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MOLECULAR TUMOUR BOARDS AND PRECISION CANCER MEDICINE

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LEARNING OBJECTIVES

Understanding the concept of precision cancer medicine

Understanding the challenges of precision cancer medicine

Understanding the concept of histology-agnostic therapeutics

Understanding the concept of a molecular tumour board

Understanding the concept of ESCAT

PRECISION MEDICINE IN ONCOLOGY

"Precision 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 **use of therapeutics** expected to confer benefit to a **subset of patients** whose cancer displays **specific molecular or cellular features**"

ESMO Precision Medicine Glossary 2017.

PRECISION CANCER MEDICINE

Glossary

Mutation: Alteration in DNA sequence that may be somatic (acquired during an individual's lifetime) or germline (inherited). Includes point mutations, translocations and copy number changes.

Cancer gene: A mutated normal gene that promotes cancer development and/or progression. Includes oncogenes and tumour suppressor genes.

Driver mutation: A mutation in a cancer gene (or its regulatory regions) that has a critical role in the development and/or maintenance of the malignant phenotype, including initiation, progression, maintenance or growth.

ESMO Precision Medicine Glossary 2017.

CLASSIC PRECISION CANCER MEDICINE

Originally considered (nearly) **synonymous** with **targeted therapy**

Single agents used in presence of defined **genetic 'driver' alterations:**

- BCR-ABL1 directed agents Chronic Myeloid Leukaemia
- HER2 directed agents in Breast Cancer
- EGFR/ALK/ROS directed agents in Non-Small-Cell Lung Cancer
- BRAF directed agents in Melanoma

Molecular **markers occur** in a **subset of patients**

Biomarker-stratified trials demonstrated **clinical benefit** of targeted agents in these subsets

Adapted from: Moscow JA,*et al.* Nat Rev Clin Oncol. 2018 Mar;15(3):183-192

THE PRECISION CANCER MEDICINE PROMISE

Individualised Treatment

Less Side Effects

Cost Effective

Better Outcome

MODERN PRECISION CANCER MEDICINE

Glossary

Targetable (druggable) genomic alteration: Encodes an altered protein against which a drug exists or can be synthesised (e.g. most kinases are targetable).

Actionable genomic alteration: Includes targetable alterations and those leading to dysregulation of a pathway in which there are possible targets (e.g. alterations of the PTEN tumour suppressor gene can be targeted with PI3K/AKT inhibitors).

ESMO Precision Medicine Glossary 2017

MODERN PRECISION CANCER MEDICINE

Use of (targeted) **agents based** on (genomic) **profiling** of tumour samples

- Identification of **targetable** or **actionable** alterations

Alterations are addressed in **individual patients**

Alterations are addressed **across tumour types**

Molecular alterations differ in frequency across cancer types

Adapted from: Moscow JA, *et al.* Nat Rev Clin Oncol. 2018 Mar;15(3):183-192

DIFFERENCES BETWEEN "CLASSIC" & "MODERN"

Precision Cancer Medicine

Classic precision cancer medicine

- Based on biomarker/drug combinations
- Evidence from large clinical trials
- Molecular testing part of clinical routine
- Test results immediately guide clinical decision making
- Mostly disease specific

Modern precision cancer medicine

- Based on increased use of molecular tumour testing
- Evidence from smaller clinical trials or case series/observations (real world evidence)
- Molecular testing under special circumstances
- Test results can inform/guide clinical decision making
- Increasingly disease-agnostic

Adapted from: Moscow JA, *et al.* Nat Rev Clin Oncol. 2018 Mar;15(3):183-192

CHALLENGES IN MODERN PRECISION CANCER MEDICINE

More precise testing

More precise drugs

Less precise evidence

Adapted from: Moscow JA, *et al.* Nat Rev Clin Oncol. 2018 Mar;15(3):183-192

CHALLENGES IN MODERN PRECISION CANCER MEDICINE

More precise testing

More precise drugs

Less precise evidence

- Technical advances in "next generation sequencing" (NGS)
- Broader availability
- Faster turn around times
- Declining costs

Adapted from: Moscow JA, *et al.* Nat Rev Clin Oncol. 2018 Mar;15(3):183-192

CHALLENGES IN MODERN PRECISION CANCER MEDICINE

More precise testing

More precise drugs

Less precise evidence

- Technical advances in drug design
- Next generations small molecules
- Targeting rare/specific alterations
  - NTRK fusions
  - RET alterations
  - ...

