RANKING GENOMIC ALTERATIONS FOR PRECISION MEDICINE: ESCAT PROJECT

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Joaquin Mateo, Vall d’Hebron, Spain
DISCLOSURE SLIDE

- Research grant and/or consultant/speaker compensated to the hospital: Novartis, Astra, Pfizer, Daiichi Sankyo, Lilly, Roche

- Founder: Pegacsy
MULTIGENE SEQUENCING FOR TREATMENT DECISION

Patients → Tumor specimen → Multigene sequencing: Assess all genomic alterations (validated or not) in a single assay → Report: Interface biologist-oncologist List of genomic alterations → Treatment matched to genomic alterations
BOTTLENECKS

- Patient education
- Sample acquisition
- NGS assay
- Bionformatics
- Reporting
- Tumor board
- Match to available drug

Yield, quality, representative, heterogeneity, evolution
Analytical validation, costs, availability, scalability
Standardization, manual curation
Prioritization, Clinical Relevance (Prognosis, Predictive, Resistance)
Scalability outside academia
Drug availability
Comorbidities, other factors
OBJECTIVES

A framework to rank genomic alterations as targets for cancer precision medicine

- Advance towards **harmonized terminology** in NGS reports
- **Categorize levels of evidence** for precision medicine approaches, irrespectively of national/regional regulatory aspects
- Assist in **the interpretation of clinical trial data**
- Facilitate discussions at tumor clinical-molecular boards (**clinically-oriented**)
- **Adjust patient expectations** when discussing targeting agents
- **Assist clinicians and patients to prioritize precision medicine strategies more likely to impact positively in patient outcome**
# ESCAT: A MULTI-INSTITUTION, INTERNATIONAL EFFORT

**ESCAT Project team**
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- Fabrice Andre, France
- Lajos Pusztai, US
- Joaquin Mateo, Spain

Building from previous efforts, accounting for diversity

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**ESMO Translational Research and Precision Medicine Working Group**

**ESCAT Project Team**

**ESMO Leadership**
PRIORITIES

- Randomized clinical trial data as stratification criteria
- Efficacy (PFS/OS) + Antitumor activity (Response)
- Magnitude of benefit
- Evidence for the match in other tumor types
- Evidence in other biologically similar mutations
- Facilitating dynamic classification as new data emerges

ACTIONABILITY + CLINICAL BENEFIT

- FDA/EMEA registration status
- One Tier = One Clinical Action
- Not aiming to judge pathogenicity of mutations (biological relevance)
- Not based the drug alone but in the match
ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Publication of ESCAT in Annals of Oncology

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


Table 2. The ESCAT

<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>I. for routine use</td>
<td>I: Altered drug target is associated with improved outcomes in clinical trials</td>
<td>Experimental (evidence from clinical trials is not available)</td>
<td>Drug administered to patients with the specific molecular alteration has led to improved clinical outcomes in prospective clinical trials</td>
</tr>
<tr>
<td>I. Investigational</td>
<td>I: Altered drug target is associated with antitumour activity, but magnitude and benefit is unknown</td>
<td>Experimental (evidence from clinical trials is not available)</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>I. Hypothetical</td>
<td>I: Altered drug target is suggested to improve outcome based on clinical trial data in other tumour types or with similar molecular alteration</td>
<td>Experimental (evidence from clinical trials is not available)</td>
<td>Treatment to be considered preferably in the context of evidence collection or as a prospective clinical trial</td>
</tr>
<tr>
<td>M. Pre-clinical evidence of actionability</td>
<td>M: Evidence that the alteration is a functional driver in experimental models</td>
<td>Pre-clinical (evidence from pre-clinical models)</td>
<td>Actionability is predicted based on preclinical studies, no conclusive clinical data available</td>
</tr>
<tr>
<td>Combination development</td>
<td>V: Altered drug target is associated with objective response, but without clinically meaningful benefit</td>
<td>Pre-clinical (evidence from pre-clinical models)</td>
<td>Drug is active but does not prolong PFS or OS, probably unable to impact the treatment paradigm</td>
</tr>
<tr>
<td>Combination development</td>
<td>V: Altered drug target is associated with objective response, but without clinically meaningful benefit</td>
<td>Pre-clinical (evidence from pre-clinical models)</td>
<td>No evidence that the genomic alteration is therapeutically actionable</td>
</tr>
<tr>
<td>Combination development</td>
<td>V: Altered drug target is associated with objective response, but without clinically meaningful benefit</td>
<td>Pre-clinical (evidence from pre-clinical models)</td>
<td>There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target</td>
</tr>
</tbody>
</table>

