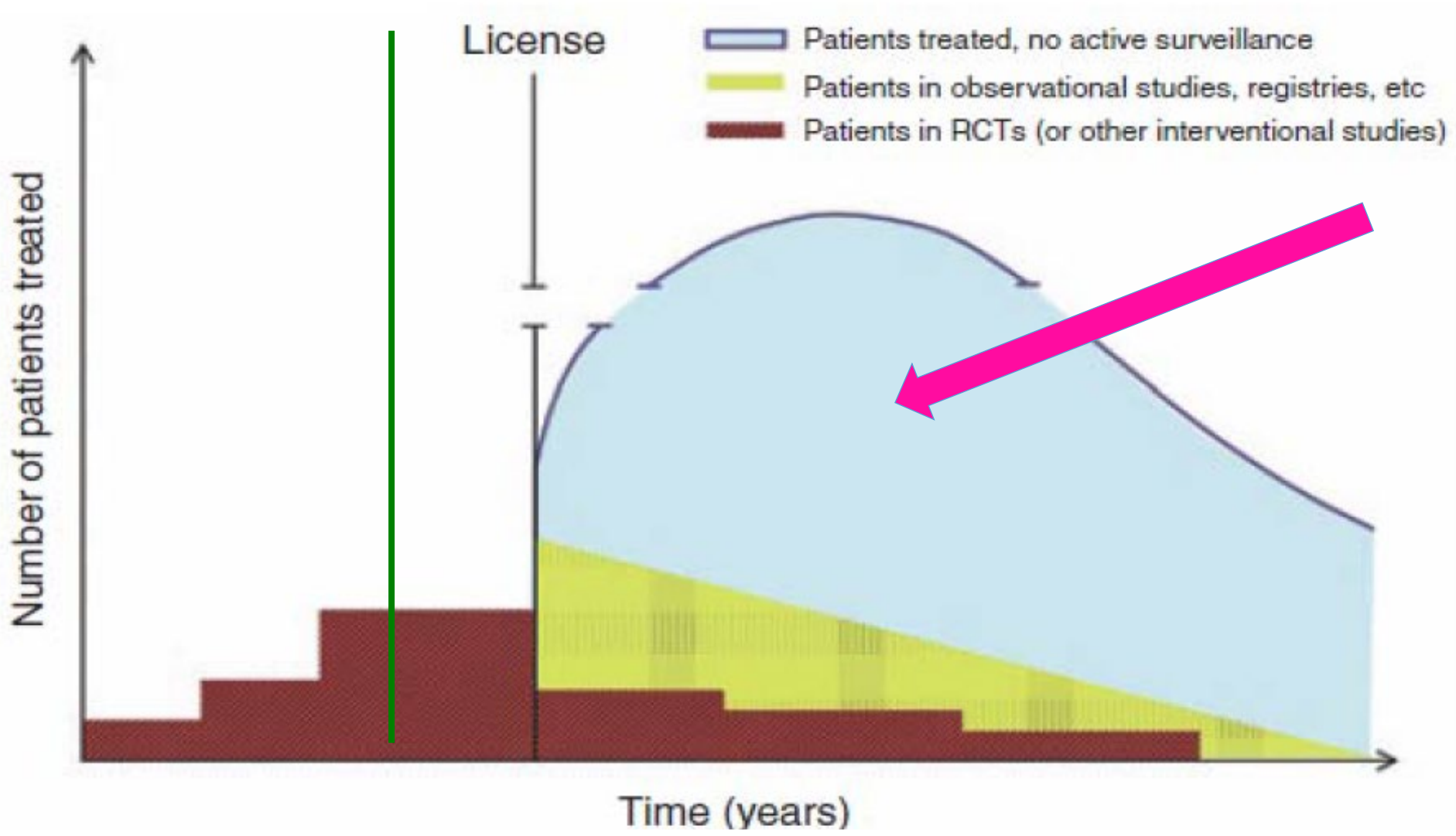


# Lights and sheds of early approval of new drugs in clinical routine

Carmen Criscitiello, MD, PhD  
European Institute of Oncology  
Milan, Italy

RCT 5-10% pts



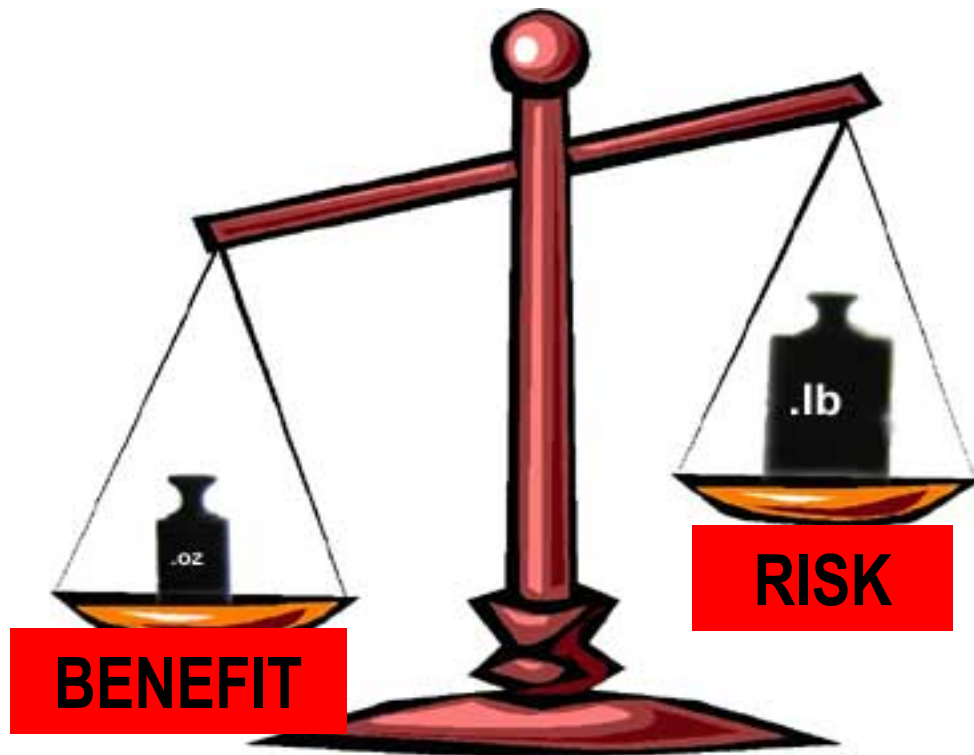
«real»  
patients  
are here

# Benefit/Risk is the key pillar of regulatory assessment

REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004

laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

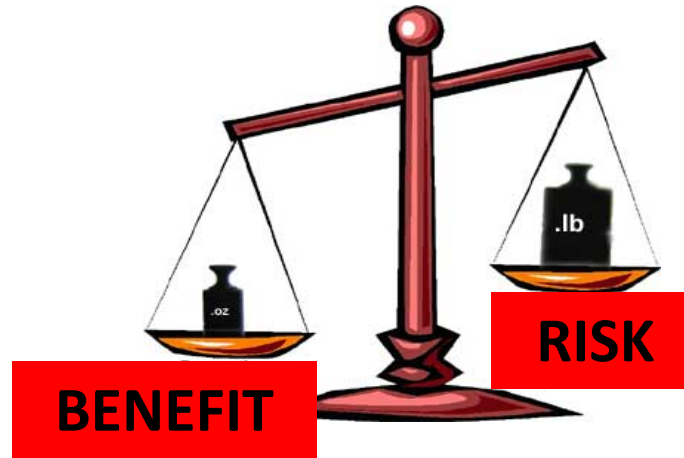


TOTALITY  
of  
EVIDENCE

# CHALLENGES

Timely (early) access  
to innovative drugs

Flexibility



Robustness of  
evidence

Tolerance of risk



**MAJOR CHALLENGE**

**EARLY REGULATORY APPROVAL**



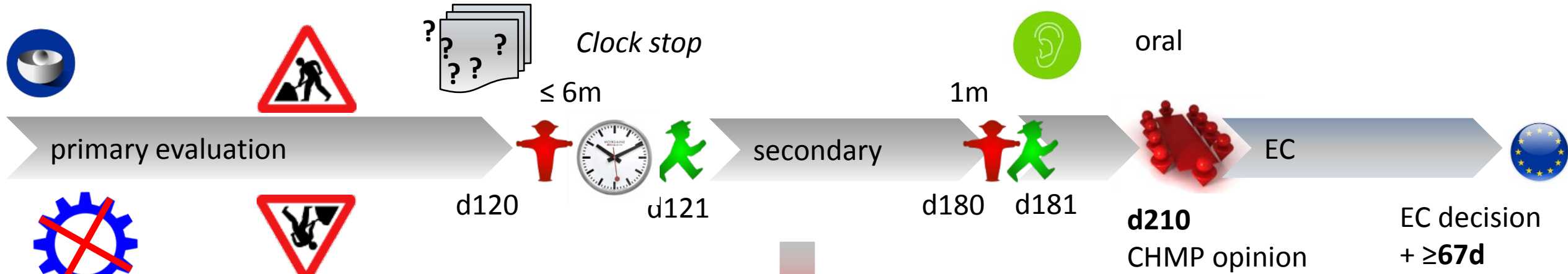