Adapted from: Moscow JA, *et al.* Nat Rev Clin Oncol. 2018 Mar;15(3):183-192

CHALLENGES IN MODERN PRECISION CANCER MEDICINE

More precise testing

More precise drugs

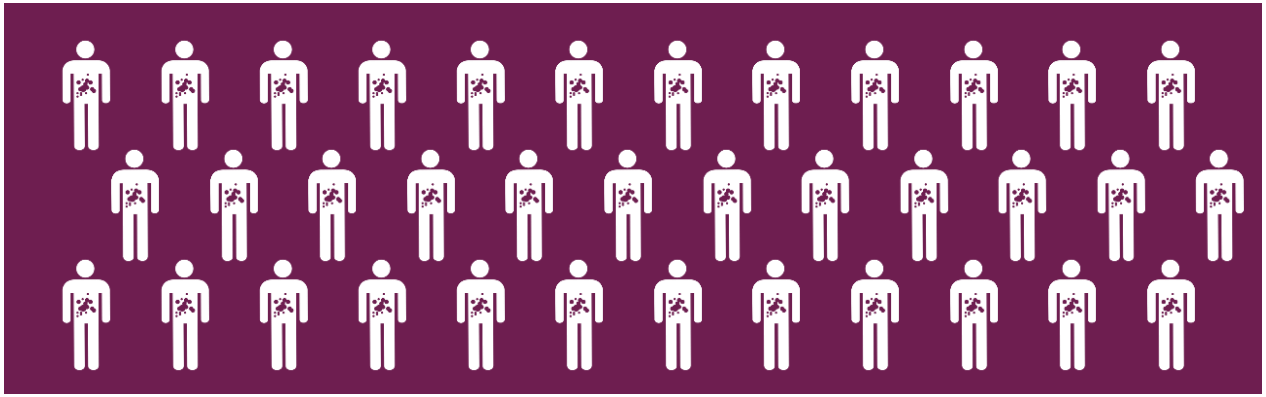
Less precise evidence

- Individualised treatment based on molecular profiles/patient characteristics
- Randomised clinical trials lacking / not feasible