Mateo et al, Ann Oncol. 2018 Sep 1;29(9):1895-1902.
## General use

<table>
<thead>
<tr>
<th>Tier I</th>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier I</td>
<td>Alteration-drug match is associated with improved outcome in clinical trials</td>
<td>I-A: Prospective, <strong>randomized</strong> clinical trials show the alteration-drug match in a specific tumor type results in a clinically meaningful improvement of a survival endpoint.</td>
<td>Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trials.</td>
<td>Access to the treatment should be considered standard of care for patients with <strong>EGFR mutations, ALK translocation lung cancer</strong>.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I-B: Prospective, <strong>non-randomized</strong> clinical trials show that the alteration-drug match in a specific tumor type results in clinically meaningful benefit (as defined by ESMO MCBS 1.1).</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>I-C: Clinical trials in other tumor types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumor types.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**General use**

- **EGFR mutations, ALK translocation lung cancer**
- **ROS1 translocations**
- **NTRK fusions**
<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>II: Alteration-drug match is associated with antitumor activity, but magnitude of benefit is unknown</td>
<td>II-A: Retrospective studies show patients with the specific alteration-drug match is associated with antitumor activity, but magnitude of benefit is unknown</td>
<td>Drug administered to a molecularly defined population is likely to result in clinical benefit in a given tumor type, but additional data is needed</td>
<td>Treatment to be considered preferable in the context of evidence collection either as a prospective registry or as a prospective clinical trial</td>
</tr>
</tbody>
</table>

**PTEN loss in TNBC, ESR1 mutations**

**AKT1 & ERBB2 mutations in breast cancers**

treated with a match drug, however no data currently available on survival endpoints.
## ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT)

### Tier III

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: Alteration-drug match suspected to improve outcome based on clinical trial data in other tumor 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 tumor 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 molecularly defined subset in another tumor type, or with a molecular alteration expected to cause a similar effect</td>
<td>Clinical trials to be discussed with patients</td>
</tr>
</tbody>
</table>

III-B: An alteration with expected similar biological functional impact as a match with level I/II, but without clinical data.
## ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

### Tier IV

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV: Pre-clinical evidence of actionability</td>
<td>IV-A: Evidence that the alteration or a functionally similar alteration alters 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>
<td>Treatment should only be considered in the context of early clinical trials.</td>
</tr>
<tr>
<td></td>
<td>IV-B: Actionability predicted in silico</td>
<td></td>
<td>Lack of clinical data should be stressed to patients</td>
</tr>
</tbody>
</table>
**ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)**

**Tier V**

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteration-drug match is associated with objective response, but without clinically meaningful benefit</td>
<td><strong>Prospective study show that targeted therapy is associated with objective responses, but this does not lead to improved outcome</strong></td>
<td>Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation</td>
<td>Clinical trials assessing drug combination strategies could be considered.</td>
</tr>
</tbody>
</table>
## ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

### Tier X

<table>
<thead>
<tr>
<th>Evidence tier</th>
<th>Required level of evidence</th>
<th>Clinical Class</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>X: Proven lack of clinical value</td>
<td>Evidence that the genomic alteration is not actionable</td>
<td>Conclusive clinical evidence exists for a genomic alteration not to be useful to select patients for a particular targeted agent</td>
<td>The result of the biomarker assay should not be taken into account for clinical decision</td>
</tr>
</tbody>
</table>

The lack of data demonstrating value is not the same than having data demonstrating lack of value!
ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Strengths and Limitations

- ESCAT is clinically-oriented (clinical action is the endpoint)
- Clinical trial data as the center of ESCAT
- Provides a shared vocabulary to physicians, patients, drug development stakeholders, NGS developers
- ESCAT goes beyond regulatory status, regulatory markets: creating a joint framework

ROOM FOR IMPROVEMENT:

- Easier rules to upgrade/downgrade targets
- Target vs biomarker
- Account for tumour type particularities on magnitude of benefit (PFS, OS)
- Improve assessment of combination of targets and prioritization of same-level targets
- Prognostic vs predictive, positive vs negative predictive value (response/resistance)
## EXAMPLE: METASTATIC BREAST CANCERS

