RANKING GENOMIC ALTERATIONS FOR PRECISION MEDICINE: ESCAT PROJECT

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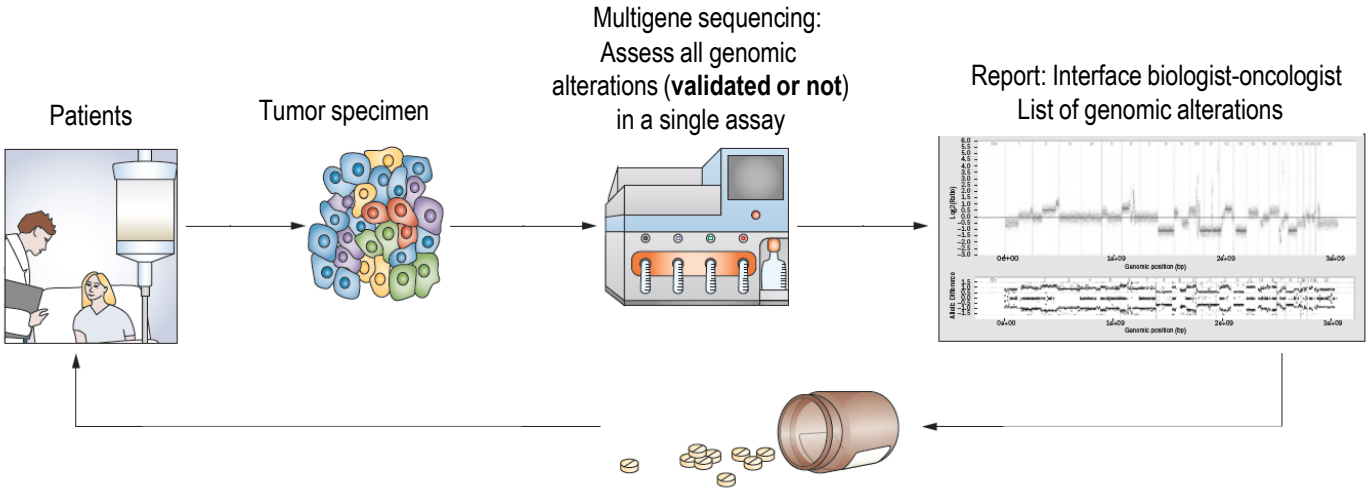
DISCLOSURE SLIDE

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

- Founder: Pegacsy

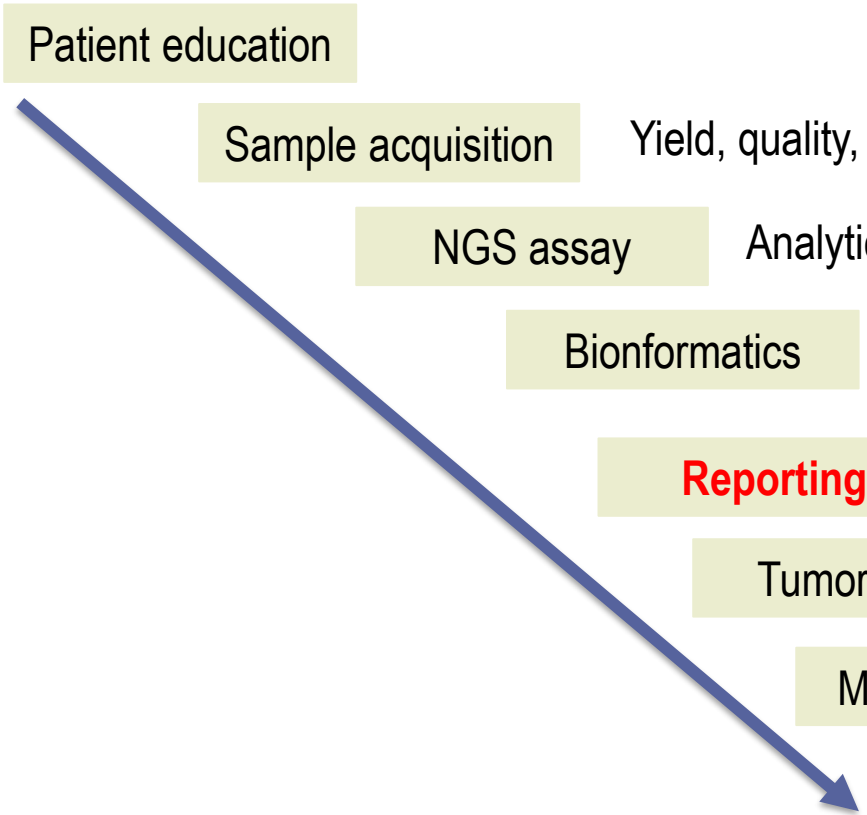
MULTIGENE SEQUENCING FOR TREATMENT DECISION



