A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)


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Background: In order to facilitate implementation of precision medicine in clinical management of cancer, there is a need to harmonise and standardise the reporting and interpretation of clinically relevant genomics data.

Methods: The European Society for Medical Oncology (ESMO) Translational Research and Precision Medicine Working Group (TR and PM WG) launched a collaborative project to propose a classification system for molecular aberrations based on the evidence available supporting their value as clinical targets. A group of experts from several institutions was assembled to review available evidence, reach a consensus on grading criteria and present a classification system. This was then reviewed, amended and finally approved by the ESMO TR and PM WG and the ESMO leadership.

Results: This first version of the ESMO Scale of Clinical Actionability for molecular Targets (ESCAT) defines six levels of clinical evidence for molecular targets according to the implications for patient management: tier I, targets ready for implementation in routine clinical decisions; tier II, investigational targets that likely define a patient population that benefits from a targeted drug but additional data are needed; tier III, clinical benefit previously demonstrated in other tumour types or for similar molecular targets; tier IV, preclinical evidence of actionability; tier V, evidence supporting co-targeting approaches; and tier X, lack of evidence for actionability.

Conclusions: The ESCAT defines clinical evidence-based criteria to prioritise genomic alterations as markers to select patients for targeted therapies. This classification system aims to offer a common language for all the relevant stakeholders in cancer medicine and drug development.

Key words: precision medicine, targeted therapies, biomarkers, genomics, next-generation sequencing, classification system

Introduction

As our understanding of the cancer biology evolves, and the accessibility to tumour genomic sequencing technologies increases, genome-driven cancer treatment emerges as a promising strategy [1]. Consequently, more and more patients undergo multigene sequencing of their cancer in the hope of finding genomic alterations that could effectively be targeted with matched drugs [2].
Adjusting physician and patient expectations to clinical reality is critical for maintaining trust in clinical research and providing the best care.

A major challenge for oncologists in the clinic is to distinguish between findings that represent proven clinical value or potential value based on preliminary clinical or preclinical evidence, from hypothetical gene–drug matches and findings that are currently irrelevant for clinical practice. Almost all commercial and academic laboratories that provide multigene panel sequencing of patient tumour samples report ‘actionable’ mutations that can fall into any of the above categories. Most multigene sequencing reporting systems do not prioritise alterations, nor do they use a standardised clinical utility-based ranking system. This lack of harmonisation in terminology and utility-based ranking creates a potential threat to precision medicine since patients could be recommended ineffective drugs matched to hypothetical (i.e., clinically unproven) targets, while alterations with proved clinical value could be missed due to lack of clear prioritisation.

The European Society for Medical Oncology (ESMO) initiated a project to propose a unified framework to classify targets for precision cancer medicine based on clinical evidence of utility. The primary aim is to aid oncologists to prioritise potential targets for clinical use when receiving reports of broad gene sequencing panels. This classification system would provide a common language that could be adopted by all the cancer medicine and drug development stakeholders to place targets within their clinical context. We recognise that as evidence is generated from clinical studies, targets will move from one tier to another. Also, a given molecular alteration can be supported by different levels of evidence in different cancer types and therefore it can fall into different clinical utility classes depending on disease context.

Several institutions and organisations have proposed clinical classification systems for molecular alterations detected in cancer into different clinical utility classes depending on disease context. These classifications are only partially overlapping, with greatest overlap in the top tiers, and none of them have been broadly implemented in clinical practice. Top tier designation in each system is often based on regulatory approval status in their geographic regions that introduces bias in the context of global cancer research. In lower tiers, each schema uses different principles to weigh the evidence available and therefore different classifications may assign the same alteration into discordant clinical utility categories. The vocabulary to define utility categories are also variable from system to system making it difficult to use a common terminology across reports and studies.

Understanding these limitations, ESMO has assembled a dedicated project group within its Translational Research and Precision Medicine Working Group (TR and PM WG), including authors from some of the earlier classification schemas, to propose guiding principles for a single classification system that could be used globally.

**The ESMO Scale of Clinical Actionability for molecular Targets**

- **ESMO Scale of Clinical Actionability for molecular Targets**

  **ESCAT Tier I**: target suitable for routine use and recommend specific drug when specific molecular alteration is detected (Table 2).

