ESMO ADVANCED COURSE ON NTRK GENE FUSION:

The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

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Barcelona, October 2019

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DISCLOSURE OF INTEREST

- I have served as paid advisor for AstraZeneca, Roche, Amgen, Janssen
- I have participated at symposiums sponsored by Janssen, Astellas, AstraZeneca.
- I have received research funds from AstraZeneca

STANDARDIZING LANGUAGE

Precision medicine (preferred term)/personalised medicine. A healthcare approach with the primary aim of identifying which interventions are likely to be of most benefit to which patients based upon the features of the individual and their disease. In cancer, the term usually refers to the use of therapeutics that are expected to confer benefit to a subset of patients whose cancer displays specific molecular or cellular features (most commonly genomic changes and gene or protein expression patterns). Nevertheless, the term also includes the use of prognostic markers, predictors of toxicities and any parameter such as environmental and lifestyle factors that leads to treatment tailoring. Characterisation approaches in the future are expected to encompass a wider range of technologies such as functional imaging.

ence for this newer term. The first was proposed by the National Research Council that suggested that the term 'personalised' could be 'misinterpreted to imply that treatments and preventions are being developed uniquely for each individual' [7]. A sec-

The European Society for Medical Oncology (ESMO) Precision Medicine Glossary

L. R. Yates[1], J. Seoane[2,3], C. Le Tourneau[4,5], L. L. Siu[6], R. Marais[7], S. Michiels[8,9], J. C. Soria[10], P. Campbell[11], N. Normanno[12], A. Scarpa[13], J. S. Reis-Filho[14], J. Rodon[15], C. Swanton[16] & F. Andre[10]*

SEEKING PERSONALIZED OR PRECISION MEDICINE

- Knowing more about the tumor
  - Genomics – molecular stratification of prostate cancer
  - Clonal evolution
  - Precision Imaging

- Knowing more about the patient
  - Social, personal circumstances
  - Comorbidities
  - Expectations, fears

PERSONALIZED MEDICINE is not a new concept, we are just trying to **deliver** it better by adding more variables (PRECISION)

ESMO PRECISION MEDICINE WORKING GROUP

ESMO members:
Interrogated via surveys

Committee: 18 members
+ two ESMO officers

Define the needs and transform them into projects

11 Projects of recommendations
200 experts (academics, regulatory agencies)

XX e- , v-learnings

MAP conference
400 attendees

Dissemination: ESMO Annual meeting, MAP, Annals of Oncology, ESMO website

AIM OF DEVELOPING NGS TOOLS: IMPROVING PATIENT CARE

- Advances in NGS technology need to be paired by policies to favor implementation in clinical practice: SCALABILITY
- Awareness + Education
- Access to technology could be (potentially) resolved by outsourcing resorts, but interpretation of medical tests is at the core of the physician-patient relationship
- We should prevent NGS becoming a source of health disparity:
  - Access to technology
  - **Expertise to implement it**