Adapted from: Moscow JA, *et al.* Nat Rev Clin Oncol. 2018 Mar;15(3):183-192

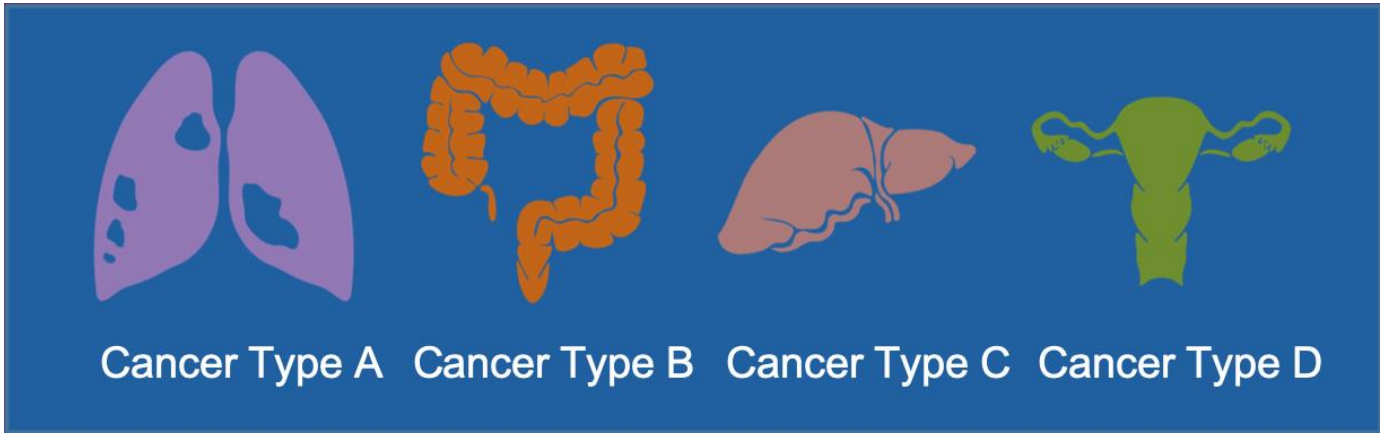
CLASSICAL CANCER THERAPEUTICS

- Classically, cancer patients are treated based on:
  - Histology/definable subgroup
  - Molecular profile in a subgroup
- Evidence stems from larger clinical trials
  - Groups/subgroups are large
  - Benefit for the individual hard to predict



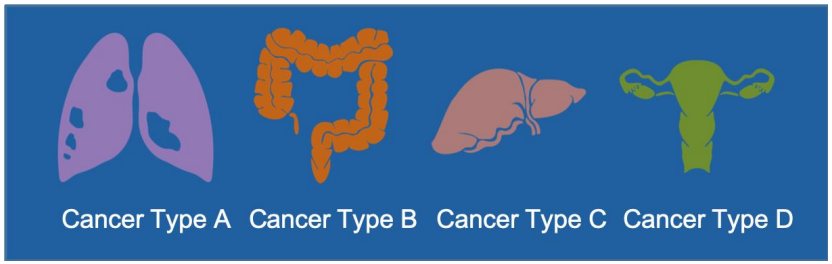
HISTOLOGY-AGNOSTIC TREATMENTS

- Histology-agnostic treatments are based on specific (rare) characteristics found across different malignancies
- Patient (sub)-groups can be (very) small
- Evidence stems from basket/umbrella trials or clinical observations
- Benefit is seen across cancer types