  Randomised trials provide the highest level of clinical evidence in drug development, but novel trial designs may be occasionally needed to validate the clinical relevance of infrequent molecular alterations where randomised trials are difficult to conduct.

We consider a target ‘tier I-A’, if prospective, randomised clinical trial data in a given tumour type has demonstrated clinically meaningful improvement of a survival endpoint in patients with the molecular alteration treated with a matching drug. Hallmark examples include the anti-HER2 antibody, trastuzumab, for ERBB2 (HER2) amplification breast cancer [10–12] and EGFR inhibitors for non-small-cell lung cancer (NSCLC) harbouring EGFR activating mutation [13, 14].

‘Tier I-B’ targets are supported by data from prospective, non-randomised clinical trials that, while unable to provide evidence for survival improvement, have demonstrated clinically meaningful benefit as defined by the ESMO Magnitude of Clinical Benefit Scale (MCBS) 1.1 [15] in a biomarker selected sub-population. Examples of tier I-B targets include ROS1-rearrangement in NSCLC that defines eligibility for crizotinib or ceritinib therapy. Both of these compounds inhibit the ana-plastic lymphoma kinase (ALK) and previously demonstrated improved survival in patients with NSCLC harbouring ALK rearrangements in randomised clinical trials (which qualifies ALK as tier I-A target for these drugs in lung cancer) [16–18]. However, crizotinib and ceritinib also inhibit the ROS receptor tyrosine kinase (ROS1) that is rearranged in 1%–2% of NSCLC through gene fusions leading to its constitutive activation. High objective tumour response rates were demonstrated with these drugs in ROS1-rearranged NSCLC in a series of single arm studies [19, 20]. Considering the rarity of this genomic alteration, conducting a large randomised trial in a timely manner to demonstrate improved survival would not have been feasible and the large clinical benefit observed in the single-arm studies was sufficient for endorsement of routine clinical use of these drugs in this rare molecularly defined subset of lung cancer.

Targets are designated ‘tier I-C’ if clinical trials in multiple tumour types, or basket clinical trials, have demonstrated a clinically meaningful benefit for the target–drug pair with similar magnitude of benefit across the different tumour types. In this scenario, the clinical value of a target–drug match can be accepted across cancers that harbour the target abnormality. An example is larotrectinib, an inhibitor of the neurotrophic receptor tyrosine kinase (a.k.a. tropomyosine receptor kinase, TRK) family showed substantial antitumour activity in cancers of diverse histological tumour type sharing activating fusions in TRK genes [21]. Similarly, the anti-PD1 checkpoint inhibitor pembrolizumab has shown broad, histology independent activity in mismatch repair deficient cancers [22]. It is important to remember that in basket trials, the number of patients with a given cancer type are often low; therefore, the confidence intervals around the estimated benefit in small tumour subsets is broad, consequently the true drug activity remains uncertain.

- **ESCAT Tier II**: Investigational targets that likely define a patient population that benefits from a targeted drug but additional data are needed.
Acetate and steroids. While the addition of ipatasertib failed to show strong association between the presence of activating AKT1 or PTEN expression in the tumour (NCT03072238). These data may even- tually provide evidence to move this target to tier I or relegate it accordingly.

We consider a target ‘tier II-B’ if at least one prospective clinical trial demonstrated higher tumour response rates in patients with advanced prostate cancer were given the pan-AKT inhibitor ipatasertib (GDC0068) or placebo combined with abiraterone acetate and steroids. While the addition of ipatasertib failed to prolong progression-free survival in the general trial population, a retrospective analysis showed a significant reduction of radiological progression risk in the sub-group of patients presenting tumours harbouring loss of PTEN protein expression [23]. This retrospective observation has led to the design of an ongoing validation phase III trial. This randomised study is now stratifying patients based on the presence or the absence of PTEN protein expression (NCT03072238). These data may eventually provide evidence to move this target to tier I or relegate it accordingly.