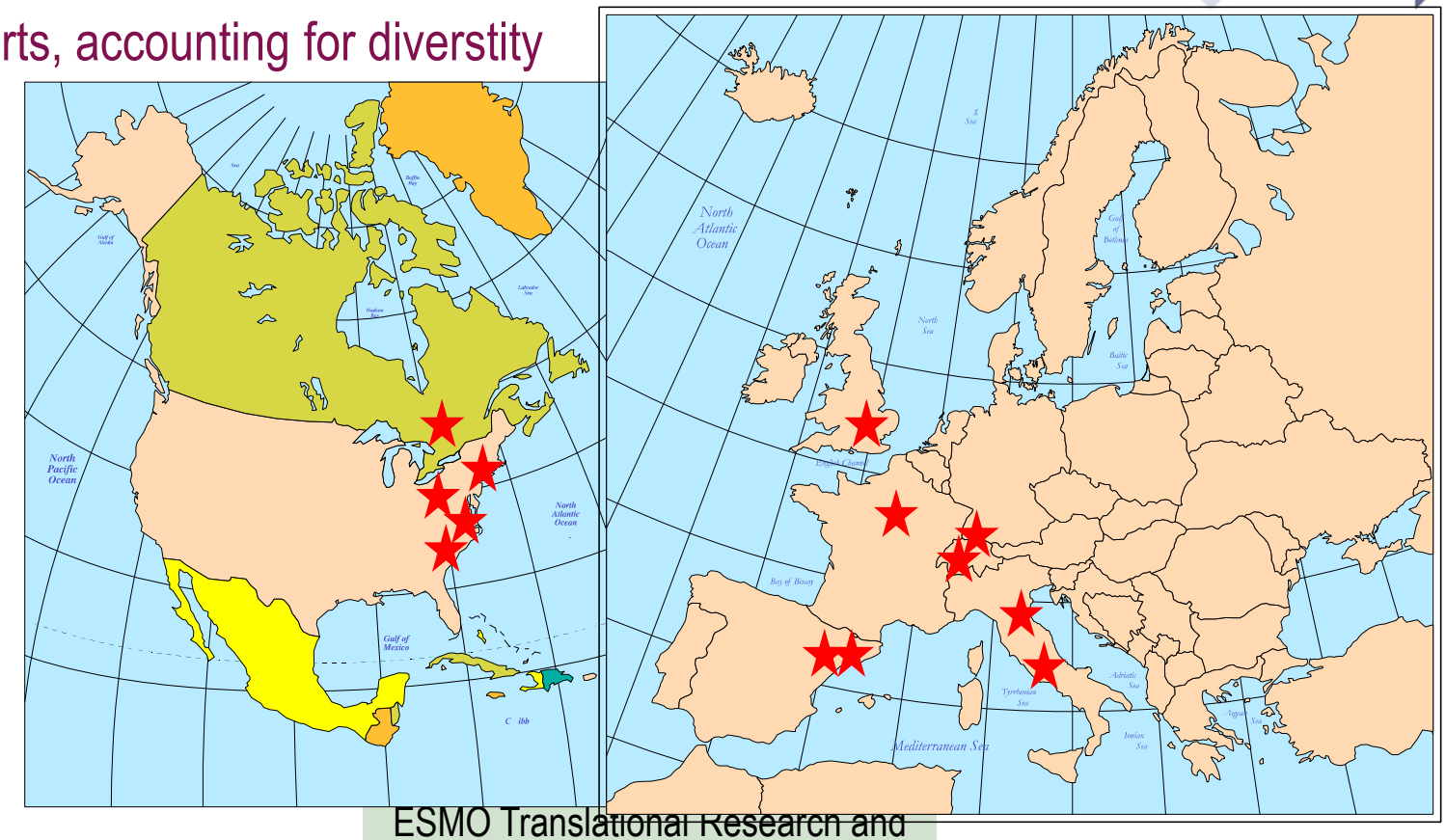
ESMO

ESCAT: A MULTI-INSTITUTION, INTERNATIONAL EFFORT

Building from previous efforts, accounting for diverstity

ESCAT Project team

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



ESMO Translational Research and Precision Medicine Working Group

ESCAT Project Team

ESMO Leadership

BARRIERS FOR IMPLEMENTATION OF GENOMICS INTO ROUTINE CLINICAL PRACTICE

DISEASE-SPECIFIC

- Tumor evolution
- Spatial heterogeneity
- Difficult to access metastatic biopsies
- Predominance of loss-of-function vs oncogenic events
- Small biopsies, fragmented DNA

ASSAYS

- Analytical validation
- Clinical qualification
- Bioinformatics

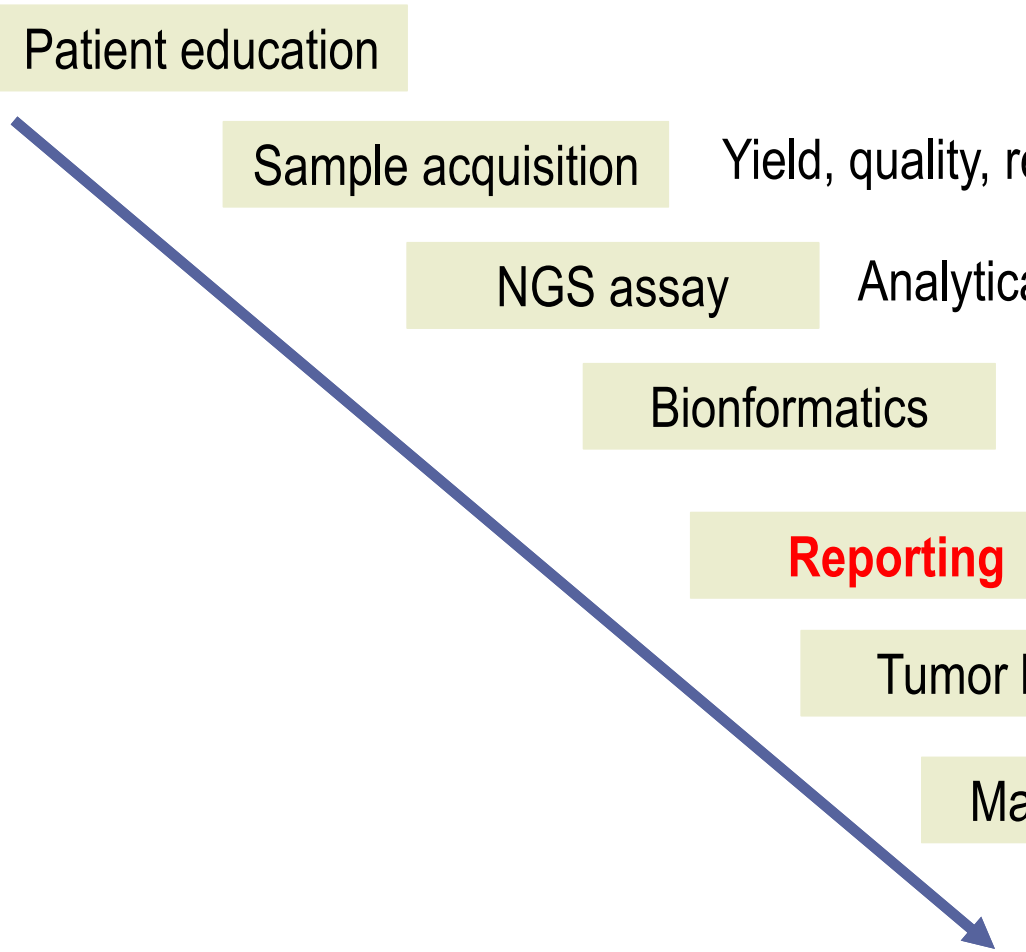
DATA INTERPRETATION

- **Lack of standardized interpretation systems for somatic variants**
- **New variants discovery**
- **Data sharing**
- **Lack of expertise at tumor boards**

TECHNOLOGY ACCESS

- Inequalities in healthcare access
- Financial toxicity (insurances)
- Test for individual biomarkers vs multiplexed profiling