Shared alteration

HISTOLOGY-AGNOSTIC TREATMENTS



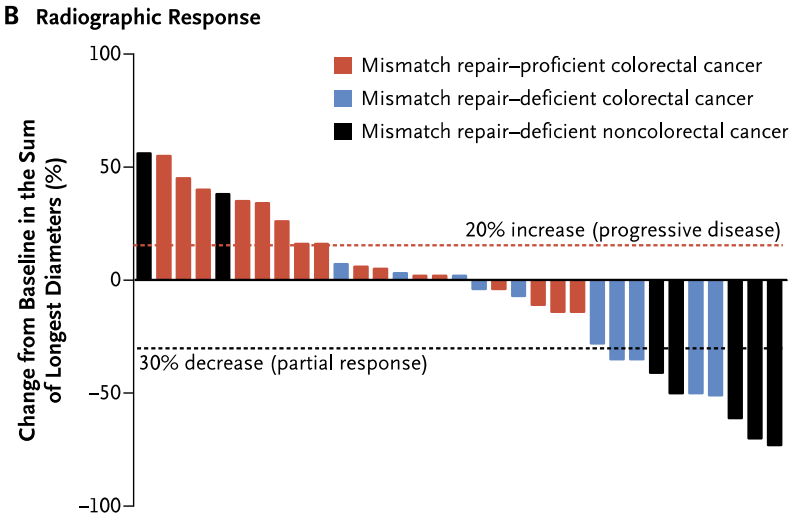
Shared alteration

Identify/diagnose alteration

Histology-agnostic drugs

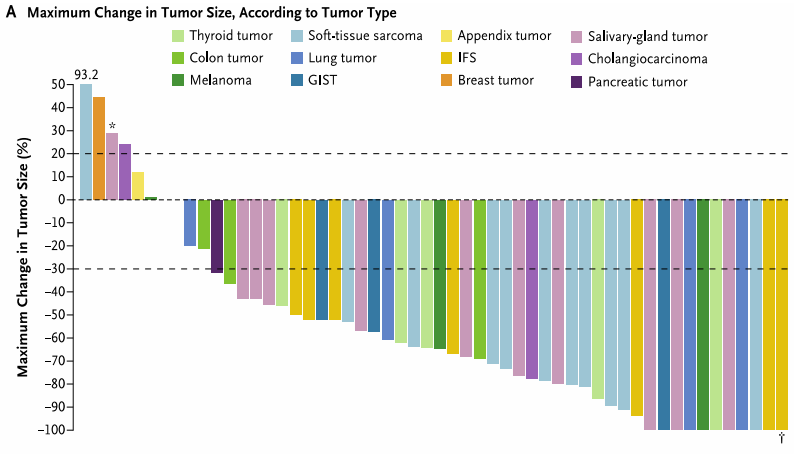
FIRST HISTOLOGY-AGNOSTIC DRUGS ARE AVAILABLE

2017: Pembrolizumab in dMMR Cancers[1]



From N Engl J Med, Le DT, *et al.* PD-1 Blockade in Tumors with Mismatch-Repair Deficiency, 372, 2509–20. Copyright © 2015, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

2018: Larotrectinib in NTRK-fusion cancers[2]



From N Engl J Med, Drilon A, *et al.* Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children, 378, 731–9. Copyright © 2018, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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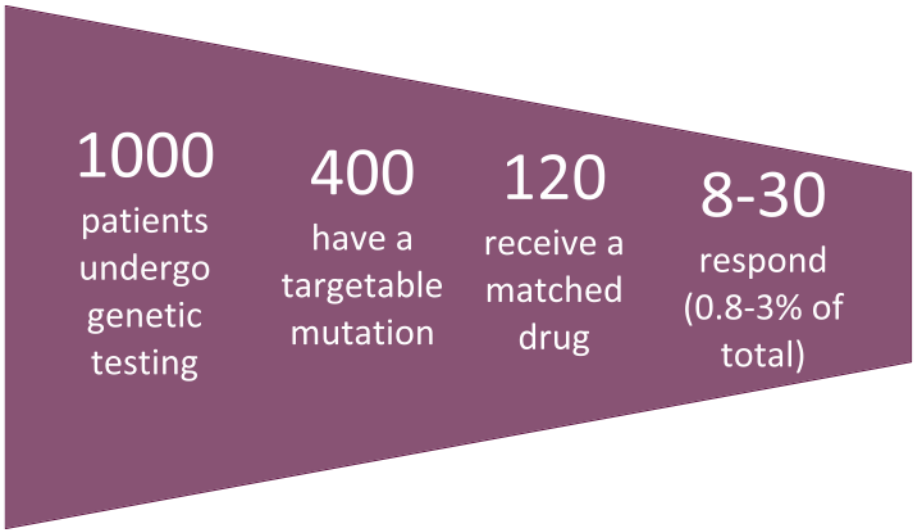
HOWEVER: UNTIL NOW, NO CONVINCING BENEFIT FROM LARGE SCALE TUMOUR AGNOSTIC STUDIES

11 trials, including more than 13,000 patients

Various gene panels (including 49-87 genes) and tissue microarrays



Tannock IF & Hickman JA, Ann Oncol 2019, 30(5): 661-663

POTENTIAL OBSTACLES OF TUMOUR AGNOSTIC STRATEGIES

- During the time needed for molecular profiling (and selection of a matching drug), patients may progress and no longer be suitable for treatment
- Lack of availability of a matched targeted agent (in general or not being available / registered)
- Futility: Poor response to a targeted agent despite matching.
  - Related to incomplete pathway inhibition
  - bio- chemical plasticity in response to drugs
  - presence of other driver mutations
  - effectiveness of targeted therapy being dependent on tumour type
  - Also the matched drug must target the encoded proteins rather than the primary DNA sequence, and the structure and function of these proteins are regulated by multiple molecular factors that remain poorly understood.
  - changes in common cancer genes: those may not be 'drivers' of subsequent malignancy but are passengers
  - Inability to combine most targeted agents because of toxicity
- Intra-tumour heterogeneity may represent only one part of the tumour and its metastatic sites; the analysis of a single biopsy is insufficient to capture genetic heterogeneity