We consider a target ‘tier II-B’ if at least one prospective clinical trial demonstrated higher tumour response rates in patients with a target molecular alteration but there is no definitive data available on improvement of the more important survival end points. An example includes a recently presented basket trial that showed strong association between the presence of activating

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Table 1. Comparison of previous classification schemas that assign clinical utility to molecular alterations used to select targeted therapies in cancer

<table>
<thead>
<tr>
<th>Data type and classification variable</th>
<th>Andre et al., Ann Oncol 2014</th>
<th>Van Allen et al., Nat Med 2014</th>
<th>Meric-Bernstam et al., JNCI 2015</th>
<th>Chakravarty et al., JCOPO 2017 (OncoKB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data have been generated in randomised clinical trials</td>
<td>Yes, but allow into the same level of evidence targets supported by multiple non-randomised trials</td>
<td>Does not discriminate between clinical data generated by randomised versus non-randomised trials</td>
<td>Does not discriminate between clinical data generated by randomised versus non-randomised trials</td>
<td>Does not discriminate between clinical data generated by randomised versus non-randomised trials</td>
</tr>
<tr>
<td>Data come from prospective clinical trials</td>
<td>Does not discriminate prospective versus retrospective clinical studies</td>
<td>Not specifically considered</td>
<td>Data from prospective versus retrospective study are assigned different levels of evidence</td>
<td>Not specified, refers to ‘compelling clinical data’</td>
</tr>
<tr>
<td>Regulatory approval (FDA/EMA for the drug)</td>
<td>Not specifically considered</td>
<td>FDA approval is the principal variable to assign category</td>
<td>FDA approval is the principal variable to assign category</td>
<td>FDA approval is the criteria for top evidence level (1A) assignment</td>
</tr>
<tr>
<td>Validation of the assay used for biomarker detection</td>
<td>Not specifically considered</td>
<td>Not specifically considered</td>
<td>Not specifically considered</td>
<td>Accounts for FDA recognition of the biomarker under consideration</td>
</tr>
<tr>
<td>Clinical data have been generated in same or different tumour types</td>
<td>Includes specific category IC for level I supportive data generated in a different tumour type, recommending treatment different tumour type in the context of clinical trials</td>
<td>Use different categories depending on supportive data generated in the same or different tumour types</td>
<td>Use different categories based on data generated in the same or different tumour types</td>
<td>Categories 2 and 3 are subdivided based on whether data were generated in same or different tumour types</td>
</tr>
<tr>
<td>Considers magnitude of benefit (OS, PFS, RR)</td>
<td>Not specifically considered</td>
<td>Not specifically considered</td>
<td>Not specifically considered</td>
<td>Not specifically considered</td>
</tr>
<tr>
<td>Considers preclinical data</td>
<td>Includes specific category for predictions of actionability based on preclinical data</td>
<td>Includes specific category for predictions of actionability based on preclinical data</td>
<td>Includes specific category for predictions of actionability based on preclinical data</td>
<td>Includes specific category for predictions of actionability based on preclinical data</td>
</tr>
<tr>
<td>Considers if clinical efficacy is known for the biomarker negative population</td>
<td>Yes, but effect in marker-negative group does not impact clinical recommendation</td>
<td>Not specifically considered</td>
<td>Not specifically considered</td>
<td>Not specifically considered</td>
</tr>
<tr>
<td>Other comments</td>
<td>Considers predictive versus prognostics versus diagnostic value evidence</td>
<td>Considers data coming from case reports as level 3A</td>
<td>Includes grading of evidence for resistance biomarkers</td>
<td></td>
</tr>
</tbody>
</table>
mutations in the AKT1 gene (E17K) and tumour response to the AKT inhibitor AZD5363 [24, 25]. Further trial data are now necessary to assess how this increased responsiveness translates to improved patient outcome.

In target–drug matches that we consider as tier II, further investigation in clinical trials or through prospective registries is necessary before incorporating the target–drug match to routine care.

<table>
<thead>
<tr>
<th>ESCAT evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical value class</th>
<th>Clinical implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ready for routine use</td>
<td>I: Alteration-drug match is associated with improved outcome in clinical trials</td>
<td>I-A: prospective, randomised clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival end point</td>
<td>Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)</td>
</tr>
<tr>
<td>Investigational</td>
<td>II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown</td>
<td>II-A: retrospective studies show patients with the specific alteration in a specific tumour type experience clinically meaningful benefit with matched drug compared with alteration-negative patients</td>
<td>Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumour type, but additional data are needed</td>
</tr>
<tr>
<td>Hypothetical target</td>
<td>III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration</td>
<td>III-A: clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumour type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types</td>
<td>Drug previously shown to benefit the molecularly defined subset in another tumour type (or with a different mutation in the same gene), efficacy therefore is anticipated for but not proved</td>
</tr>
<tr>
<td></td>
<td>IV: pre-clinical evidence of actionability</td>
<td>IV-A: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical in vitro or in vivo models</td>
<td>Actionability is predicted based on preclinical studies, no conclusive clinical data available</td>
</tr>
<tr>
<td>Combination development</td>
<td>V: alteration-drug match is associated with objective response, but without clinically meaningful benefit</td>
<td>V-A: prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome</td>
<td>Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation</td>
</tr>
<tr>
<td></td>
<td>X: lack of evidence for actionability</td>
<td>No evidence that the genomic alteration is therapeutically actionable</td>
<td>There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target</td>
</tr>
</tbody>
</table>
**Table 3. Most relevant databases and public data resources for interrogating tumour genomics and clinical actionability data**