Precision medicine for metastatic breast cancer—limitations and solutions

Monica Arnedos, Cecile Vicier, Sherene Loi, Celine Lefebvre, Stefan Michiels, Herve Bonnefoi and Fabrice Andre

BOTTLENECKS



Patient education

Sample acquisition — Yield, quality, representative, heterogeneity, evolution

NGS assay — Analytical validation, costs, availability, scalability

Bionformatics — Standardization, manual curation

Reporting — **Prioritization, Clinical Relevance (Prognosis, Predictive, Resistance)**

Tumor board — **Scalability outside academia**

Match to available drug — 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

- Debyani Chakravarty, US
- Rodrigo Dienstmann, Spain
- Svetlana Jezdic, ESMO
- Abel Gonzalez Perez, Spain
- Nuria Lopez Bigas, Spain
- Charlotte KY Ng, Switzerland
- Philippe L Bedard, Canada
- Giampaolo Tortora, Italy
- Jean-Yves Douillard, ESMO
- Eli Van Allen, US
- Nikki Schultz, US
- Charles Swanton, UK
- Fabrice Andre, France
- Lajos Pusztai, US
- Joaquin Mateo, Spain

Building from previous efforts, accounting for diverstity

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

- 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

ACTIONABILITY + CLINICAL BENEFIT

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)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J.-Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12*] & L. Pusztai[13]

Mateo et al, Ann Oncol. 2018 Sep 1;29(9):1895-1902.
doi: 10.1093/annonc/mdy263.

Table 2. The ESCAT

	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcome in clinical trials	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 I-B: prospective, non-randomised clinical trials show that the alteration-drug match in a specific tumour type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1 I-C: clinical trials across tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumour types	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial(s)	Access to the treatment should be considered standard of care
Investigational	II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	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 II-B: prospective clinical trial(s) show the alteration-drug match in a specific tumour type results in increased responsiveness when treated with a matched drug, however, no data currently available on survival end points	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	Treatment to be considered 'preferable' in the context of evidence collection either as a prospective registry or as a prospective clinical trial
Hypothetical target	III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration	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 III-B: an alteration that has a similar predicted functional impact as an already studied tier I abnormality in the same gene or pathway, but does not have associated supportive clinical data	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	Clinical trials to be discussed with patients
	IV: pre-clinical evidence of actionability	IV-A: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical *in vitro* or *in vivo* models IV-B: actionability predicted *in silco*	Actionability is predicted based on preclinical studies, no conclusive clinical data available	Treatment should 'only be considered' in the context of early clinical trials. Lack of clinical data should be stressed to patients
Combination development	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcome	Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation	Clinical trials assessing drug combination strategies could be considered
	X: lack of evidence for actionability	No evidence that the genomic alteration is therapeutically actionable	There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target	The finding should not be taken into account for clinical decision

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier I

	Evidence tier	Required level of evidence	Clinical Class	Clinical Implication
General use	I: Alteration-drug match is associated with improved outcome in clinical trials	I-A: Prospective, <u>randomized</u> clinical trials **EGFR mutations, ALK translocation lung cancer** improvement of a survival endpoint. I-B: Prospective, <u>non-randomized</u> clinical trials show that **ROS1 translocations** in a specific tum… …nically meaningful benefit (as defined by ESMO MCBS 1.1) I-C: Clinical trials in other tumour types or basket clinical tr… …nefit associated with **NTRK fusions** …match, with similar benefit observed <u>across tumor types</u>	Drug administered to … the … …cular alteration has led to improved clinical outcome in prospective clinical trial	**Access to the treatment should be considered standard of care**

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier II

	Evidence tier	Required level of evidence	Clinical Class	Clinical Implication
Investigational	II: Alteration-drug match is associated with antitumor activity, but magnitude of benefit is unknown	II-A: Retrospective studies show patients with the specific alteration experience clinically meaningful benefit with matched drug compared to alteration-negative patients II-B: Prospective clinical trial(s) show the alteration-drug match in a specific tumor type results in <u>treated with a match drug</u>, however no data currently available on survival endpoints.	Drug administered to a molecularly defined population is likely to result in clinical benefit in a given tumor type, but additional data is needed	**Treatment to be considered preferable in the context of evidence collection either as a prospective registry or as a prospective clinical trial**

