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Commentary

Tumor-Agnostic Biomarkers: Heed Caution, and Why Cell of Origin Still Matters

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Simple Summary: The advent of precision oncology has led to growing promise for tumor-agnostic biomarkers, in which molecular biomarkers may select targeted or immunotherapies regardless of the tumor type. Despite this, it remains critical not to disregard the potential importance of the tumor cell of origin. Numerous examples, in which the response to targeted therapies may be markedly influenced by the tumor type, or where there is a predilection for a specific oncogenic driver alterations in a certain tumor type, underlines this. Consequently, an understanding of cell lineage dependency and lineage-survival oncogenes may still offer significant mechanistic insights into disease biology to ultimately identify further therapeutic vulnerabilities.

Abstract: Since the very beginnings of cancer therapy with chemotherapy, tumors have been treated according to the organ or tissue of origin. The advent of precision medicine however, has recently led to growing promise for tumor-agnostic biomarkers for targeted therapies and immunotherapies, such as *NTRK* fusions. Despite this, prominent examples such as *BRAF* V600E mutations in melanoma compared to colorectal cancer, in which the site of tumor origin dramatically influences the efficacy of targeted therapies, heeds caution against disregarding the importance of cell of origin. Indeed, another illustrative example, is the almost complete absence outside of cancers originating from the lung of the classical activating *EGFR* mutations—exon 19 deletions and exon 21 L858R mutations. Consequently, an understanding of lineage dependency and lineage-survival oncogenes may still offer significant mechanistic insights into the malignant transformation of tumors to ultimately identify further therapeutic vulnerabilities.

Keywords: cancer cell lineage; lineage oncogenes; tumor-agnostic biomarkers; tumor biomarkers

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1. Introduction

Since the very beginnings of cancer therapy with chemotherapy, tumors have been treated according to the organ or tissue of origin [1]. The advent of precision oncology, however, has recently led to growing promise for tumor-agnostic biomarkers for targeted therapies and immunotherapies [2]. Tumor-agnostic or tissue-agnostic biomarkers are molecular signatures or biomarkers used to select therapies regardless of the tumor site of origin [3]. Prominently, NTRK inhibitors entrectinib and larotrectinib are United States (US) Food and Drug Administration (FDA)-approved therapies for patients with advanced solid tumors harboring an *NTRK* gene fusion. Entrectinib was approved on the basis of an integrated analysis from three multicenter, single-arm, open-label phase 1–2 trials: ALKA, STARTRK-1 and STARTRK-2 [4]. From this pooled subgroup of adult patients with unresectable or metastatic solid tumors with an *NTRK* gene fusion, there were 54 efficacy-evaluable patients with an objective response rate (ORR) of 57% (95% CI 43.2–70.8) and a median duration of response (DOR) of 10 months (95% CI 7.1 to not estimable). This patient population consisted of ten different tumor types with 19 different histologies, including, most commonly, sarcoma (24%), non-small cell lung cancer (NSCLC; 19%), mammary

analogue secretory carcinoma-salivary (13%) and breast cancer (11%). Larotrectinib was similarly approved on the basis of an integrated analysis from three multicenter, single-arm, open-label phase 1–2 trials: LOXO-TRK-14001, SCOUT and NAVIGATE [5]. From 55 patients with solid tumors with an *NTRK* gene fusion, the ORR was 75% (95% CI 61–85) and the median DOR had not been reached. This initial patient population consisted of 17 tumor types, including, most commonly, salivary gland tumors (22%), other soft tissue sarcomas (20%), infantile fibrosarcoma (13%) and thyroid tumors (9%).