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

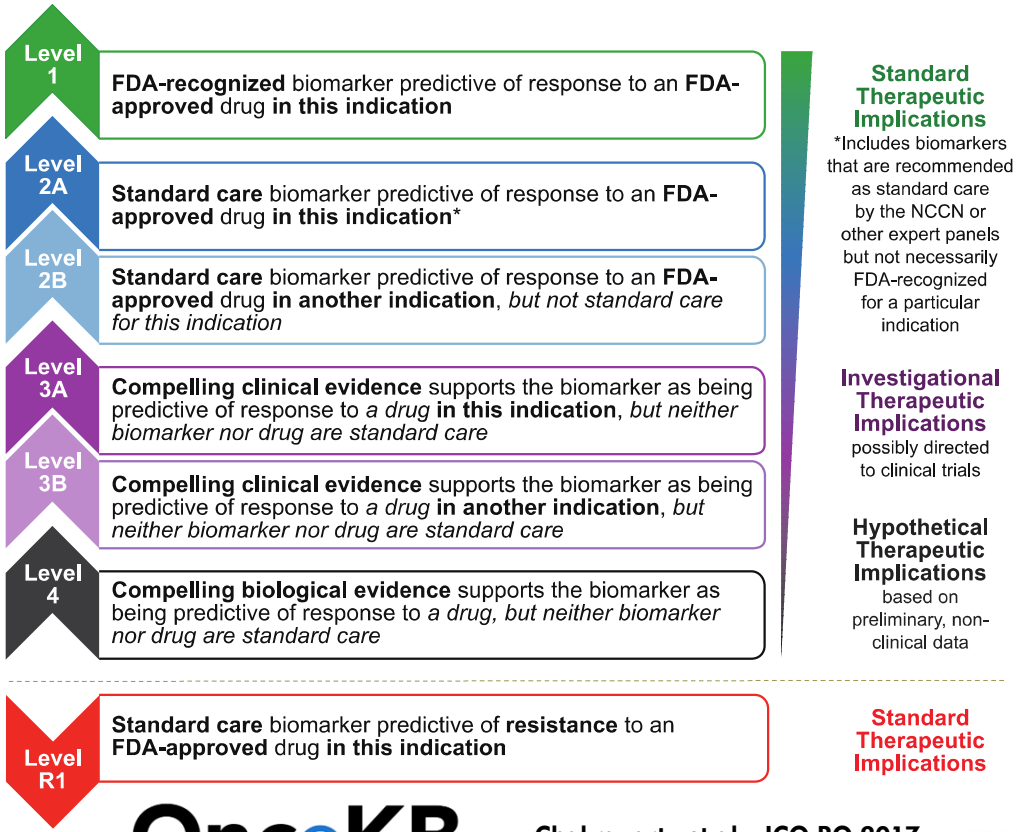
- **Assist clinicians and patients to prioritize precision medicine strategies more likely to impact positively in patient outcome**

PRIOR CLASSIFICATION SYSTEMS

Why do we need another one?

CATEGORY:	LEVEL A	LEVEL B	LEVEL C	LEVEL D	LEVEL E
Predictive – FDA-approved therapies	There is a **validated association** between this alteration and response/resistance to this agent ***for this indication***	There is **limited clinical evidence** (early or conflicting data) for an association between this alteration and response/resistance to this agent ***in this tumor type***	There is **clinical evidence** for an association between this alteration and response/resistance to this agent in ***another tumor type ONLY***	There is **preclinical evidence** for an association between this alteration and response/resistance to this agent	There is an **inferential association** between this alteration and response/resistance to this agent
Predictive – Therapies in clinical trials	This alteration is used or has been used as an **eligibility criterion** for clinical trials of this agent or class of agents	There is **limited clinical evidence** (early or conflicting data) for an association between this alteration and response/resistance to this agent or class of agents ***in this tumor type***	There is **clinical evidence** for an association between this alteration and response/resistance to this agent or class of agents in ***another tumor type ONLY***	There is **preclinical evidence** for an association between this alteration and response/resistance to this agent or class of agents	There is a **inferential association** between this alteration and response/resistance to this agent or class of agents
Prognostic	There is a **validated association** between this alteration and prognosis in this tumor type	There is **limited evidence** for an association between this alteration and prognosis in this tumor type			
Diagnostic	There is a **validated association** between this alteration and a diagnosis	There is **limited evidence** for an association between this alteration and a diagnosis			

Van Allen et al, Nat Med 2014



OncoKB

Chakravarty et al., JCO PO 2017

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PRIOR CLASSIFICATION SYSTEMS

Why do we need another one?

Level of evidence	A	B	C	Clinical implications
I: Molecular alteration validated in several robust early phase trials or at least one phase III randomized trials	Alteration validated in the disease under consideration, targeted therapies have shown to be uneffective in patients who are lacking the genomic alteration	No evidence that the therapy does not work in the absence of the molecular alteration	Level I molecular alteration, but not in the disease under consideration	A/B: Patients must be treated with the targeted therapy C: Patients should be considered for clinical trials
II: Efficacy of targeting molecular alteration suggested in single and underpowered phase I/II trials	Alteration validated in the disease under consideration, targeted therapies have shown to be ineffective in patients who are lacking the genomic alteration	No evidence that the therapy does not work in the absence of the molecular alteration	Level I molecular alteration, but not in the disease under consideration or anecdotal evidence of response to targeting molecular alteration in single patient case reports	Patients should be considered for clinical trials testing the targeted therapy
III: Target suggested by preclinical studies	Preclinical studies include human samples, cell lines and animal models	Preclinical studies that lack either cell lines or animal models	NA	Inclusion in clinical trials is optional
IV: Target predicted but lack of clinical or preclinical data	Genomic alteration is a known cancer-related gene	Genomic alteration is not known as cancer-related gene	NA	Inclusion in clinical trials is optional

Different clinical attitude within same tier

Same recommendation for different tiers

Andre et al, Ann Oncol 2014

LEVERAGE FOR ESCAT: ROOM FOR IMPROVEMENT

Why do we need another one?