<table>
<thead>
<tr>
<th>Resource</th>
<th>Declared aim</th>
<th>Focus alterations (if applicable)</th>
<th>Interface</th>
<th>Annotation process</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Genome Interpreter (CGI)</td>
<td>The CGI is a web platform dedicated to the interpretation of variants identified in patient’s tumours</td>
<td>Point mutations and structural variants</td>
<td>Browser, download, API, Interactive reports are provided as a result of analysis of a patient’s tumour</td>
<td>Semi-automated annotation and manual curation of literature. Oncologists’ review of biomarkers. In house tools</td>
<td>cancergenomeinterpreter.org</td>
</tr>
<tr>
<td>cBioPortal</td>
<td>Resource collecting alterations observed across patients’ tumours (probed at whole-exome, whole-genome or gene panel level)</td>
<td>Point mutations and structural variants</td>
<td>Browser, download, API</td>
<td>Automated annotation and analysis of tumour alterations data</td>
<td><a href="http://www.cbiportal.org/">www.cbiportal.org/</a></td>
</tr>
<tr>
<td>Catalog of somatic mutation in cancer (COSMIC)</td>
<td>Resource collecting alterations observed across patients’ tumours (probed at whole-exome, whole-genome or gene panel level) and cancer cell lines</td>
<td>Point mutations and structural variants</td>
<td>Browser, download, API</td>
<td>Automated annotation and analysis of tumour alterations data</td>
<td>cancer.sanger.ac.uk/cosmic</td>
</tr>
<tr>
<td>Clinical Interpretation of Variants in Cancer (CiVIC)</td>
<td>Clinical relevance of variants in cancer</td>
<td>Point mutations and structural variants</td>
<td>Browser and API</td>
<td>Community-driven annotation and curation. Experts review</td>
<td>civicdb.org/</td>
</tr>
<tr>
<td>Database of Curated Mutations(DoCM)</td>
<td>Database of known, disease-causing mutations with direct links to source citations</td>
<td>Point mutations (SNVs and short indels)</td>
<td>Browser, download</td>
<td>Manual curation of literature</td>
<td><a href="http://docm.info/">http://docm.info/</a></td>
</tr>
<tr>
<td>Jackson Laboratory</td>
<td>Database cataloguing cancer alterations and biomarkers</td>
<td>Point mutations and structural variants</td>
<td>Browser</td>
<td>Semi-automated annotation and manual curation of literature</td>
<td>ckb.jax.org</td>
</tr>
<tr>
<td>MyCancerGenome</td>
<td>Database of validated driver alterations in a list of cancer genes and their influence on the response to a range of therapeutic agents, with links to clinical trials</td>
<td>Point mutations and structural variants</td>
<td>Browser</td>
<td>Manual curation of literature</td>
<td><a href="http://www.mycancer">www.mycancer</a> genome.org</td>
</tr>
<tr>
<td>Precision medicine knowledgebase (PMKB)</td>
<td>Information (including clinical relevance) about cancer variants</td>
<td>Point mutations and structural variants</td>
<td>Browser</td>
<td>Community-driven annotation and curation. Review by cancer pathologists</td>
<td>pmkb.weill.cornell.edu/</td>
</tr>
<tr>
<td>OncokB</td>
<td>Information about the effects and treatment implications of specific cancer gene alterations</td>
<td>Point mutations and structural variants</td>
<td>Browser, download, API</td>
<td>Manually curated by a network of clinical fellows, research fellows, and faculty members at MSK from resources and literature</td>
<td>oncokb.org/</td>
</tr>
<tr>
<td>T-Quest</td>
<td>Open source platform to link molecular abnormalities to potential therapies</td>
<td>Point mutations and structural variants</td>
<td>Browser, download, API</td>
<td>Automated text search of clinicaltrials.gov database and public databases</td>
<td><a href="http://tquest.us/">http://tquest.us/</a></td>
</tr>
</tbody>
</table>