**EARLY ACCESS for PATIENTS**

# EU drug approval process

active evaluation time **max. 210 days** (+ 'clock-stops')

## filing strategy

- not 'rolling' submission (full dossier at validation)
- apply for indication extension (90d+) after initial MA granted
- non-/orphan cannot be combined in same MA
- no conditional variations



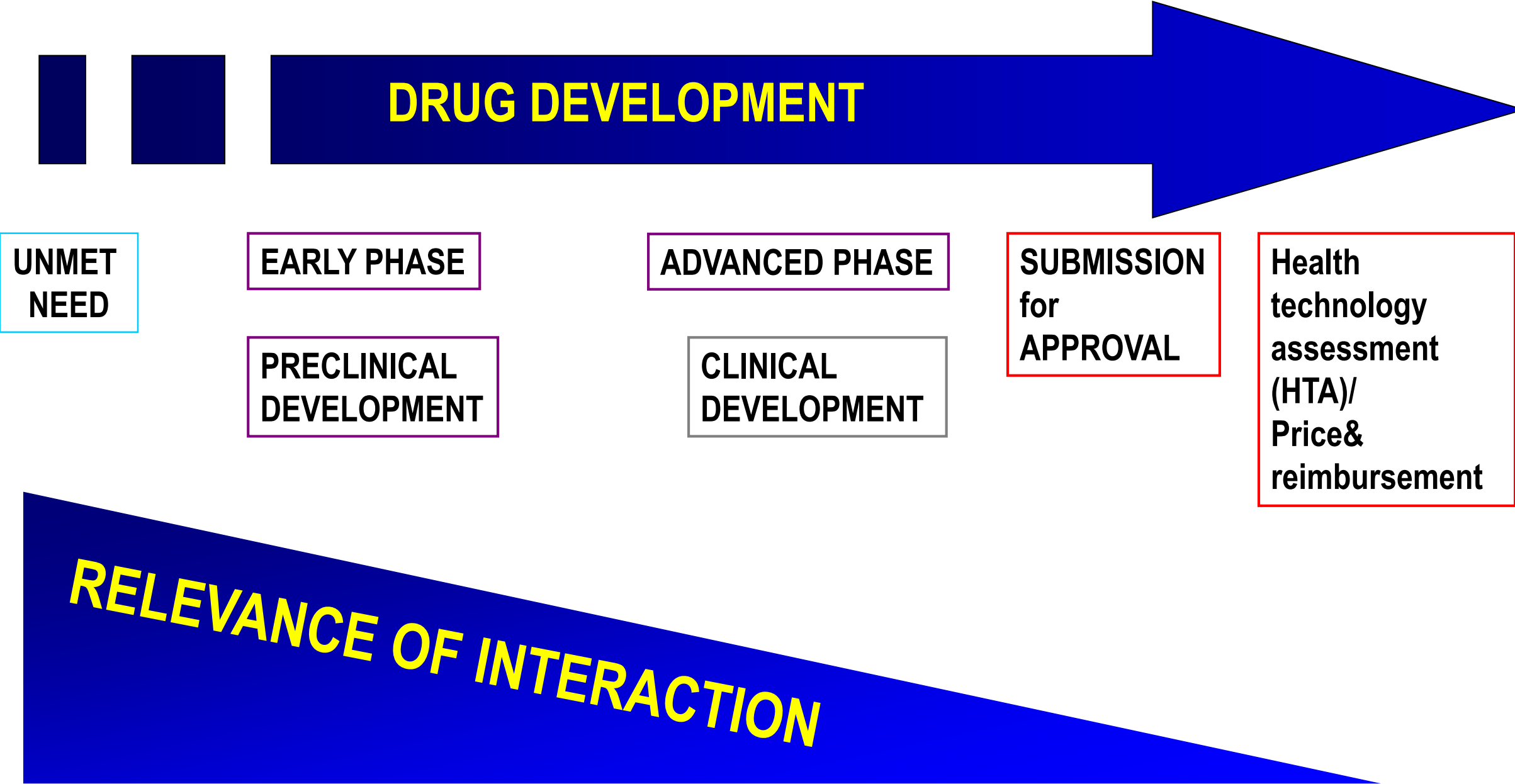
2 teams, active review time  $\leq 210$  d  
(+ clock-stops)