- 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

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Publication of ESCAT in Annals of Oncology

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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 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
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)

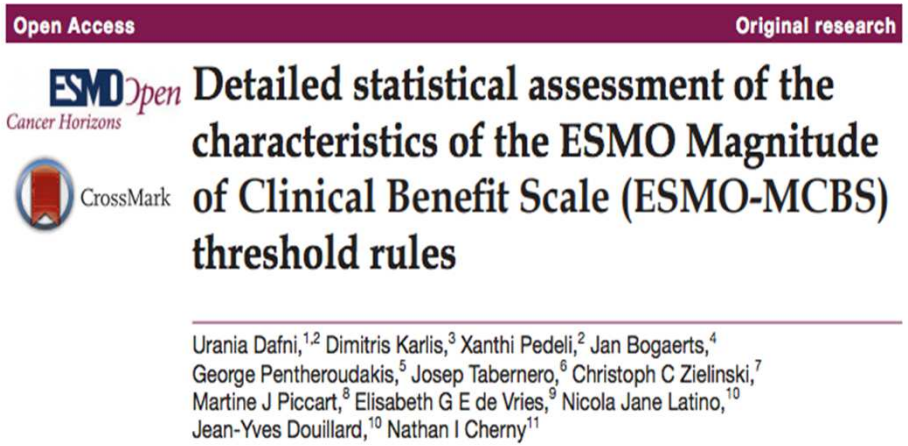
Tier I

	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, randomized clinical trials show the alteration-drug match in a specific tumour type results in a clinically meaningful improvement of a survival endpoint. I-B: Prospective, non-randomized 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 in other tumour types or basket clinical trials show clinical benefit associated with the alteration-drug match, with similar benefit observed across tumor types	Drug administered to patients with the specific molecular alteration has led to improved clinical outcome in prospective clinical trial	**Access to the treatment should be considered standard of care**

ESMO MAGNITUDE OF CLINICAL BENEFIT SCALE (ESMO-MCBS)

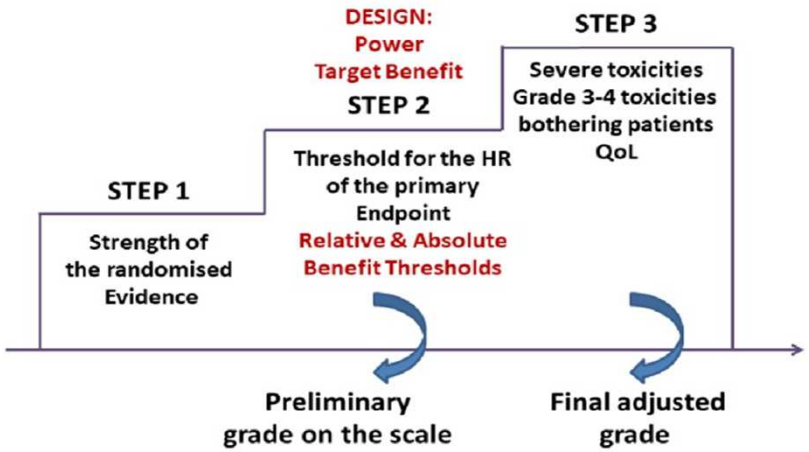
- AIM: to provide a validated and reproducible tool to assess the magnitude of clinical benefit from new cancer therapies

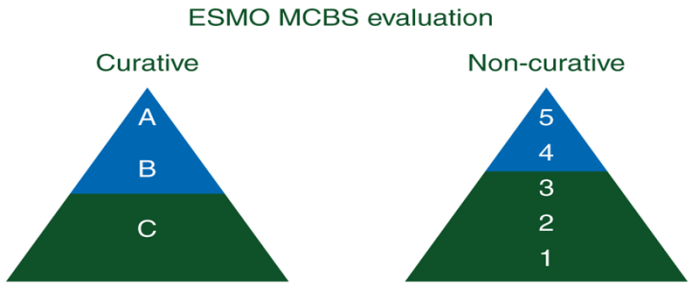
  - Integrate both relative and absolute benefit
    - Considering the LL95%CI rule aims to penalize wide CI : small trials
    - Considering the mean absolute benefit aims to penalize trials that are so big that detect non-clinically relevant differences
  - Adjust clinical relevance of benefit based on prognosis
  - Impact of PFS/OS in different tumour types
  - Integrate QOL data into evaluation



ESMO MAGNITUDE OF CLINICAL BENEFIT SCALE (ESMO-MCBS)

