patients with previously treated refractory advanced disease typically employ endpoints that reflect the experimental treatment activity such as tumour shrinkage, which can be measured within a reasonable time frame. ORR is most often the primary endpoint, complemented by duration of response, despite not being validated as a surrogate endpoint of overall survival. Single-arm trials with response rates poorly control for the ‘true’ false-positive and false-negative rates if the null response rate is incorrectly specified.<sup>107</sup> This limitation can significantly influence the conclusions drawn from the trial. Nonetheless, in this setting, spontaneous tumour size regression is not expected, so proper statistical assumptions using ORR may be sufficient for exploratory evidence of activity. Other surrogates of activity should be investigated and validated to assess activity in cancers where radiological objective response is hard to measure (e.g. ovarian cancer), such as proliferative index, early metabolic response, or clearance of circulating tumour DNA. Digital technologies can help efficiently capture important patient-reported outcomes pertaining to both health-related quality of life and safety/tolerability.<sup>108,109</sup> While exploratory endpoints may provide clues and hypotheses for biomarker development, it is unlikely they can contribute to regulatory decision making.

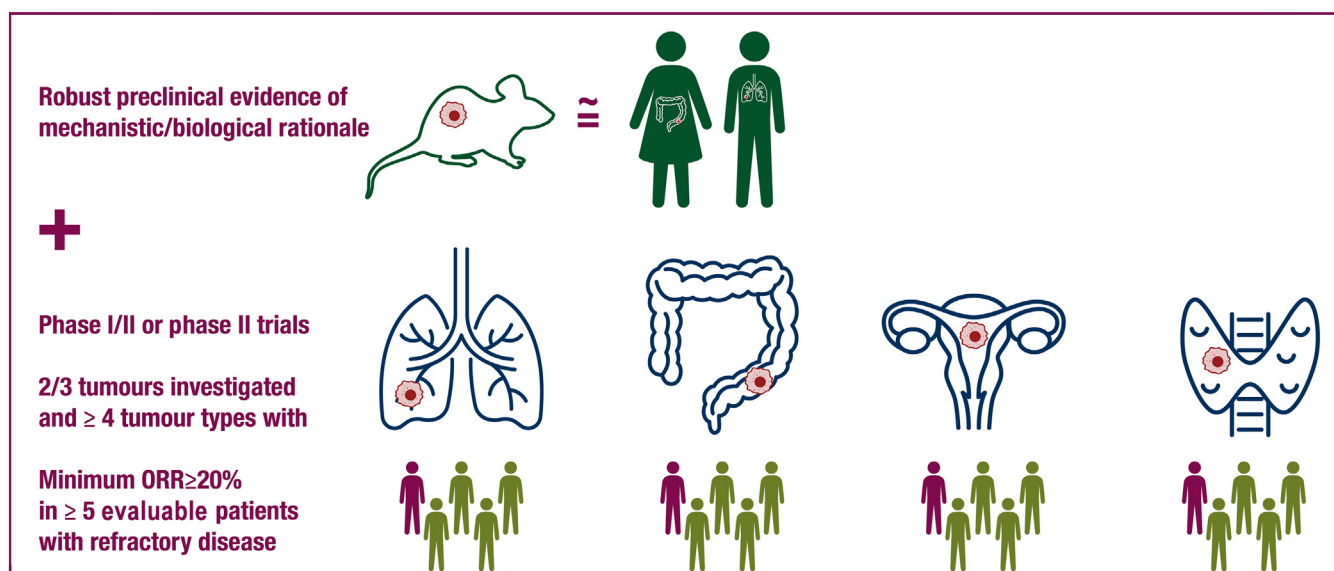
#### **The need for minimum eligibility requirements for tumour-agnostic potential: the ESMO Tumour-Agnostic Classifier and Screener (ETAC-S)**