PTEN loss in TNBC, ESR1 mutations

AKT1 & ERBB2 mutations in breast cancers

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier III

	Evidence tier	Required level of evidence	Clinical Class	Clinical Implication
Hypothetical	III: Alteration-drug match suspected to improve outcome based on clinical trial data in other tumor type(s) or with similar molecular alteration	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 III-B: An alteration with expected similar biological functional impact as a match with level I/II , but without clinical data.	Drug, previously shown to benefit molecularly defined subset in another tumor type, or with a molecular alteration expected to cause a similar effect	Clinical trials to be discussed with patients

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier IV

	Evidence tier	Required level of evidence	Clinical Class	Clinical Implication
Hypothetical	IV: Pre-clinical evidence of actionability	IV-A: Evidence that the alteration or a functionally similar alteration alters drug sensitivity in preclinical in-vitro or in-vivo models. IV-B: Actionability predicted in silico	Actionability is predicted based on preclinical studies, no conclusive clinical data available	Treatment should only be considered in the context of **early clinical trials.** **Lack of clinical data should be stressed to patients**

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier V

	Evidence tier	Required level of evidence	Clinical Class	Clinical Implication
Comb Develop	V: Alteration-drug match is associated with objective response, but without clinically meaningful benefit	**Prospective study show that targeted therapy is associated with objective responses, but this does not lead to improved outcome**	Drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation	**Clinical trials assessing drug combination strategies could be considered.**

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier X

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

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

Alterations	Alteration considered	Alteration not considered	LOE	References
ERBB2 amplification	Focal amplification (DNA copy number ≥6; size ≤10 Mb)	DNA gain (DNA copy number <6)	IA	Romond et al. [13] Fehrenbacher et al. [14] Di Leo et al. [15] Perou CM, Nature 2000 [16]
Germline *BRCA1/2* mutations	Truncated mutations: InDel, splice-site, non-sense (except known truncating poly-morphic variant, i.e. *BRCA2* K3326X). Rare known inactivating missense mutations (pathogenic variant class 5)	Most of missense variants (classes 1–4)	IA	Robson et al. [17] Litton et al. [18]
PIK3CA mutations	Major hot-spot activating missense mutations (E542K, E545K/A, H1047R/L)	Other missense mutations. Truncated mutations (InDel, splice-site, nonsense)	IA	Andre et al. [19] Hortobagyi et al. [20]
Microsatellite instability (MSI)			IC	Cortes-Ciriano et al. [21] Le et al. [22] Pembrolizumab package insert [23]
NTRK translocations			IC	Amatu et al. [24] Drilon et al. [25]
ESR1 mutations	Hot-spot activating missense mutations (E380Q, Y537S/C/N, D538G)	Other missense mutations. Truncated mutations (InDel, splice-site, nonsense)	IIA	Fribbens et al. [26]
PTEN loss	Homozygous deletions. Loss-of-function mutations: truncated mutations and known inactivating missense mutations (Ex: R130Q/G)	Other missense mutations	IIA	Schmid et al. [27]
AKT1 mutations	E17K	Other mutations	IIB	Hyman et al. [28] Emma Dean et al. [29]
ERBB2 mutations	Hot-spot activating missense mutations (e.g. S310F/Y, L755S, V777L) In-frame insertion exon 20 (Ex : Y772_A775dup)	Not hot-spot missense mutations. Truncated mutations (InDel, splice-site, nonsense)	IIB	Hyman et al. [30] Ma et al. [31]

Number to test to get benefit: 20 (5% benefit)
Number to test to get drug access: 2 (50% benefit)

Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

R. Condorelli[1,2], F. Mosele[1*], B. Verret[1], T. Bachelot[3], P. L. Bedard[4], J. Cortes[5], D. M. Hyman[6], D. Juric[7], I. Krop[8], I. Bieche[9], C. Saura[10], C. Sotiriou[11], F. Cardoso[12], S. Loibl[13], F. Andre[1] & N. C. Turner[14]

Academic Institutions with NGS/PM programs

Pharmaceutical industry

Precision Medicine WG

Patient advocacy

NGS/diagnostic laboratories

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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Jean-Yves Douillard