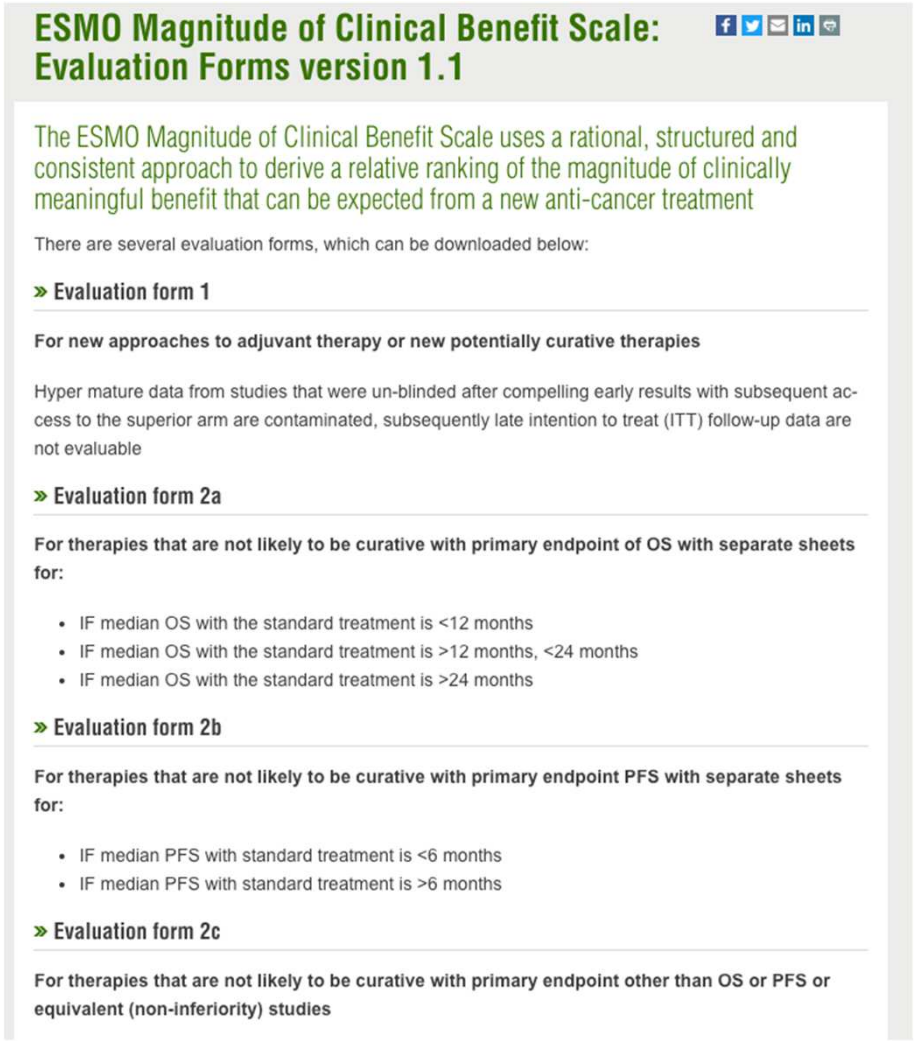
Maximal preliminary scores
Treatments with curative intent (form 1)
>5% improvement of survival at ≥3-year follow-up
Improvements in DFS alone HR <0.60 (primary end point) in studies without mature survival data
Treatments with non-curative intent (form 2)
Primary outcome OS (form 2a)
Control ≤12 months
HR ≤0.65 *AND* gain ≥3 months *OR*
Increase *in* 2-year survival alone ≥10%
Control >12 months
HR ≤0.70 *AND* gain ≥5 months *OR*
Increase *in* 3-year survival alone ≥10%
Primary outcome PFS (form 2b)
Control ≤6 months
HR ≤0.65 *AND* gain ≥1.5 months
Control >6 months
HR ≤0.65 *AND* gain ≥3 months





Curative-Evaluation form 1: for new approaches to adjuvant therapy or new potentially curative therapies

Non-curative-Evaluation forms 2a, b or c: for therapies that are not likely to be curative



ESMO Magnitude of Clinical Benefit Scale: Evaluation Forms version 1.1

The ESMO Magnitude of Clinical Benefit Scale uses a rational, structured and consistent approach to derive a relative ranking of the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment

There are several evaluation forms, which can be downloaded below:

» Evaluation form 1

For new approaches to adjuvant therapy or new potentially curative therapies

Hyper mature data from studies that were un-blinded after compelling early results with subsequent access to the superior arm are contaminated, subsequently late intention to treat (ITT) follow-up data are not evaluable

» Evaluation form 2a

For therapies that are not likely to be curative with primary endpoint of OS with separate sheets for:

- IF median OS with the standard treatment is <12 months
- IF median OS with the standard treatment is >12 months, <24 months
- IF median OS with the standard treatment is >24 months

» Evaluation form 2b

For therapies that are not likely to be curative with primary endpoint PFS with separate sheets for:

- IF median PFS with standard treatment is <6 months
- IF median PFS with standard treatment is >6 months

» Evaluation form 2c

For therapies that are not likely to be curative with primary endpoint other than OS or PFS or equivalent (non-inferiority) studies

https://www.esmo.org/Guidelines/ESMO-MCBS/Scale-Evaluation-Forms-v1.0-v1.1/Scale-Evaluation-Forms-v1.1

NTRK FUSIONS – ESCAT TIER I CLASSIFICATION

- High prevalence in very rare cancers; conducting phase III trials is not feasible
- Very low prevalence in common cancers
- Similar level of antitumor activity observed across tumour types in basket trials
- Durability of responses (OS is difficult to evaluate in non-randomized trials)