**Accel Rev d150**  
~ priority review

**SAG opt**

*major interest for public health,  
therapeutic innovation*

# Early dialogue is needed



# Early licensing tools: conditional & exceptional circumstances

## **Accelerated assessment** (~ US FDA priority review):

major public health interest, unmet need, innovative

- 120/150 days **active CHMP review** (instead of 210 d)

## **Conditional approval** (~ US FDA accelerated approval)

**unmet need:** orphans, emergency threats, life-threat

- **B/R+** pending ongoing/new **confirmatory studies**
- valid for one year (**renewable**)
- **conversion** into normal: initial + obligations
- **only initial** approval (legal basis not supplements)

## **Exceptional circumstances**

comprehensive data **cannot be provided** (rare, unethical)

- data initial + obligations < normal
- annual reassessment B/R, focus safety, **registries**



## US Accelerated Approval (since 1992)

## EU Conditional MA (since 2006)



# US Accelerated Approval vs EU Conditional approval

New drugs and biological products

NCEs/NBEs qualifying for **Centralized procedure**

**Serious and life threatening illness**

**unmet medical need** for →

**Meaningful therap. benefit over existing therapies**

- seriously debilitating or life-threat. diseases
- or products used in **emergency situations**,
- or **orphan drugs**

based on

- a **surrogate endpoint** considered reasonably likely to predict clinical benefit
- an **effect on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) and reasonably likely to predict IMM/clinical/other benefit**

CMA Guideline (2016):

Justify that it is necessary to introduce new methods when

- no satisfactory methods exist, or
- it is necessary to provide a major improvement over the existing methods

MA granted on basis of **less complete data**

Demonstration of **positive benefit-risk balance**, based on scientific data, but with pending confirm.

Likely that comprehensive data can be provided; **benefit of immediate availability outweigh risk**

Studies to **confirm clinical benefit** post-approval

Further clin. studies to **verify benefit/risk balance** →

- Adequate & well-controlled studies
- usually underway at time of AA
- conducted with due diligence

Feasibility of confirmatory trials to be addressed

**Approval is not limited in time** (withdrawal possible)

**Authorisation valid for one year** (renewable) until pending results are provided

Possible for **initial NDA/BLA** and **supplemental NDA/BLA** (new indication)

Possible for **initial MAA of NCEs/NBEs** but not for Type II variations for new indications



