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Applicability of ESMO-MCBS and ESCAT for molecular tumor boards

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Summary Scoring systems for classifying genomic alterations (GAs) with respect to their potential targeted anticancer therapies (TTs) may be useful for rational and evidence-based decision-making, for example in molecular tumor boards. Therefore, a working group of the European Society for Medical Oncology (ESMO) has developed a comprehensive and reproducible classification score that allows the ranking of GAs and TTs according to their level of evidence and clinical relevance. This score is called the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). Another score not explicitly developed for TTs but helpful in grading novel TTs is the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). This tool was designed to objectively quantify the clinical benefit of novel approved therapies. The current review summarizes the status quo of these scores and their applicability for molecular tumor boards.

Keywords European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets · Magnitude of Clinical Benefit Scale · Genetic profiling · Targeted therapy · Genomic alteration · Next-generation sequencing

Introduction

The information about genomic alterations (GAs) involved in carcinogenesis is exploding due to increased use of next-generation sequencing (NGS) methods. Consequently, also the number of targeted cancer therapies (TTs) is growing rapidly. A total of 14 new TTs were approved annually by the European Medicine Agency (EMA) between 2015 and 2020 compared to 9 new TTs per year between 2009 and 2014 [1]. Currently 18,271 biomarkers are listed at the website MyCancerGenome.org. NGS is a fast and cost-effective tool to detect GAs, but the vast majority of GAs are of unknown clinical relevance [2] and only 18.8% of recently approved TTs are considered clinically relevant [1].

Several oncological centers have established molecular tumor boards (MTBs) to jointly discuss the relevance of GAs and the potential applicability of TTs for the individual patient. However, the amount of information is immense, and the interpretation of NGS results remains challenging. A common language for classifying GAs and TTs is needed to facilitate decision making, to identify relevant GA–TT combinations, to avoid overinterpretation of hypothetical targets and to enable fair allocation of resources.

A working group of the European Society for Medical Oncology (ESMO) has developed a comprehensive and reproducible classification score that allows the ranking of GAs and TTs according to their level of evidence and clinical relevance. This score is called the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) [3]. Another score not explicitly developed for TTs but also potentially helpful in grading novel TTs is the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) [4]. This tool was designed to objectively quantify the clinical benefit of novel approved therapies.

The current review summarizes the status quo of these scores and their applicability for MTBs.

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ESCAT Tiers			Examples
Tier-I	Clinically relevant	A: survival benefit in prospective, randomised trials	ERBB2 amplification in breast cancer, BRCA 1/2 somatic and germline mutation in breast and prostate cancer PIK3CA mutation in HR+ breast cancer BRAF mutation in melanoma
		B: clinical benefit in prospective, single-arm trials	ROS1 fusion or BRAF V600E mutation in NSCLC
		C: clinical benefit in basket trials	NTRK1 fusion in NSCLC or gastric cancer
Tier-II	Potentially clinically relevant	A: clinical benefit in retrospective trials	PIK3CA mutation in prostate cancer
		B: increased responsiveness and outcome in prospective trials	ERBB2 mutation in breast cancer
Tier-III		A: clinical benefit in other tumor entities	PIK3CA mutation in NSCLC
		B: biomarker is located in the same gene/pathway as Tier I-IIIA targets	ERBB3 mutation in breast cancer
Tier-IV	Evidence from preclinical studies	A: improved drug sensitivity in in-vitro or in-vivo models	IGF1R, MYC, SF3B1 in breast cancer
		B: actionability shown in in-silico models	CCND1 and FGFR1 amplifications in breast cancer
Tier-V		Improved objective response in prospective trials	PTEN
Tier-X	No relevance	Biomarkers are not actionable	TET2

Fig. 1 ESMO Scale for Clinical Actionability of Molecular Targets (*ESCAT*) tiers and examples. *NSCLC* non-small-cell lung cancer; *PIK3CA* phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha gene; *ERBB2* erythroblastic oncogene B; *BRCA* breast cancer gene; HR+ hormone receptor positive; *ROS1* c-ros oncogene 1; *BRAF* B-Raf proto-oncogene; *NTRK* neurotrophic tyrosine receptor kinase; *IGRF1R* insulin-like growth factor 1 receptor; *MYC* MYC proto-oncogene; *SF3B1* splicing factor 3B subunit 1 gene; *CCND1* cyclin D1 gene; *FGFR1* fibroblast growth factor receptor 1; *PTEN* phosphatase and tensin homolog gene; *TET2* tet methylcytosine dioxygenase 2 gene

ESCAT

The ESCAT was developed to systematically analyze the clinical relevance of genomic alterations (GAs) based on available scientific evidence [3]. GAs are classified into eleven tiers from tier I-A to tier X with descending clinical relevance (Fig. 1). Its aim is to identify actionable GAs of cancer patients and to facilitate decision making about the use of targeted therapies (TTs). The ESCAT score of each GA depends on the individual treatment setting and indication. For example, a *PIK3CA* hotspot mutation (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) is classified as tier I-A in breast cancer [5, 6], as tier II-A in prostate cancer and as tier III-A in non-small-cell lung cancer (NSCLC) [7]. The score depends on the current level of evidence and, thus, can change over time according to newly available data [8].