**Minimum eligibility requirements for tumour-agnostic potential.** The increased uptake of precision oncology and accelerated targeted drug development underscore the need to standardise the way we screen and claim tumour-agnostic potential of investigational therapies. Therefore, establishing a list of minimum requirements that may not be sufficient, but are necessary to assign tumour-agnostic potential, would be instrumental to support drug development and further evidence generation for regulatory assessment. Based on robust preclinical and mechanistic rationales, the approved tumour-agnostic indications as of 31 December 2023 originated from analyses of up to five non-randomised, open-label, single-arm phase I-II trials, mostly with multiple tumour-specific cohorts, or alternatively with cohorts enrolling different tumour types (Figure 2). By analysing the data of these seven indications, we explored different scenarios to identify a robust

combination of three critical components for claiming tumour-agnostic activity—a minimum expected ORR in different tumour types with a given minimum number of evaluable patients. In the setting of refractory disease, we found that each of the seven indications presented data establishing an objective response in at least one out of five patients ( $\text{ORR} \geq 20\%$ ) in two-thirds of the investigated tumour types (and in at least four tumour types) with at least five evaluable patients per tumour type (Table 1 and Figure 3). Thus, the expert panel agreed that these three components could serve as the proposed, pragmatic screening tool (ETAC-S).

**Testing of ETAC-S in tumour-agnostic approved indications during the first half of 2024.** After establishing these minimum requirements to claim tumour-agnostic potential, we tested this screening tool using the data from the two most recent tumour-agnostic indications approved during the first half of 2024 (Figure 2). In April 2024, the antibody-drug conjugate trastuzumab deruxtecan was granted accelerated FDA approval for patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive (immunohistochemistry 3+) solid tumours, based on the analysis of data from 192 adult patients enrolled in three multicentre clinical trials (Figure 2) with an ORR of 50% (95% CI 43% to 57%).<sup>110–114</sup> Among the 16 tumour types included, the objective response was  $\geq 20\%$  in eight out of nine (89%) tumour types with at least five evaluable patients per tumour type (Supplementary Material Section 2, Table S5, available at <https://doi.org/10.1016/j.annonc.2024.07.730>). In June 2024, the FDA granted accelerated approval to repotrectinib as the third kinase inhibitor for the treatment of adult patients with locally advanced or metastatic solid tumours with the presence of an *NTRK* gene fusion.<sup>115</sup> The supportive evidence was based on data from 88 adult patients with solid tumours harbouring *NTRK* gene fusions enrolled in one multicentre single-arm open-label multi-cohort phase I/II clinical trial (Figure 2) with an ORR of 53% (95% CI 42% to 64%).<sup>116,117</sup> Out of the 15 tumour types included, 4 were represented by at least five evaluable patients and all these 4 tumour types obtained an  $\text{ORR} \geq 20\%$  (Supplementary Material Section 2, Table S5, available at <https://doi.org/10.1016/j.annonc.2024.07.730>). We meticulously applied our screening tool to scrutinise these approvals for tumour-agnostic potential and the data used for these approvals met the minimum requirements of ETAC-S (Supplementary Material Section 2, Table S5, available at <https://doi.org/10.1016/j.annonc.2024.07.730>). Based on the data analysed, we believe that ETAC-S is easily applicable in the early phase of drug development for identifying MGTs with potential tumour-agnostic activity. Such tumour-agnostic potential should be further validated in properly designed clinical trials for graduation or rejection and further regulatory assessment.