# Common principles for accelerated (AA - US) and conditional (CMA - EU) approval



## Criteria to support AA or CA

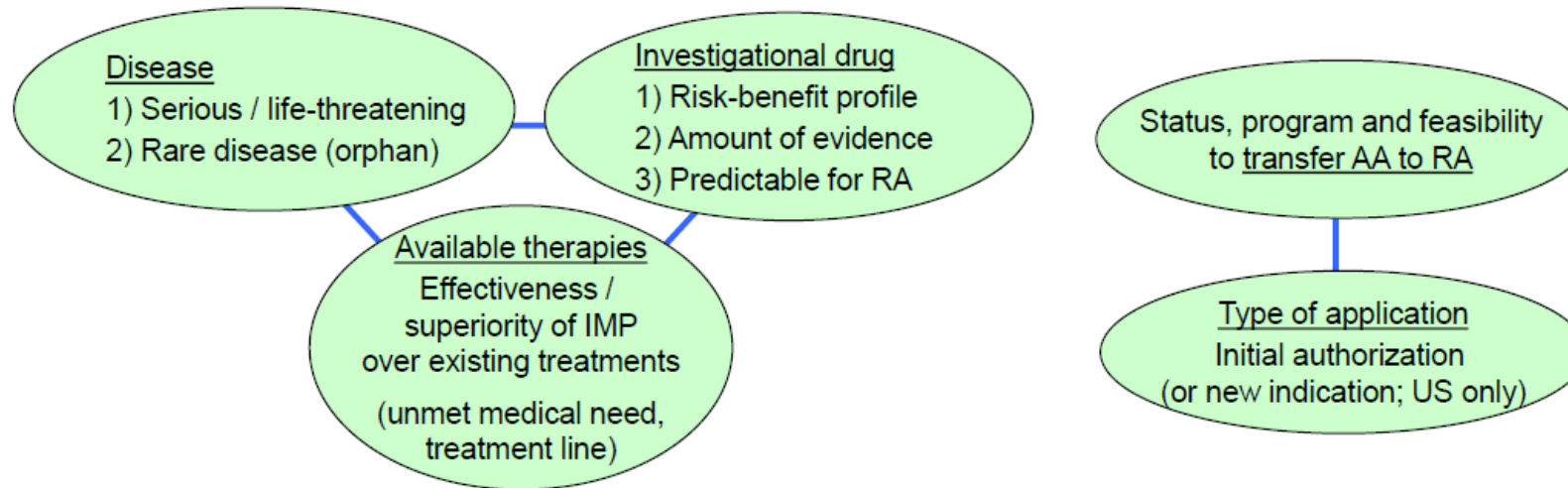
Early availability of new, promising therapies

Balance  
↔

Efficacy and safety demonstrated by sufficient evidence

HA concerns with AA/CMA:

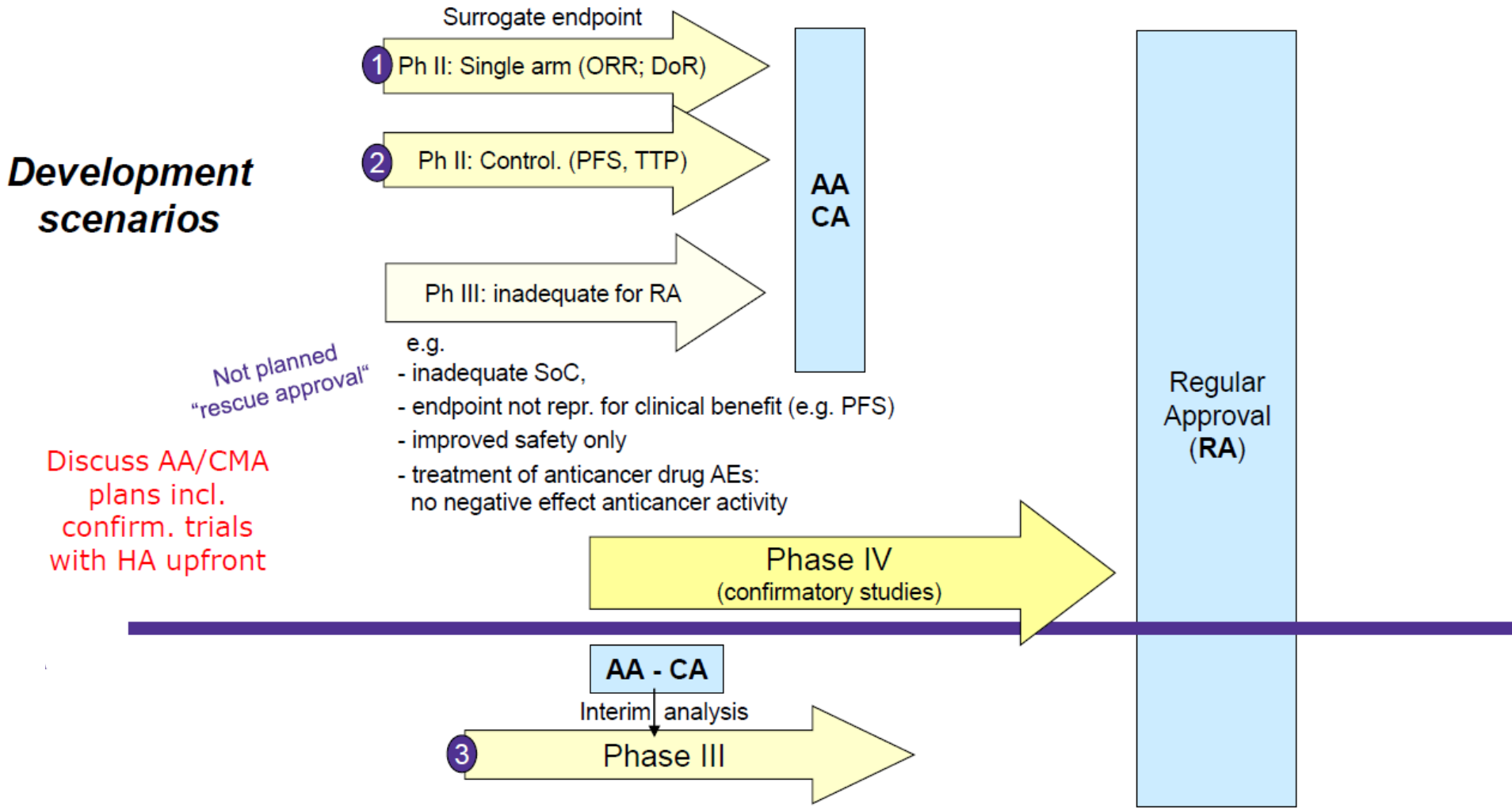
- Approval of potentially ineffective drugs
- Lack of due diligence in conducting post-approval trials