In detail, tier I GAs are clinically relevant and should be implemented in clinical practice because a clinical trial demonstrated a statistically significant and clinically relevant survival benefit of a certain GA–TT combination. The difference between tier I-A, I-B and I-C is the level of evidence; thus, the study design of the clinical trial in which the biomarker was analyzed (I-A: prospective, randomized; I-B: prospective, single-arm and I-C: basket trial).

Tier II targets are potentially relevant but require additional evidence as current knowledge was only derived from retrospective clinical trials (IIA) or from prospective clinical trials but without survival benefits (IIB: only increased response rates).

Tier III targets are also potentially relevant but require additional evidence in the certain tumor stetting. III-A GAs are relevant in other tumor entities. III-B GAs are located in the same pathway as other GAs; however, no evidence about the clinical implications of the specific GA is available.

Tier IV targets show actionability in preclinical studies (IV-A: in vitro or in vivo models, IV-B: in silico models). Tier V targets have co-targeting approaches as they improve objective response rates. Tier X targets have no evidence for actionability and shall not be regarded for treatment decisions [9].

In MTBs, the ESCAT allows to identify settings where off-label use of TTs might be justified. The level of evidence needs to be seen in context with the individual patient's setting and the individual clinical unmet need. However, to date, no publicly available overview of ESCAT scores exists. The tier of each GA must be individually researched. The following papers provide information about the ESCAT score of several GAs per indication. Most papers were published in the field of breast cancer [5, 10, 11]–, followed by lung cancer [12–14]. Further information about ESCAT tiers were published in the field of colorectal cancer [12], head and neck squamous cell carcinoma [15], pancreaticoduodenal cancer [16], metastatic salivary gland tumors [17], thyroid cancer [12], cholangiocarcinoma [12], bladder cancer [12], gastric cancer [12] and ovarian cancer [12].

ESMO-MCBS

The ESMO-MCBS was developed to assess the clinical benefit of newly approved oncological therapies (including TTs) and to distinguish novel therapies which actually provide a clinical benefit for patients versus therapies which provide only a (marginal) statistical benefit but no substantial improvement of overall sur-

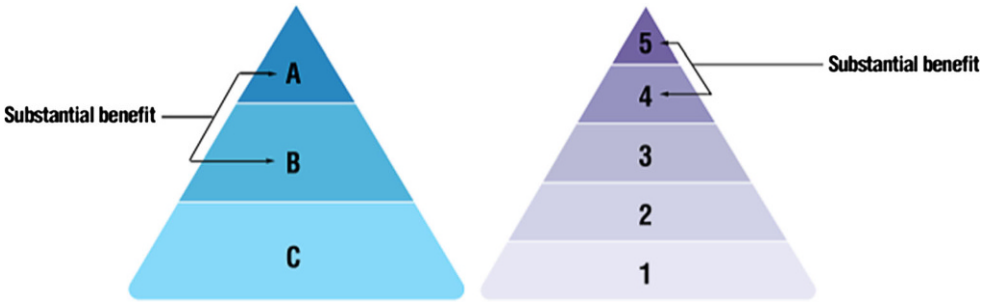

Fig. 2 ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) score in the curative vs. palliative setting

vival (OS) and/or quality of life (QoL) [4]. The ESMO-MCBS allows to systematically analyze the outcomes of clinical studies considering the predefined primary study endpoint, toxicity data and—if applicable—QoL data. While the first version of the ESMO-MCBS included only assessment of comparative studies, the revised version 1.1 allows also scoring of single arm trials. This was due to a change in the approval market with increasingly drugs in the orphan/salvage setting being approved by authorities based on non-comparative studies. Several investigations have proved the applicability of the ESMO-MCBS in clinical [18–22] and pharmacoeconomic settings [1, 23–29]. In contrary to the ESCAT, ESMO-MCBS scores of approved TTs are publicly available on the ESMO website with the relevant references attached [30]. These "ESMO-MCBS scorecards" are regularly updated by ESMO members.

As mentioned above, the score was developed for studies resulting in approval only and in MTBs commonly non-approved drugs are recommended. However, we suggest that particularly the ESMO-MCBS criteria in form 3 (which has been developed for orphan/salvage settings) can present helpful cut-offs to estimate the clinical benefit of drugs in an off-label setting if specific phase I/II data are available. To individually calculate the ESMO-MCBS score for any clinical trial (single-arm or randomized), all forms can be downloaded at the ESMO website [31]. Eight different forms exist and the choice of the right form depends on the study setting (curative or palliative), the study design (single-arm or randomized) and the primary study endpoint (OS, progression-free survival [PFS], toxicity, QoL or overall response rate [ORR]). Therapies are per common consensus considered "clinically relevant" if their ESMO-MCBS score is A or B in the curative setting (range A–C) or 5 or 4 in the palliative setting (range 5–1) (Fig. 2).