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

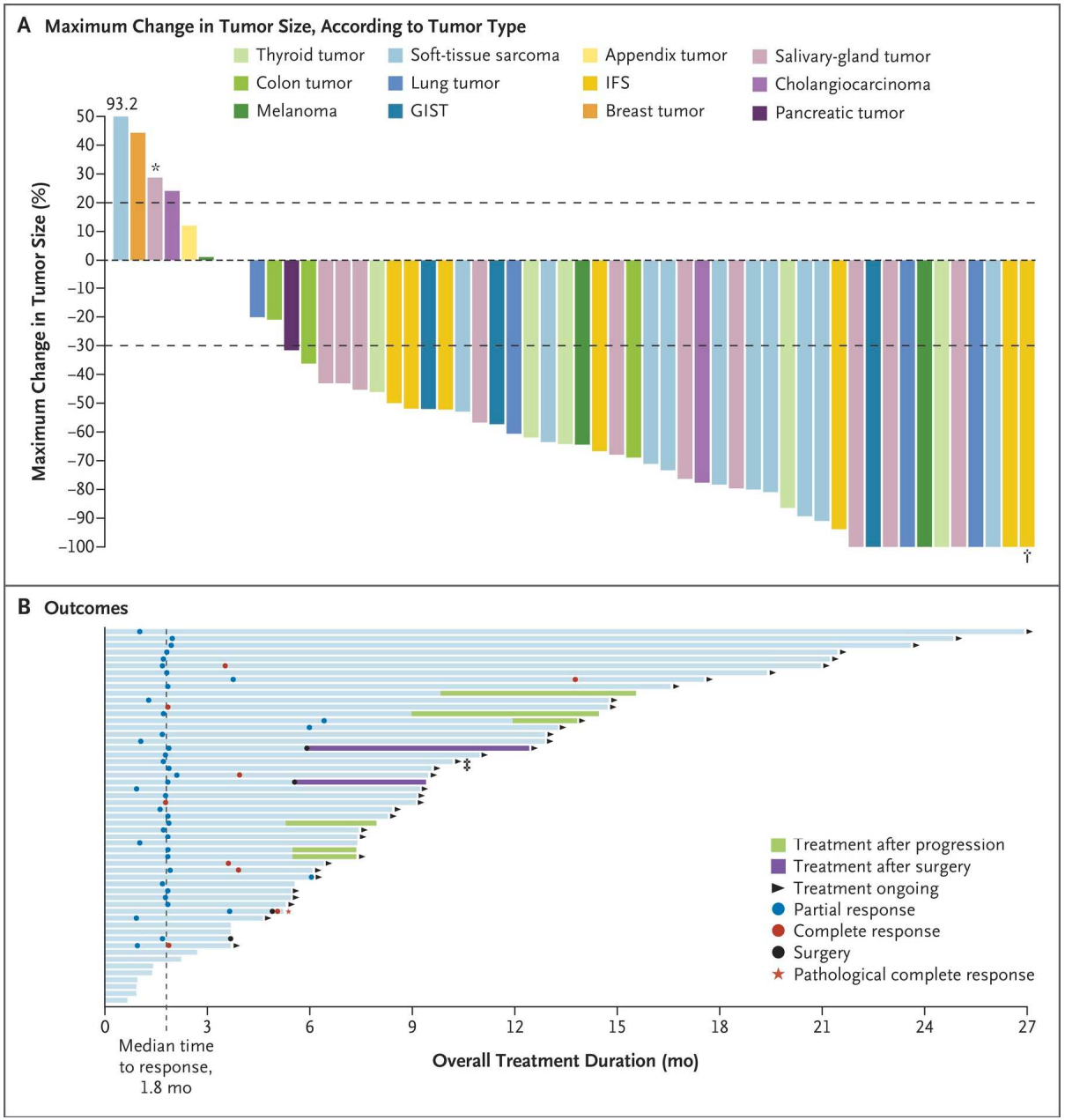
Tier II

	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 in a specific tumor type 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 increased responsiveness when treated with a match drug, however no data currently available on survival endpoints.	Drug administered to a molecularly defined patient 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**

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Tier III

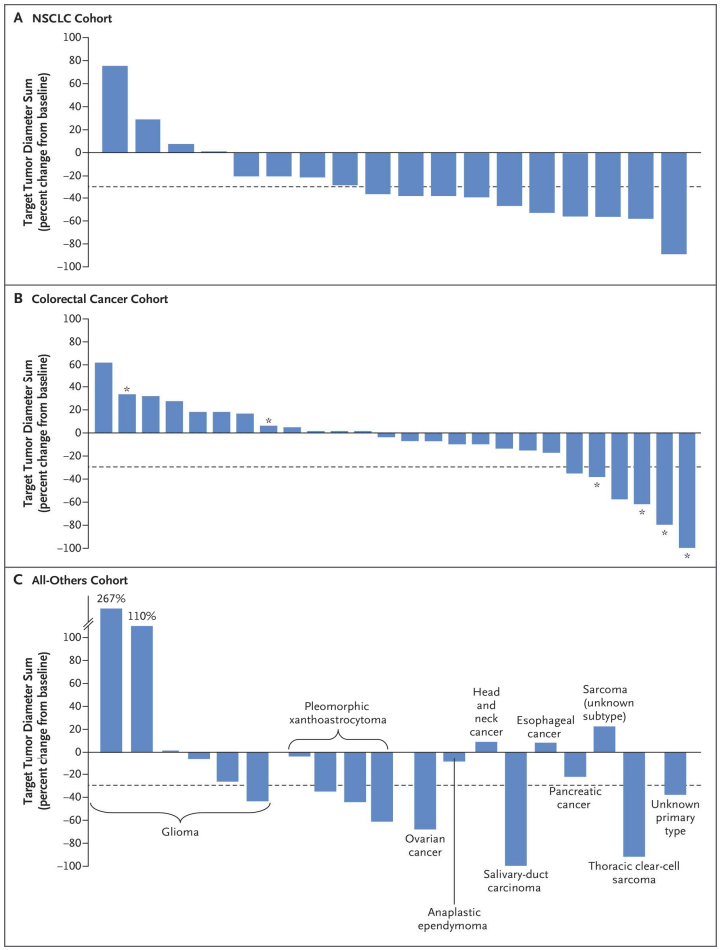
	Evidence tier	Required level of evidence	Clinical Class	Clinical Implication
Hypothetical	III: Alteration-drug match suspected to improve outcome based on clinical trial data in other tumor type(s) or with similar molecular alteration	III-A: Clinical benefit demonstrated in patients with the specific 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