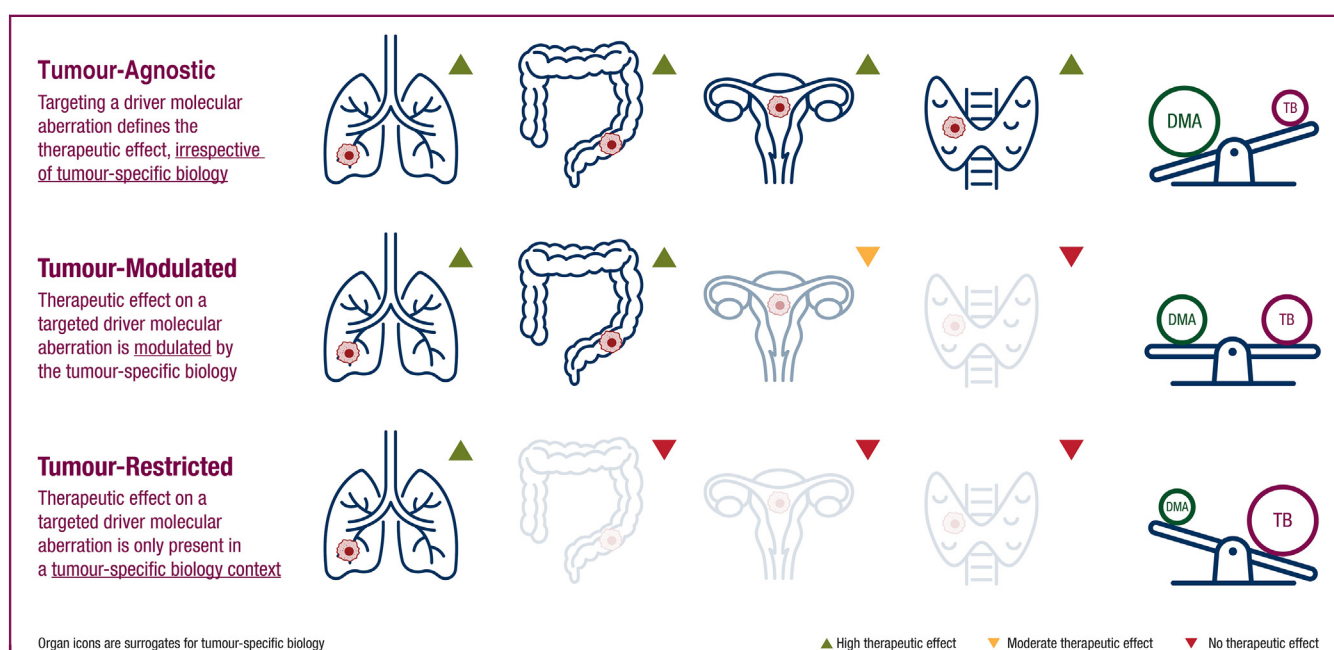
**Taxonomy for therapeutic effect of molecularly guided treatment options.** In contrast to therapies that ultimately demonstrate confirmatory evidence of tumour-agnostic



**Figure 3. ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): minimum eligibility requirements for tumour-agnostic potential.** Robust preclinical evidence associated with prospective clinical evidence from phase I-II trials demonstrating an objective response in at least one out of five patients (ORR  $\geq 20\%$ ) in two-thirds of the investigated tumour types (and in at least four tumour types) with at least five evaluable patients per tumour type, in the setting of refractory disease. ORR, objective response rate.

activity, certain MGTs have their therapeutic effect on the targeted driver molecular aberration substantially modulated by tumour-specific biology (e.g. PARP inhibitors in tumours harbouring *BRCA1/2* mutation/homologous recombination deficiency) or established activity only in a tumour-specific biology context (e.g. PI3K inhibitors in *PIK3CA*-mutated breast cancer). Although the therapeutic effect is driven by targeting of a key molecular aberration, it

could be substantially modulated by the tumour-specific biology. The actionability of a driver molecular aberration might be affected by alternative activated pathways responsible for mechanisms of resistance to novel targeted therapies, or other complex factors of the complete biological context of the tumour (Figures 1 and 4). Therefore, we propose the interplay of targeted 'driver molecular aberration' with 'tumour-specific biology' as a pragmatic



**Figure 4. Proposed ESMO Tumour-Agnostic Classifier (ETAC) taxonomy: tumour-agnostic (e.g. TRK inhibitors in tumours harbouring *NTRK* gene fusions), tumour-modulated (e.g. PARP inhibitors in tumours harbouring *BRCA1/2* mutation/homologous recombination deficiency), or tumour-restricted (e.g. PI3K inhibitors in *PIK3CA*-mutated breast cancer).**

*BRCA*, breast cancer gene; *DMA*, targeted driver molecular aberration; *NTRK*, neurotrophic tropomyosin receptor kinase gene; *PARP*, poly (ADP-ribose) polymerase; *PI3K*, phosphatidylinositol 3-kinases; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha gene; *TB*, tumour-specific biology; *TRK*, tropomyosin receptor kinase.

conceptual basis for a taxonomy for therapeutic effect of MGTs based on three categories (Figure 4):