MTBs and clinical applicability of classification scores

Molecular tumor boards (MTBs) were implemented in cancer centers to support rational and evidence-driven treatment recommendations based on molecular profiling results (e.g., next-generation sequencing) [32, 33]. According to some studies, patients who receive MTB-recommended regimens (versus physician choice) have significantly longer OS and PFS [34]. Furthermore, MTBs can improve access to TTs on a regional level [35]. No legally binding requirements for MTBs exist but quality standards are recommended [36]. Treatment recommendations by MTBs should combine individual patient factors and the level of evidence of GAs and TTs.

Patients who experience tumor progression after having received all standard therapies may be offered genetic profiling. NGS may allow to identify further therapeutic options and gain additional scientific evidence. However, before offering NGS testing the realistic outcome has to be thoroughly discussed with the patient in order to avoid unrealistic hope as the majority of patients will not be identified for a targeted therapy on the basis of their NGS results. Relevant scientific literature can support the decision for which a precision panel might be useful. Furthermore, genetic testing for all patients without considering the indication reasonably would result in a considerable economic burden with questionable clinical benefit. A special expertise for interpreting genetic variants is necessary, wherefore MTBs should include a molecular pathologist or a clinical geneticist (e.g., a clinical laboratory geneticists) specialized in precision medicine, as well as the treating oncologist. Clinical molecular geneticists are helpful for discussing implications related to germline mutations. Bioethicists should be included when experimental drugs are recommended. Bioinformatic specialists may help to translate large amounts of whole-genome-/whole-exome sequencing data. Another important factor in genetic profiling is the turnaround time as patients in the relapsed/refractory setting are often in need of timely treatment decisions. The optimum turnaround time for MTBs are 16 days [33].

At the Medical University of Vienna, Division of Oncology, both the ESCAT and the ESMO-MCBS are used in tumor boards to justify off-label treatment recommendations. However, the scores always need to be seen within the specific treatment setting/available scientific evidence and can only represent one factor in the decision-making process. Machine-based classification scores of GAs are available, but only partially feasible, for example, for variants with high frequency. As most automatically scores neither distinguish the

type of GA nor the given indication, a manual workup of the GA's evidence is more or less mandatory. The ESCAT is therefore a useful guide to systematically evaluate GAs. For example, common *EGFR* mutations such as *Del19*, *T790M-exon-20* and *L858R* are classified as tier I-A versus uncommon *EGFR* mutations such as *G719X-exon-18*, *L861Q-exon-21* and are classified as tier I-B, according to ESCAT [37]. Other GA-classification scores are not transparent; thus, their tiering of GAs is not comprehensible.

Apart from the ESMO, many other academic institutions as well as industry partners have developed classification scores for GAs. Of those, the American College of Medical Genetics and Genomics (ACMG) published their first recommendations for the standardization of interpretation and reporting of sequence variations in 2000 [38] followed by a revised version published in 2007 [39] and an additionally revised version published in 2015 in collaboration with the Association for Molecular Pathology (AMP) and the College of American Pathologists [40]. In comparison to the ESCAT, the ACMG/AMP classification groups variants into the five categories "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign".

Conclusion

Patients who failed standard therapies have limited treatment options and it is very challenging to choose the right therapy for them. Genetic profiling can potentially allow identification of further treatment options in this setting, but the flood of available data requires a systematic algorithm to proceed with results. Classification scores as presented in this review can support decision making in molecular tumor boardes to make rational, evidence-based, genetically guided treatment decisions based on NGS data. The ESMO-MCBS has been widely studied and its applicability is proven. TTs with a high ESMO-MCBS score are clinically relevant [18] and the score can be used for common and rare tumor entities [19]. ESMO-MCBS scores of approved targeted therapies are published on the ESMO website. While the ESMO-MCBS was designed for approved drugs only, we suggest that it is also potentially helpful for preliminary scoring of yet unapproved drugs if applicable data are available. The score can easily be calculated individually for off-label treatment recommendations. It is furthermore a useful tool to analyze the cost effectiveness of therapies [27] as well as the percentage of FDA- and EMA-approved drugs which actually provide a clinically relevant benefit [1, 23, 24].

The ESCAT score of genomic alterations is not publicly available and has to be researched individually, but in contrast to other GA-classification scores [41–45], the ESCAT is a comprehensive and reproducible tool which regards the type of GA, the level of evidence and clinical implications. An online database with regularly updated ESCAT scores would facilitate its use in MTBs.

Take home message

While multiple factors need to be considered for treatment recommendations in MTBs, ESMO-MCBS and ESCAT represent helpful tools for reasonable decision making.

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Conflict of interest L. Wolff and B. Kiesewetter declare that they have no competing interests.

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