Notably, there are also tumor-agnostic approvals for pembrolizumab. This includes for patients with advanced solid tumors that are microsatellite instability-high or mismatch repair deficient (MSI-H/dMMR), and patients with advanced solid tumors that are tumor mutational burden-high (TMB-H). In patients with advanced MSI-H/dMMR tumors, pembrolizumab has been evaluated in numerous different trials. In KEYNOTE-016, in patients with 12 different tumor types, the ORR was 53% (95% CI 42–64) with no significant difference between colorectal cancer (CRC) and non-CRCs [6]. A larger cohort of MSI-H tumors in KEYNOTE-158 demonstrated an ORR of 34.3% (95% CI 28.3–40.8). This MSI-H cohort consisted of 27 different tumor types, with endometrial (21%), gastric (10.3%), cholangiocarcinoma (9.4%) and pancreatic (9.4%) cancers being most common [7]. In this trial, which comprised other separate non-MSI-H cohorts of less frequently occurring types of solid tumors, a prospective exploratory biomarker analysis was conducted (excluding the aforementioned MSI-H cohort) [8]. There were 102 (13%) out of 790 patients with tissue TMB-H status (assessed as $\geq$10 mutations per megabase on FoundationOne CDx assay testing), including patients with small cell lung cancer (SCLC; 33%), cervical cancer (16%), endometrial cancer (15%) and anal cancer (14%). The ORR was 30% (95% CI 21–39), with the median duration of response not reached.

The approval of NTRK inhibitors and pembrolizumab with tissue-agnostic indications has generated significant interest with an increased understanding of the molecular aberrations that may be shared across multiple tumors with distinct sites of origin [9]. This has been driven, in part, by powerful sequencing technologies which allow for the rapid and deep interrogation of tumor samples and generation of large molecular datasets. Consequently, there are increasing numbers of basket trials evaluating therapies across multiple tumor types. For instance, there are promising signs of efficacy for selective RET inhibitors for solid tumors harboring *RET* alterations [10]. Despite this, prominent examples such as *BRAF* V600E mutations in melanoma compared to CRC and other tumor types, in which the site of tumor origin dramatically influences the efficacy of targeted therapies [11], heed caution against disregarding the importance of the cell of origin (Figure 1). Whilst *BRAF* V600E mutations may become targetable in CRC with the addition of an EGFR inhibitor [12], the innate resistance to BRAF inhibitor monotherapy remains fundamentally linked to the tissue of origin. For instance, adaptive feedback signaling networks with reactivation of MAPK signaling are driven by induction of RAS activity from receptor tyrosine kinase (RTK) signaling, particularly EGFR, to a much greater degree, in colorectal cancer compared to melanoma [13,14]. For melanoma, the melanocyte master regulator MITF has also been implicated as a lineage survival oncogene and may cooperate with *BRAF* V600E for oncogenic transformation [15]. Furthermore, although certain alterations such as *NTRK* gene fusions may be found across tumor types, there remains a predilection for certain cancers with incidences of >90% in mammary analogue secretory carcinomas (MASC) and secretory breast carcinoma, the reasons for which are not fully understood [16]. Conversely, targetable alterations may be seen in a predominant tumor type. Indeed, the almost complete absence outside of cancers originating from the lung of the classical activating *EGFR* mutations—exon 19 deletions and exon 21 L858R mutations—is especially illustrative [17]. For immunotherapy biomarkers such as TMB, there is also ongoing debate over the reliability of thresholds across the spectrum of solid tumors to predict response to PD-1 blockade [18,19]. Greater variability in TMB calculation based on NGS targeted panels has also been demonstrated for certain tumor types such as uterine, bladder and CRC compared to lung and head and neck cancers [20]. Our evolving understanding

of mutational signatures which may be diverse across tumor types and the subsequent insights into the developmental history of tumors also have important implications for the interpretation of tumor-agnostic biomarkers [21,22]. Therefore, as we strive to optimize therapeutic strategies targeted to the molecular characteristics of an individual patient's tumor under the premise of precision oncology [23], it is imperative to remain cognizant of the influence of the tumor cell of origin on disease biology.