**ESCAT Tier III: clinical benefit previously demonstrated in other tumour types or for related molecular targets.**

‘Tier III-A’ targets include alterations that define a patient population with proven benefit from a targeting agent in a specific tumour type, but the alteration is now detected in a different, previously not studied, tumour type. Therefore, while a strong rationale exists to try the targeted therapy in these patients, there is limited or no clinical evidence for efficacy in these other tumour types. These clinical scenarios are an ideal setting for prospective studies.

Vemurafenib is a B-Raf enzyme inhibitor, and significantly extends survival of patients with metastatic melanomas that harbour the tier I-A target BRAF V600E mutation [26]. The same mutation is also present in rare instances of other cancers types,
but in contrast to the examples of tier I-C discussed above, the antitumour activity of vemurafenib in V600E mutated cancer has been shown to differ significantly from one tumour type to another. The most relevant example is the limited activity of vemurafenib in BRAF-mutated colorectal cancers [27]. Hence, identification of a BRAF V600E mutation will need to be interpreted in a tumour type-specific manner, not qualifying it broadly as a tier I-C target.

‘Tier III-B’ alterations have a predicted functional impact similar to an already studied tier I abnormality in the same gene, or in a gene with similar function, but lack sufficient supportive clinical data.

Poly(ADP-ribose) polymerase (PARP) inhibitors were tested in clinical trials in *BRCA1* or *BRCA2* loss-of-function germline mutated breast and ovarian cancers under the premise of synthetic lethality [i.e. two events that are not lethal separately (i.e. PARP inhibition and loss of BRCA function) become lethal when occur simultaneously] [28–30]. These trials demonstrated improved outcome and therefore germline *BRCA1* or *BRCA2* mutations are tier I targets in these diseases [31, 32]. Moreover, preliminary clinical data suggest antitumour activity in a subset of prostate and pancreatic cancers also carrying *BRCA1/2* loss-of-function alterations [33–36]. The *BRCA1/2* genes are members of a large functionally related gene group that mediate homologous recombination during DNA repair. For example, PALB2 (Partner and localizer of BRCA2, a.k.a. FANCN) is a protein that interacts with BRCA2, and PALB2 loss impairs DNA repair through a similar mechanism as BRCA2 loss-of-function [37]. Hence, testing PARP inhibitors in clinical trials in patients with PALB2-deficient tumours is conceptually reasonable and qualifies PALB2 loss-of-function mutations as tier III-B.

- **ESCAT Tier IV: Preclinical evidence of actionability.**

‘Tier IV-A’ targets represent potential drug targets that are only supported by preclinical evidence showing that the alteration influences drug sensitivity in *vitro* or *in vivo* cancer models. ‘Tier IV-B’ targets represent pathway alterations at different molecular levels that are predicted to alter drug sensitivity based on *in silico* bioinformatic predictions. Tier IV targets are hypothetical and are best considered as qualifying evidence for future clinical testing. They may also be appropriate for enrichment of patients in early phase clinical trials that test new molecular entities targeting the affected pathway. Patients being considered for these studies need to be carefully informed of the lack of clinical evidence and the preliminary nature of the data available for such compounds, both from the safety and efficacy perspective, the potential risks involved and the alternative therapeutic options.

- **ESCAT Tier V: Evidence of relevant antitumour activity, not resulting in clinical meaningful benefit as single treatment but supporting development of co-targeting approaches.**

Tier V targets include alterations associated with responses to a matched targeted drug that do not translate into prolonged outcome; however, these could be suitable targets for combination therapy strategies. For example, over one-third of estrogen receptor-positive, HER2-negative breast cancers have activating mutations of *PIK3CA*. Clinical trials demonstrated that targeting PI3K leads to objective responses in patients with activating *PIK3CA* mutations. However, the responses did not impact outcome [38]. This may be explained by the upregulation of compensatory pathways in response to PI3K inhibition due to complex feedback mechanisms [39]. Understanding the mechanisms of adaptation to PI3K inhibitors could further lead to test effective double or triple combinations.