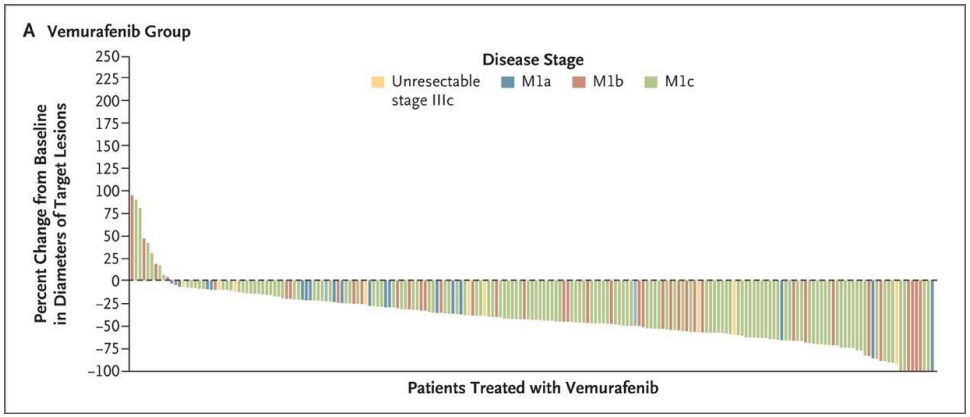
Larotrectinib

Drilon et al, NEJM 2018

TIER III-A AND BASKET TRIALS: BRAF INHIBITORS EXAMPLE

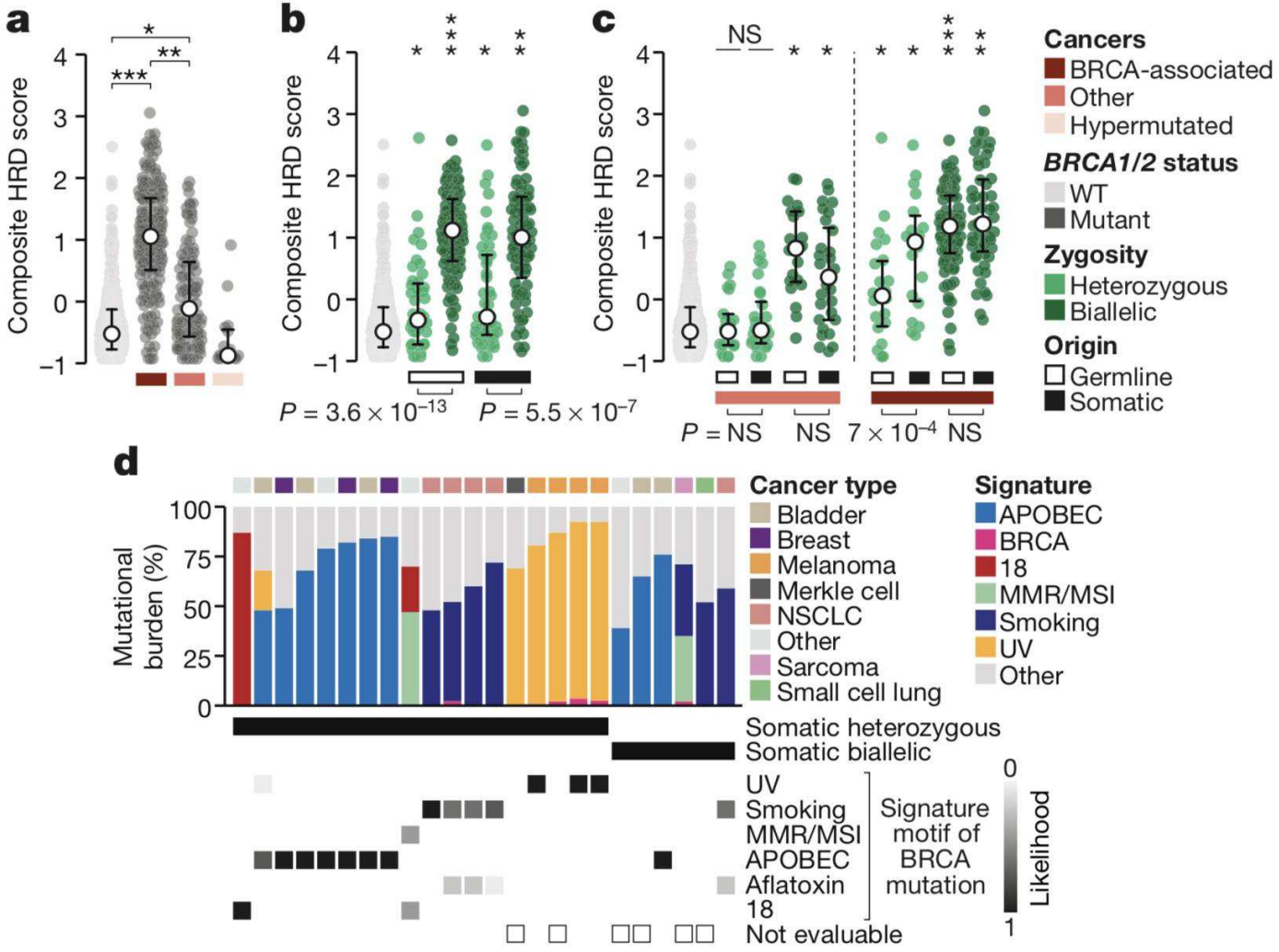


Hyman et al, NEJM 2015



Melanoman
Chapman et al, NEJM 2011

TIER III-A AND BASKET TRIALS: PARP INHIBITORS EXAMPLE



Jonsson et al, Nature 2019

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!