1. *tumour-agnostic*, when targeting a driver molecular aberration predominantly defines the therapeutic effect, irrespective of tumour-specific biology (e.g. TRK inhibitors in tumours harbouring *NTRK* gene fusions);
2. *tumour-modulated*, when the therapeutic effect on a targeted driver molecular aberration is modulated by the tumour-specific biology (e.g. PARP inhibitors in tumours harbouring *BRCA1/2* mutation/homologous recombination deficiency);
3. *tumour-restricted*, when the therapeutic effect on a targeted driver molecular aberration is only present in a tumour-specific biology context (e.g. PI3K inhibitors in *PIK3CA*-mutated breast cancer).

Categorising cancer therapies according to their molecular/tumour determinants of effect based on a robust taxonomy would profoundly change the way we treat cancer and potentially develop novel ontologies with groups of patients being better classified by a driver molecular aberration than by a cancer type.<sup>118,119</sup> Although we need further work for defining robust cut-offs that enable classification of MGTs in the three categories of this taxonomy (e.g. by systematic investigation of unsuccessful trials of tumour-agnostic drug development), such classification has the potential to optimise drug development and expedite access to effective therapies in refractory conditions with scarce alternative treatment options.<sup>119</sup> Better categorisation of this currently perceived spectrum of different therapeutic effect across tumour types would benefit regulators by proposing a standardised drug development framework and by streamlining independent scientific advice and benefit/risk assessment.

## PRINCIPLES OF A TUMOUR-AGNOSTIC DRUG DEVELOPMENT FRAMEWORK

### Preclinical proof of concept

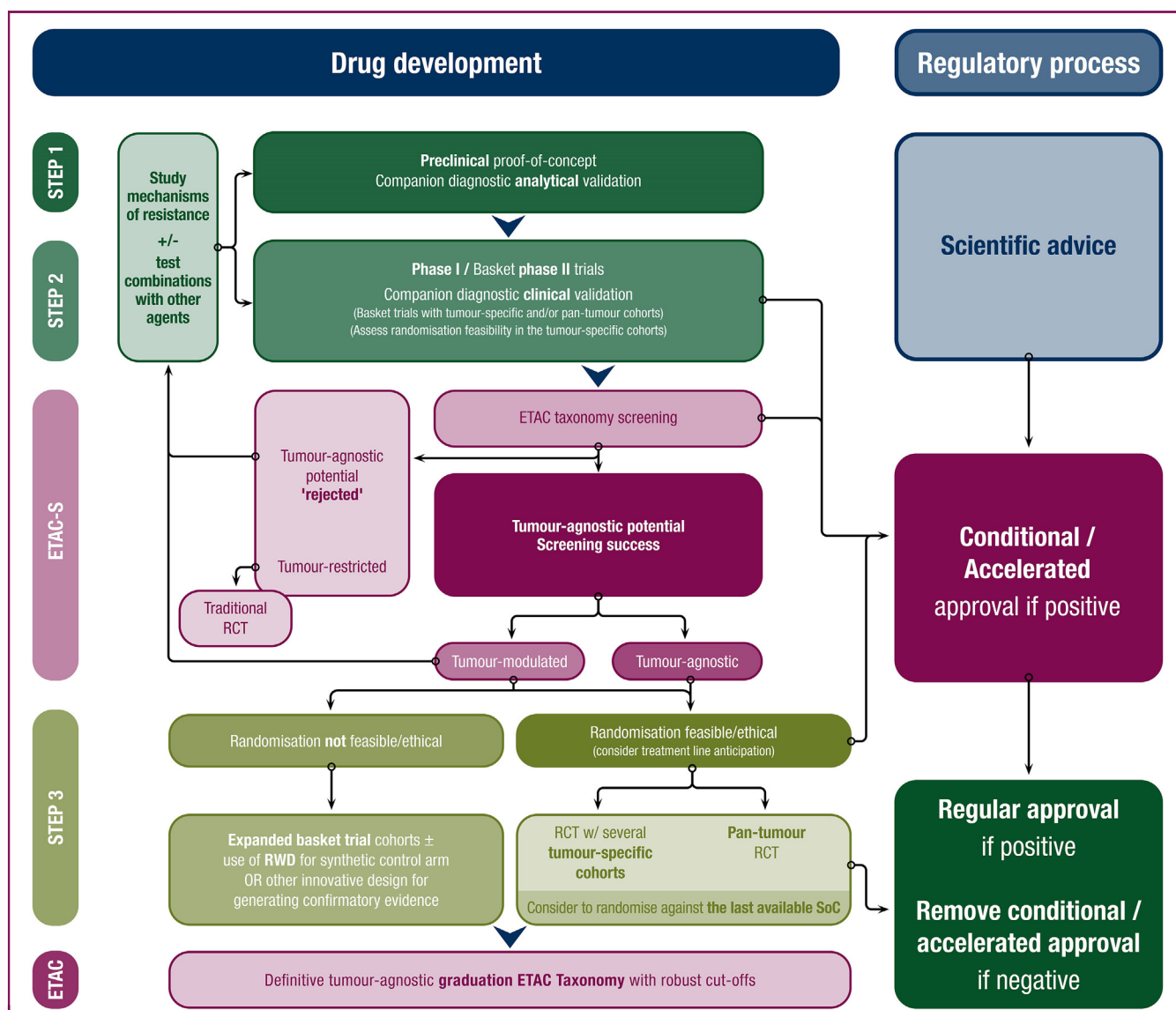
Preclinical studies play a pivotal role before embarking on early phase clinical trials, as they facilitate drug discovery, test novel hypotheses, study mechanisms of resistance, and investigate various combination strategies (Drug development—Step 1, Figure 5). Ideally, preclinical investigations will provide a strong scientific rationale to generate hypothesis-driven clinical trials across different tumour types. Key areas of focus in the preclinical setting include a robust understanding of tumour biology across various tumour types, as well as the structure/function of the molecular alterations, their interconnection to and modulation by the multidimensional molecular pathophysiology of the cancer, the mechanism of action, and mechanism of resistance to the therapeutic compound. There is a pressing need to optimise accurate biomarker co-development, whether diagnostic, prognostic, predictive, and/or surrogate, which could accelerate basic science and drug discovery, informing early drug development, dose selection, and trial design.<sup>4,120</sup> Therefore, it is critical to concurrently