<table>
<thead>
<tr>
<th>Alterations</th>
<th>Alteration considered</th>
<th>Alteration not considered</th>
<th>LOE</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERBB2 amplification</strong></td>
<td>Focal amplification (DNA copy number ≥6; size ≤10 Mb)</td>
<td>DNA gain (DNA copy number &lt;6)</td>
<td>IA</td>
<td>Romond et al. [13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fehrenbacher et al. [14]</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Di Leo et al. [15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Perou CM, Nature 2000 [16]</td>
</tr>
<tr>
<td><strong>Germ line BRCA1/2 mutations</strong></td>
<td>Truncated mutations: InDel, splice-site, nonsense (except known truncating polymorphic variant, i.e. BRCA2 K3326X)</td>
<td>Most of missense variants (classes 1–4)</td>
<td>IA</td>
<td>Robson et al. [17]</td>
</tr>
<tr>
<td></td>
<td>Rare known inactivating missense mutations (pathogenic variant class 5)</td>
<td></td>
<td></td>
<td>Litton et al. [18]</td>
</tr>
<tr>
<td><strong>PI3CA mutations</strong></td>
<td>Major hot-spot activating missense mutations (E542K, E545K/A, H1047R/V/L)</td>
<td>Other missense mutations. Truncated mutations (InDel, splice-site, nonsense)</td>
<td>IA</td>
<td>Andrè et al. [19]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hortobágyi et al. [20]</td>
</tr>
<tr>
<td><strong>Microsatellite Instability (MSI)</strong></td>
<td></td>
<td></td>
<td>IC</td>
<td>Cortes-Ciriano et al. [21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Le et al. [22]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pembrolizumab package insert [23]</td>
</tr>
<tr>
<td><strong>NTRK translocations</strong></td>
<td></td>
<td></td>
<td>IC</td>
<td>Amatu et al. [24]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drilon et al. [25]</td>
</tr>
<tr>
<td><strong>ESR1 mutations</strong></td>
<td>Hot-spot activating missense mutations (E880Q, Y537S/C/N, D538G)</td>
<td>Other missense mutations. Truncated mutations (InDel, splice-site, nonsense)</td>
<td>IIA</td>
<td>Fribbens et al. [26]</td>
</tr>
<tr>
<td><strong>PTEN loss</strong></td>
<td>Homozygous deletions. Loss-of-function mutations: truncated mutations and known inactivating missense mutations (Ex R130Q/G)</td>
<td>Other missense mutations. Truncated mutations (InDel, splice-site, nonsense)</td>
<td>IIA</td>
<td>Schmid et al. [27]</td>
</tr>
<tr>
<td><strong>AKT1 mutations</strong></td>
<td>E17K</td>
<td>Other mutations</td>
<td>IIB</td>
<td>Hyman et al. [28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Emma Dean et al. [29]</td>
</tr>
<tr>
<td><strong>ERBB2 mutations</strong></td>
<td>Hot-spot activating missense mutations (e.g. S310F/Y, L755S, V777L)</td>
<td>Not hot-spot missense mutations. Truncated mutations (InDel, splice-site, nonsense)</td>
<td>IIB</td>
<td>Hyman et al. [30]</td>
</tr>
<tr>
<td></td>
<td>In-frame insertion exon 20 (Ex : Y777_A775dup)</td>
<td></td>
<td></td>
<td>Ma et al. [31]</td>
</tr>
</tbody>
</table>

Number to test to get benefit: 20 (5% benefit)
Number to test to get drug access: 2 (50% benefit)
FUTURE USE OF ESCAT

Implementation in Clinical Practice

- Integration with public and private knowledge bases
- Should ESCAT be a classification system (educational/informative) or a medical decision-assistance tool (medical device)
- Better definition of the level of evidence derived from basket trials and prospective registries
- Do we need different ranking system to assess level of evidence for resistance biomarkers?
- How do we integrate emerging data? ESCAT needs to be an alive system.
- How do we seek feedback from end users and implements improvements.
TAKE HOME MESSAGES

- The advent of precision medicine and NGS technologies opens enormous possibilities, but also requires of adapting our medical decision making process to integrate genomics data

- Genomics data adds one more layer into the complex decision making process, does not replace other components

- In order to avoid outcome disparities and inequalities, we need tools to facilitate interpretation of NGS data and scalability of precision medicine approaches to community practice

- ESCAT provides an harmonized vocabulary, based on clinical evidence, to estimate the clinical relevance of genomic findings

- We need to work together with different stakeholders so this tool improves clinical practice
NGS REPORTS:

CLINICAL DECISION SUPPORTING SYSTEMS (DEVICE)

OR

MOLECULAR BOARDS RUN BY EXPERTS WHO USE RANKING SYSTEMS AND DATABASE?
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