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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 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
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	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)

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)

ESMO SCALE FOR CLINICAL ACTIONABILITY OF MOLECULAR TARGETS (ESCAT)

Next steps

Describe the landscape of targets and rank according to ESCAT across tumor types

Evaluate cost-efficiency, reproducibility

Implementation of ESCAT in NGS reporting from academic and private partners – audit experience, virtues and room for improvements

Integration with bioinformatics tools and public resources (on going work at VHIO and within CCE Consortium and others)

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, nonsense (except known truncating polymorphic 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]

EXAMPLE: METASTATIC LUNG CANCERS

Alteration	Alteration considered	LOE
EGFR	Mutation (Del19, L858R), Acquired T790M exon 20	IA
ALK	Rearrangement	IA
BRAF	V600E mutations	IB
ROS1	Rearrangements	IB
RET	Rearrangements	IIB
NTRK	Rearrangements	IC
MET	Mutation exon 14 skipping / amplification	IB / IIB
HER2	Mutation / amplification	IIB
NRG1	Fusion	IVA
KRAS	Mutation	X
STK11	Mutation	X
PIK3CA	Mutation / amplification	X
NRG1	Fusion	IVA????

Number to test to get benefit: 6-7 (15% benefit)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO

TAKE HOME MESSAGES

- ESCAT provides an harmonized system to report clinical relevance of genomic findings
- Main aim is to facilitate interpretation of NGS reports for physicians and patients (improve patient care, manage expectations, facilitate communication)
- A step towards implementing precision medicine in routine clinical practice
- NTRK fusions are a example of a targetable Tier I finding
- Emerging data should be incorporated into rankings – dynamic shared databases maybe better than traditional publication format to disseminate ESCAT

ESCAT: A MULTI-INSTITUTION, INTERNATIONAL EFFORT

Building from previous efforts, accounting for diverstity

ESCAT Project team

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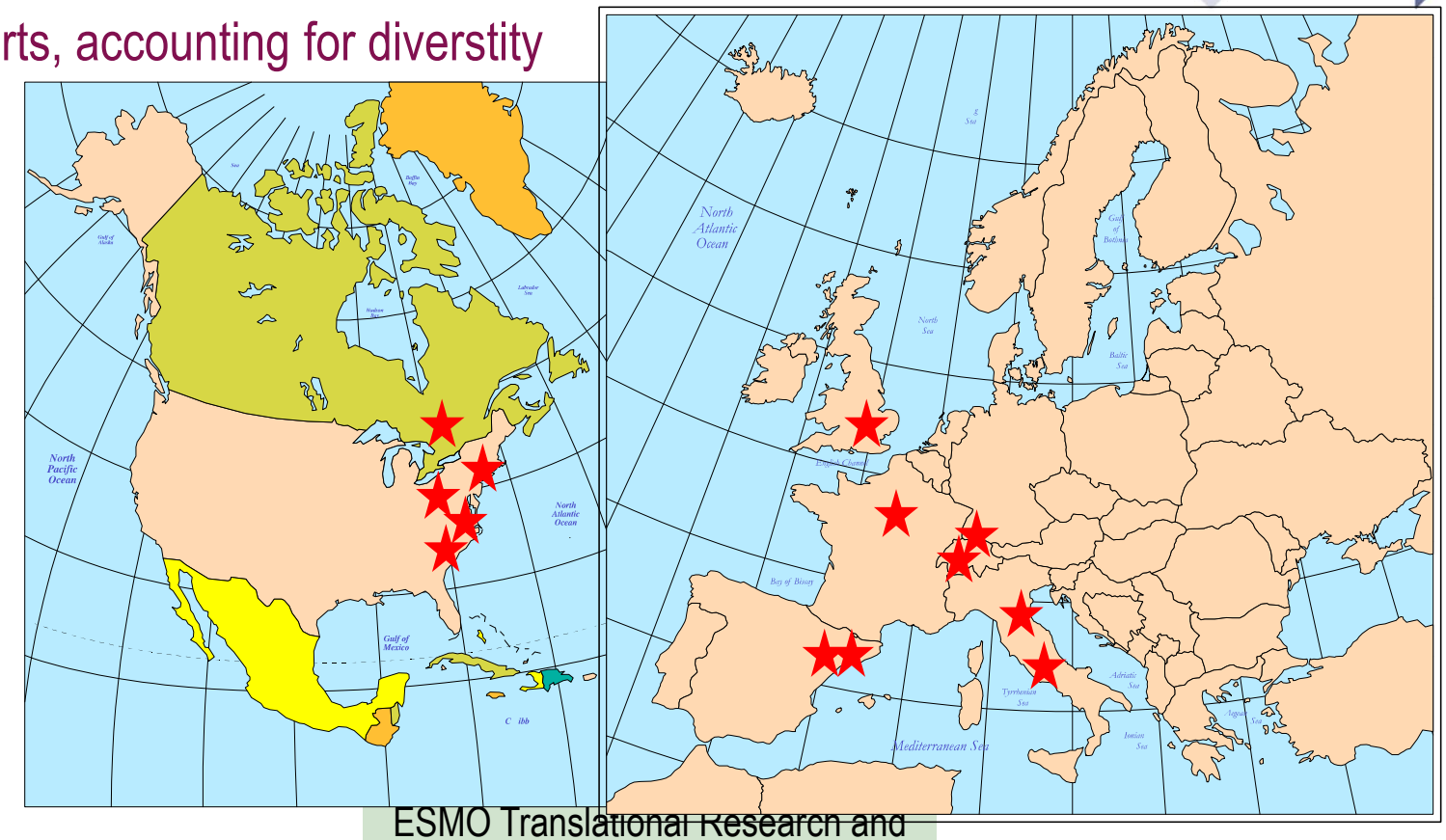

ESMO Translational Research and Precision Medicine Working Group

ESCAT Project Team

ESMO Leadership