demonstrate robust analytical validation of companion diagnostics in a tumour-agnostic context.<sup>7</sup> Given the rapidly evolving artificial intelligence methodologies, it is timely to consider their full potential to enhance all phases of drug development moving forward.<sup>121</sup>

### Early phase clinical trial setting

Novel trial designs, including basket trials with tumour-specific and/or pan-tumour cohorts, platform trials, and seamless trials served by master protocols, are ideal to test preclinical proof of concepts (Drug development—Step 2, Figure 5). In addition to the need for robust preclinical data, necessary to inform trial design, we recommend the involvement of expert statisticians and pharmacologists throughout the trial design process to optimise drug development and screening for tumour-agnostic activity. If possible, the clinical trial protocol should be adaptive and flexible, to allow for modifications. The balance between tumour-specific and pan-tumour cohorts/baskets, informed by preclinical, biological, epidemiological, and statistical parameters, are key for examining and validating efficacy hypotheses. Incorporating analytically validated companion diagnostic assays is crucial to test their tumour-agnostic clinical validity at this stage. Translational objectives may provide insights and hypotheses for biomarker development and allow for the study of mechanisms of resistance, which can loop back to preclinical drug development (Drug development—Step 1-2, Figure 5). Early and regular involvement of regulatory bodies is critical to tumour-agnostic development as it can allow for conditional/accelerated drug approval if positive signals are seen across tumours on study (Regulatory process, Figure 5).<sup>7,122-124</sup>