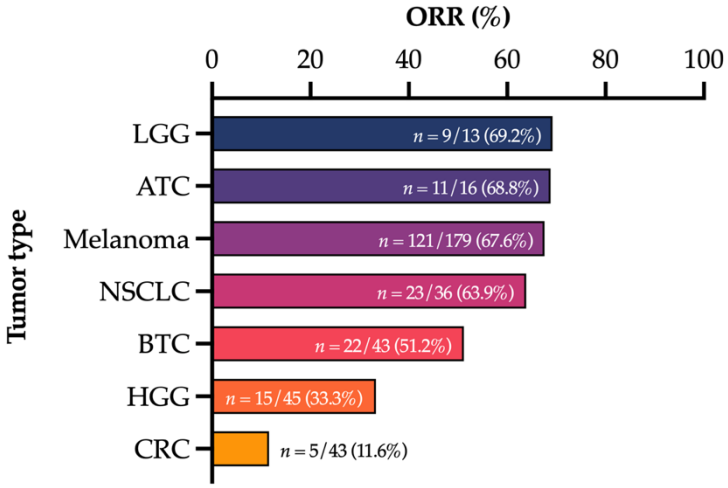

Figure 1. Spectrum of response rates to combination BRAF and MEK inhibition with dabrafenib and trametinib across a range of *BRAF* V600E-mutated tumor types.

Data from Subbiah et al. [24], Long et al. [25], Planchard et al. [26], Subbiah et al. [27], Subbiah et al. [28] and Corcoran et al. [29]. ATC—anaplastic thyroid cancer; BTC—biliary tract cancer; CRC—colorectal cancer; HGG—high-grade glioma; LGG—low-grade glioma; NSCLC—non-small cell lung cancer.

Using NSCLC as an example, the cell of origin and genetic driver lesions are increasingly suspected to play a critical role in shaping the phenotypes of lung tumors [30]. Although not definitively proven, adenocarcinomas are thought to arise predominantly from alveolar cells in the distal airways, whilst squamous cell carcinoma and small cell carcinoma arise predominantly from basal cells and neuroendocrine cells in the proximal airways [31]. In animal studies, for example, *TP53* inactivation and *RB1* loss in neuroendocrine cells have been demonstrated to be sufficient to result in SCLC [32]. The potential for tumor lineage plasticity, however, has also been demonstrated, with loss of TTF-1/NKX2-1 implicated in the development of either mucinous adenocarcinoma with concurrent oncogenic *KRAS* mutation or squamous cell carcinoma with *SOX2* gain [33]. Lineage-defining transcription factors may also shape the tumor immune microenvironment [34]. In *EGFR*-mutated NSCLC, early descriptions of *EGFR* mutations in lung adenocarcinoma identified strong correlations with immunohistochemical expression of TTF-1 (also known as NKX2-1) and anatomical terminal respiratory unit (TRU) histomorphology [35]. Importantly, TTF-1/NKX2-1 expression is used in routine clinical practice as a sensitive marker for differentiating lung adenocarcinoma from other lung cancer histologies [36]. In fact, *EGFR* and TTF-1/NKX2-1 have both been shown to be strong oncogenic drivers, sufficient to transform a pre-invasive lesion into an invasive adenocarcinoma, potentially without concurrent driver genomic alterations [37]. However, TTF-1/NKX2-1 is also a lung lineage master regulator gene, critical in lung morphogenesis and embryological development, and differentiation of distal pulmonary alveolar cells [38]. Taken together, this builds on evidence that cell lineage-specific pathways and the corresponding transcription factors that determine pulmonary epithelial differentiation may have a key role in different histologic and molecular subtypes of lung cancer [39]. In The Cancer Genome Atlas (TCGA) description of lung adenocarcinoma, validated transcriptional molecular subtypes consisting of terminal respiratory unit (TRU), proximal inflammatory (PI) and

proximal proliferative (PP) were each shown to enrich for certain oncogenic driver mutations or translocations along with other genomic features [40]. The transcriptional TRU subtype harbored the majority of *EGFR*-mutated tumors. Notably, these transcriptional molecular subtypes were originally identified from correlations with histopathological and anatomical descriptions of lung tumors [41]. Finally, histological transformation with small cell or squamous transformation as a commonly identified mechanism of resistance to the selective pressure induced by EGFR inhibition further highlights the importance of cell lineage [42]. Therefore, oncogenic dependency, phenotypic plasticity and subsequent response to therapy may all be influenced by the underlying cell of origin [43].

2. Conclusions

Despite the promise of tumor-agnostic biomarkers for precision oncology, it remains critical to not disregard the potential importance of the cell of origin. An understanding of lineage dependency and lineage survival oncogenes may still offer significant mechanistic insights into disease biology. Ultimately, this may identify further therapeutic vulnerabilities whilst remaining within the umbrella of precision oncology.

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