- **ESCAT Tier X: Lack of evidence for actionability.**

Tier X alterations would be those for which there is no clinical or preclinical evidence supporting their hypothetical utility as therapeutic target. These alterations should not be taken into account for clinical decisions.
supporting the interpretation of variants identified in each patient’s tumour. In the clinical setting, this interpretation focuses on identifying predictive biomarkers of drug response.

Databases that collect and catalogue genomic abnormalities detected in human cancer are fundamental to accumulating evidence of the biological and clinical relevance of those findings. Some of the most prominent examples of such resources are listed in Table 3. These tools would primarily focus in annotating validated oncogenic mutations and/or accumulating evidence for variants of unknown impact. An important effort was recently launched by the Global Alliance for Genomics and Health (www.ga4gh.org) to provide standards that allow users to simultaneously query several of these data repositories.

Finally, resources that collect tumour alterations and categorise them according to correlative clinical data available as prognostic of patient outcome and/or predictive biomarkers of response to specific therapies are critical. Accurate and harmonised annotation of clinical outcome data into these repositories is still partially an unmet need. Initiatives such as the AACR Project GENIE, that provide access to cancer genomic data with clinical outcome annotation for tens of thousands of cancer patients treated at multiple institutions worldwide, aim to accelerate translation of research findings to clinical benefit [42].

Conclusions

The ESCAT aims to define clinical evidence-based criteria to prioritise cancer genomic abnormalities as markers to select patients for targeted therapies. We also offer a terminology that can be broadly applicable and help clinicians to therapeutically prioritise genomic alterations described in a tumour profiling report. Clear terminology regarding clinical utility should decrease the chance for misinterpretation of results that could lead to missed opportunities for effective treatment or over-interpretation of hypothetical targets. This clinical benefit-centred classification system offers a common language for all the actors involved in clinical cancer drug development. Its implementation in sequencing reports, tumour boards and scientific communication, can enable precise treatment decisions and facilitate discussions with patients about novel therapeutic options.

Acknowledgements

The ESCAT is a project initiated by the ESMO Translational Research and Precision Medicine Working Group. We would also like to thank the ESMO President Josep Tabernero, ESMO President-Elect Solange Peters, ESMO Past President Fortunato Ciardiello, and ESMO Educational Committee Chair Andrés Cervantes for their support in this manuscript.

Funding

The Scale of Actionability and its supporting framework for ranking genomic alterations as targets for cancer precision medicine is a project funded by European Society for Medical Oncology (no grant number applies).

Disclosure

JM is supported by a Prostate Cancer Foundation YI Award and funding from ‘la Caixa’ Foundation; PB reported research funding to institution from Bristol-Myers Squibb, Sanofi, AstraZeneca, Genentech/Roche, SERVIER, GlaxoSmithKline, Novartis, SignalChem, PTC Therapeutics, Nektar, Merck, Seattle Genetics; GT is supported by AIRC grant no. 18599; EVA provides consulting/advisory to Tango Therapeutics, Genome Medicine, Invitae, Foresite and receives research support from Novartis, BMS; CS is supported by The Francis Crick Institute (FC001169, FC001202), UK, MRC (FC001169, FC001202), the Wellcome Trust (FC001169, FC001202), Cancer Research UK (TRACERx and CRUK Cancer Immunotherapy Catalyst Network), the CRUK Lung Cancer Centre of Excellence, Stand Up 2 Cancer (SU2C), the Rosetrees and Stoneygate Trusts, NovoNordisk Foundation (16584), the NIHR BRC at University College London Hospitals, and the CRUK University College London Experimental Cancer Medicine Centre, and in part by the Breast Cancer Research Foundation, he reports grant support from Cancer Research UK, UCLH Biomedical Research Council, and Rosetrees Trust, AstraZeneca, personal fees from Boehringer Ingelheim, Novartis, Eli Lilly, Roche Ventana, GlaxoSmithKline, Pfizer, Genentech, and Celgene, stock options in GRAIL, APOGEN Biotechnologies, and EPIC Bioscience and has stock options and is co-founder of Achilles Therapeutics; LP receives clinical trial research funding from AstraZeneca, Merck, Genentech, Seattle Genetics, and honorarium for consultations from Novartis, AstraZeneca, Merck, Seattle Genetics, Almac, Immunomedics, Syndax. All remaining authors have declared no conflicts of interest.

References


