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Letter to the Editor

The response rate by tumour type for tissue-agnostic approved drugs

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Dear Editor,

Increasing excitement for personalised medicine, combined with easier ability to genomically sequence tumours, has spurred research for drugs targeting a specific genetic biomarker versus targeting a specific tumour type. Several drugs have been approved recently for tissue-agnostic indications, based on genetic biomarker, but this should assume that there is good benefit across many tumour types with a given genetic biomarker. We sought to evaluate the response, by tumour type, for drugs approved for tissue-agnostic indications.

We searched for trials reporting on oncology tissue-agnostic drug approved by the US Food and Drug Administration. Initially, we searched the Food and Drug Administration labels for trial-related information. We also searched publication databases to see if there were subsequent publications of trials with more people and/or tumour types, by using the drug name and study name and/or trial name. For each drug and indication approval, we abstracted the total number of participants, the median age and the percentage of participants who were male/female. We also abstracted the total number of participants and the number of participants who responded for each tumour type and calculated the response rate for each tumour type. When multiple trials were used for a drug's approval (e.g. pembrolizumab for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours), we combined the trial data into a single set of drug/biomarker data.

We calculated frequencies for trial characteristics and response by tumour type and genetic biomarker. We calculated R^2 by performing a regression analysis with response as the dependent variable and biomarker and tumour type (grouping related tumour types) as separate independent variables. Data were organised and analysed with Microsoft Excel and R Statistical Software. All data were publicly available, and review board approval was not required.

There were 6 drugs/drug combinations approved for 6 different genetic biomarkers (larotrectinib for tumours with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, entrectinib for tumours with a NTRK gene fusion, pembrolizumab for both tumor mutational burden-high (TMB-H) and MSI/dMMR tumours, dostarlimab for dMMR, dabrafenib plus trametinib for BRAF V600 tumours and selpercatinib for tumours with rearranged during transfection (RET) gene fusion). The number of tumour types represented in each approval was 15 (range: 9–31). The median age was 57 years. The percentages of participants who were

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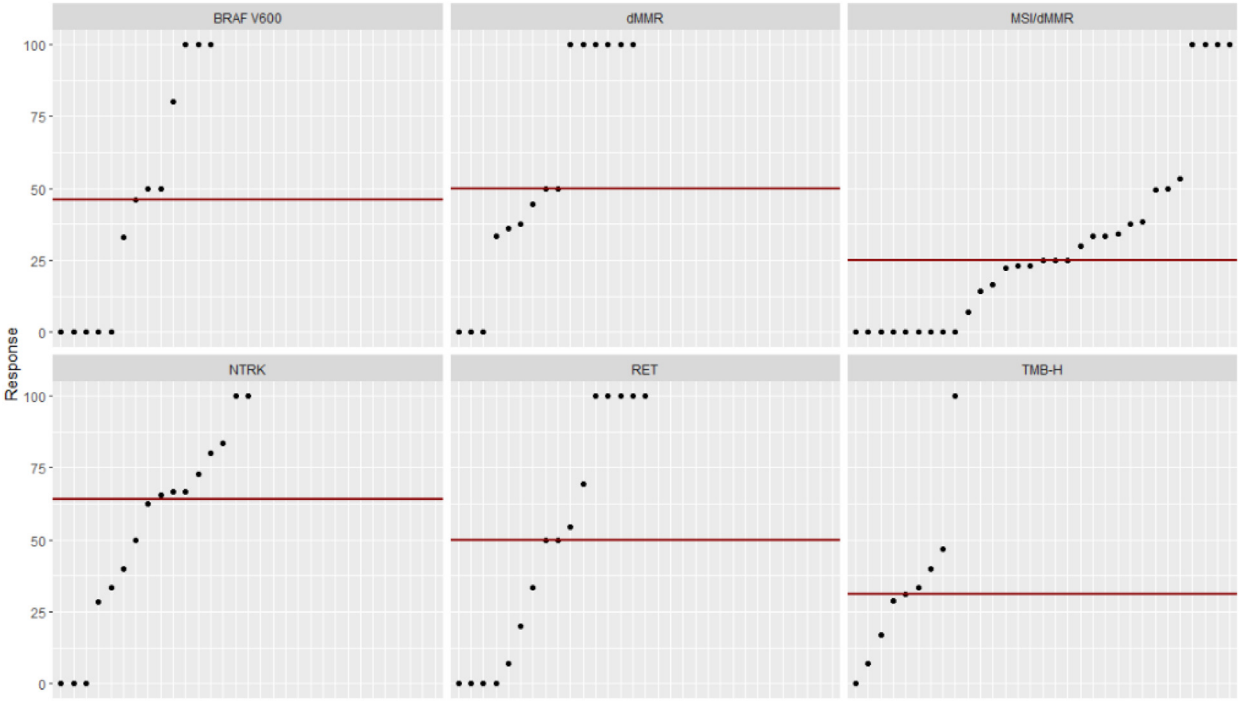

Fig. 1. Percent of response for tumour type and genetic biomarker for drugs approved for a tissue agnostic indication. Each point represents a tumour type. Red line indicates the median response for the different tumour types with the genetic biomarker.

male or female were 44.3% and 55.7%. The total number of participants was 1485 in all trials, and the median number of participants in each trial was 131 (range: 55–561). Colorectal (n = 257), endometrial (n = 202) and thyroid (n = 188) were the most commonly represented tumour types in the trials.

For all trials, the overall response rate for all trial participants was 47.5%. The response rate for each tumour type or each genetic biomarker ranged between 0 and 100% (Fig. 1). The median response for each genetic biomarker was 64% (NTRK), 50% (dMMR), 50% (RET), 46% (BRAF V600), 31% (TMB-H) and 25% (MSI/dMMR).

We found that 8% of the variation in response could be explained by the genetic biomarker and 14% could be explained by the tumour type.

We found that the response to approved tissue-agnostic drugs varied widely by tumour type. Previous studies evaluating trametinib and dabrafenib in BRAF V600 mutations have reported differential responses in clinical trials [1,2], which may be the result of interaction between multiple tumour pathways [3]. Even though these differences were known, this drug combination was approved for any tumour type with a BRAF V600 mutation. The drugs approved for tissue-agnostic indications can be very beneficial in inducing responses in some tumour types, but their use in other tumour types might actually be detrimental because of a delay in receiving other therapies that have known benefit for that specific tumour type. Given the variation in response by tissue type, further research is needed to determine if these drugs are truly tumor agnostic, or if in fact, tissue type is an important determinant of benefit/risk balance.

Authorship contribution

VP and AH conceptualised study design; AH reviewed and abstracted data; VP reviewed and confirmed abstracted data; AH wrote first draft of manuscript; and VP reviewed and revised subsequent and finalised draft of manuscript.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Vinay Prasad's Disclosures. (Research funding) Arnold Ventures (Royalties) Johns Hopkins Press, Medscape and MedPage (Honoraria) Grand Rounds/lectures from universities, medical centres, non-profits and professional societies. (Consulting)

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Data availability

Data are available upon request from the authors.

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