MOLECULAR TUMOUR BOARDS IN PRECISION CANCER MEDICINE

- Specific type of multidisciplinary tumour board
- Encompasses treatment team, molecular biologists, geneticists and bioinformaticians
- Cases are discussed on the basis of:
  - Clinical information
  - Modern molecular diagnostics

ESMO Precision Medicine Glossary 2017

AIMS OF A MOLECULAR TUMOUR BOARD

Molecular Tumour Boards aim to:

- Provide clinical recommendations.
- Provide guidance based on the best available evidence
- Guide patients towards innovative clinical trials

CHALLENGES FOR MOLECULAR TUMOUR BOARDS

Molecular Tumour Boards face challenges:

- Availability of targeted agents matching molecular alterations
- Access to clinical trials
- Existing evidence for recommendations

→ Growing number of recommendations for "off label" therapies

FRAMEWORK FOR MOLECULAR TUMOUR BOARDS

ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

Collaborative effort of the ESMO Translational Research & Precision Medicine Working Group

Classification system for molecular aberrations based on evidence supporting their value as clinical targets

Six levels of clinical evidence for molecular targets

Based on implications for patient management

Adapted from: Mateo J, *et al.* Ann Oncol 2018, 29(9): 1895–1902

FRAMEWORK FOR MOLECULAR TUMOUR BOARDS

ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

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; 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

Tier X: Lack of evidence for actionability

Adapted from: Mateo J, *et al.* Ann Oncol 2018, 29(9): 1895–1902

FUTURE DIRECTIONS PRECISION CANCER MEDICINE

Sustainable structures are needed

Guarantee access to high-quality molecular diagnostics

Guarantee multidisciplinary discussion of testing results

- Delivered in a Molecular Tumour Board

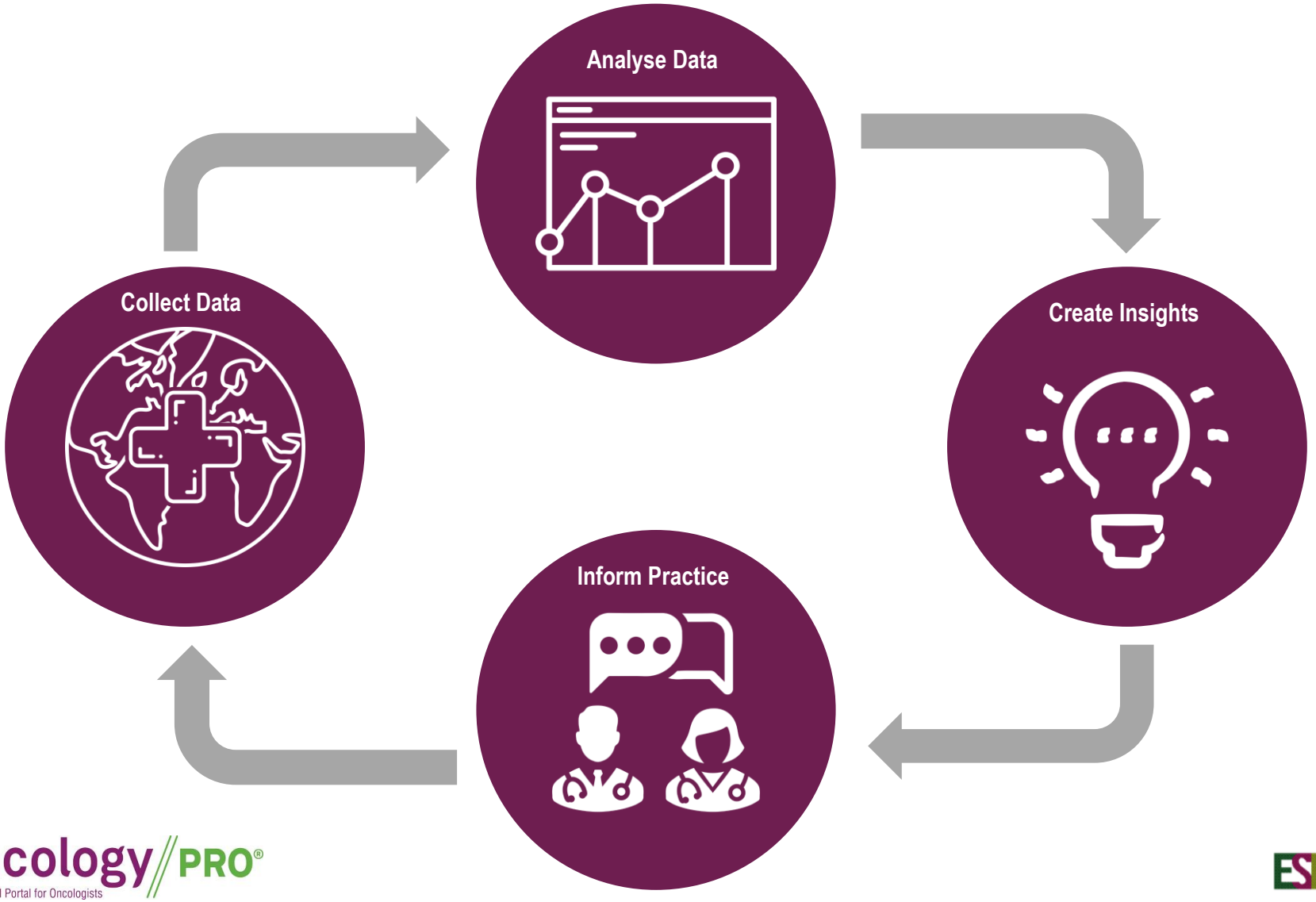
Allow for access to targeted/experimental agents