In our framework, we propose that establishing minimum eligibility requirements for tumour-agnostic potential plays an important role in early screening of an MGT (ETAC-S, Figure 5). When the therapeutic is a screen failure for tumour-agnostic potential, but shows a signal for tumour-restricted activity (ETAC tumour-restricted), we suggest that this should be further developed in the setting of traditional tumour-specific RCT or supported by the best available innovative study design using RWD when randomisation is not possible. Moreover, incentives should be provided for the study of mechanisms of resistance that could potentially explain the failure of the early clinical tumour-agnostic proof of concept (Drug development—Step 1-2, Figure 5). Investigating combination strategies could shed light on potential approaches to overcome resistance, particularly when there is a rationale for alternative signalling pathway activation driving cancer progression.<sup>75,125-127</sup> Conversely, if the therapeutic demonstrates a response in at least one out of five patients ( $ORR \geq 20\%$ ) in two-thirds of the investigated tumour types (and in at least four tumour types) with at least five evaluable patients per tumour type in the setting of refractory disease, it would screen positive by ETAC-S for tumour-agnostic potential. This may warrant generation of further confirmatory clinical trial evidence (Drug



**Figure 5. Proposed tumour-agnostic drug development framework considering the deployment of efficient modern trial designs and streamlined regulatory processes which can exploit targeted driver molecular aberrations across tumour types.** Note: Traditional RCT for MGTs with tumour-restricted may be replaced by supportive best available innovative study design using RWD when randomisation is not possible. ETAC-S, ESMO Tumour-Agnostic Classifier and Screener; MGTs, molecularly guided treatment options; RCT, randomised controlled trial; RWD, real-world data; SoC, standard of care.

Development—Step 3, Figure 5). Alternatively, in the presence of remarkable therapeutic effects in settings of unmet needs, conditional/accelerated regulatory tumour-agnostic approval may precede further confirmation (Regulatory process, Figure 5). The ETAC-S may be used to support the regulatory decision; however, the choice of any of these two strategies will be guided by disease context, unmet need, effect size, and totality of the data and should be evaluated on a case-by-case basis as per regulatory bodies' frameworks. Early and ongoing involvement of regulators with scientific advice can streamline a rolling, continuous lifecycle drug registration process.<sup>124</sup> In case of a granted conditional approval of a tumour-agnostic therapeutic, authorities should require the marketing authorisation holder to commit with generation of post-authorisation confirmatory evidence leading to regular approval or, in the absence of it, to withdrawal of the conditional/accelerated approval.<sup>128</sup>

### Confirmatory evidence

Ideally, confirmatory evidence should be generated using RCTs, which is the gold-standard design for estimating unbiased treatment effects for tangible benefit to patients (Drug development—Step 3, Figure 5). Drugs demonstrating robust tumour-agnostic performance in early phase I-II trials can proceed to testing in a pan-tumour RCT. If the MGTs seem to demonstrate a tumour-modulated effect, an RCT, which could be phase II or phase III, with several cohorts of different tumour types may be considered. At this stage, the randomisation should be undertaken against the last available efficacious standard of care, and not versus placebo, or an ineffective control in the refractory setting. If randomisation is not feasible or not ethical, the best available innovative study design may be utilised, including confirmatory basket trial designs with efficient trial expansion, pragmatic clinical trials, data sharing from

similar basket trials, hybrid/augmented control arm trials, trials within cohorts, synthetic/external control arms using RWD, or even methodologically robust trial emulation using RWD generated after conditional approval.<sup>100,129,130</sup> Preference should be given to solid survival endpoints, estimated on comparative effectiveness designs to facilitate HTA evaluation.<sup>131,132</sup>

## CONCLUSION

The ETAC-S is an easily applicable set of minimum requirements designed to identify MGTos eligible for tumour-agnostic potential. This involves robust preclinical, mechanistic evidence associated with prospective clinical evidence from phase I-II trials demonstrating an objective response in at least one out of five patients ( $ORR \geq 20\%$ ) in two-thirds of the investigated tumour types (and in at least four tumour types) with at least five evaluable patients per tumour type in the setting of refractory disease. ETAC-S is conceived as a tool with high sensitivity, though not specificity, for tumour-agnostic potential. Further methodological work to define robust classification cut-offs of relevant efficacy metrics will allow our proposed ETAC taxonomy to categorise precision therapeutics to tumour-agnostic, tumour-modulated, or tumour-restricted, based on the interplay of targeted 'driver molecular aberration' with modulating 'tumour-specific biology'. ETAC holds promise for optimising tumour-agnostic drug development and for accelerating patient access to effective therapies.

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