- Within a clinical trial
- Off label

Allow structured collection of clinical, molecular and outcome data

- Create insights and evidence
- Precision cancer medicine as a “self learning system”

LEARNING HEALTH SYSTEM



DISCLOSURES

Dirk Arnold has reported: Honoraria for Advisory Boards: Bayer Healthcare, Amgen, Merck Sharp & Dhome, Merck Serono, Eli Lilly, Bristol Myers Squibb, Servier, Roche, Terumo, Sirtex, Boston Scientific.

Honoraria for presentations: Bayer Healthcare, Amgen, Servier, Roche, Terumo, Astellas, Biocompatibles, Sirtex, ArtTempi Media, Prime Oncology, TRM Oncology. Support for congress travel: Bristol Myers Squibb, Roche, Sanofi. Consulting board role IQVIA (paid to his Institution).

Research Funding: Documentation fees with clinical trials, paid to his Institution by Sanofi, AstraZeneca, Incyte, Merck Sharp & Dohme.

Non- financial interests: Flatiron. Principal Investigator of phase III trial with MOLOGEN. Planned as principal investigator with SFJ, Pleasanton (acting as trial sponsor for Merck Serono). Planned as principal investigator with Oncolytics.

Scientific Advisory Board for Oncolytics, Biotech, SFJ, Munich Biotech

Leadership roles/Membership: ECCO Member of the Executive Board2015-2017 (on behalf of ESMO), membership of the Finance Committee. AIO in DKG: Member since 2003, Chairperson of Colorectal Cancer Working Group 2010-2018, membership in other steering committees. EORTC: Member of GI Cancer Group, Steering Committee Member since 2008; Task Force lead for Rectal Cancer and Anal Group since 2016.

Benedikt Westphalen has reported: Honoraria: Bayer, Celgene, Ipsen, Servier, Roche; Advisory Boards: Celgene, Shire/Baxalta, Rafael Pharmaceuticals, RedHill, Roche. Travel support: Bayer, Celgene, RedHill, Roche. Research Support: Roche. Leadership roles/membership: AIO in DKG: Member since 2013; steering committee pancreatic cancer, cancer of unknown primary, translational and molecular oncology.

Ian Tannock has reported no conflict of interest

THANK YOU!