Substantial improvement of IMP over existing treatments required to cope with uncertainty of

- Outcome from a surrogate endpoint to transfer into real clinical benefit (SoC approved based on clinical benefit)
- Comparison to historical controls in case of single arm trials / In case of RCT, limitations by Phase II-like studies

# Common principles for accelerated (AA - US) and conditional (CA - EU) approval



## General aspects supporting AA/CMA



- Rare cancer type
- Strong efficacy outcome clearly superior over existing therapies
- Only low to moderate activity of existing treatments / limited number of treatments / not approved
- Approval of new treatments while clinical trial of IMP is ongoing
  - Other drugs AA/CMA approved in the same clinical setting do not prevent other AA/CMA
  - New, effective drugs with full approval may prevent AA/CMA of other drugs
- Hints that the drug effect is real (predictive BM; dose-response effect shown)
- Follow-up indication: sNDA/BLA (EU: no CMA for follow-up indications possible – *higher hurdle?*)
- Confirmatory trials ongoing

# Surrogate endpoints (likely to predict clinical benefit supporting AA/CMA)

- ORR
- DoR
- TTP
- PFS
- pCR

# Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

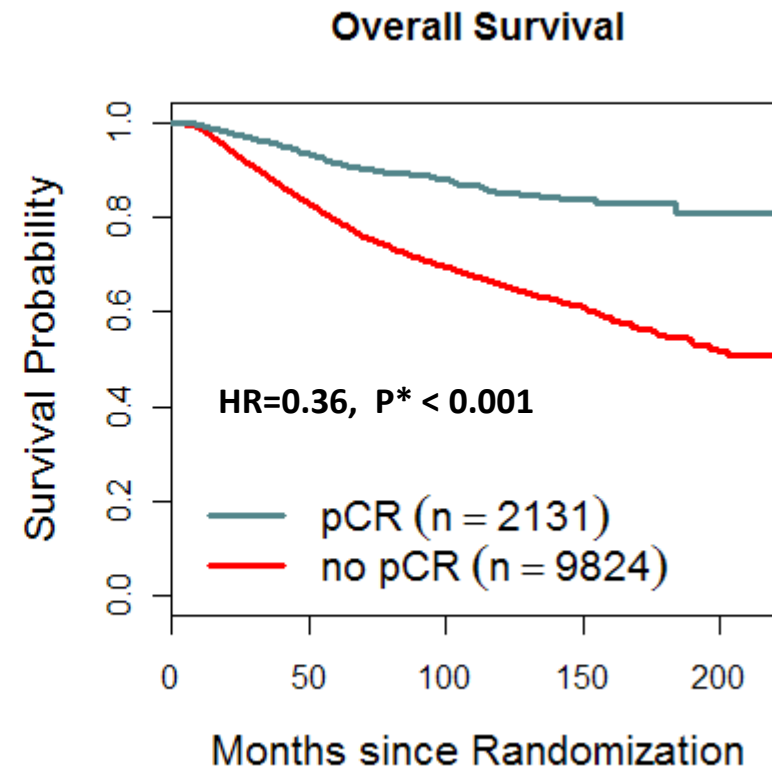
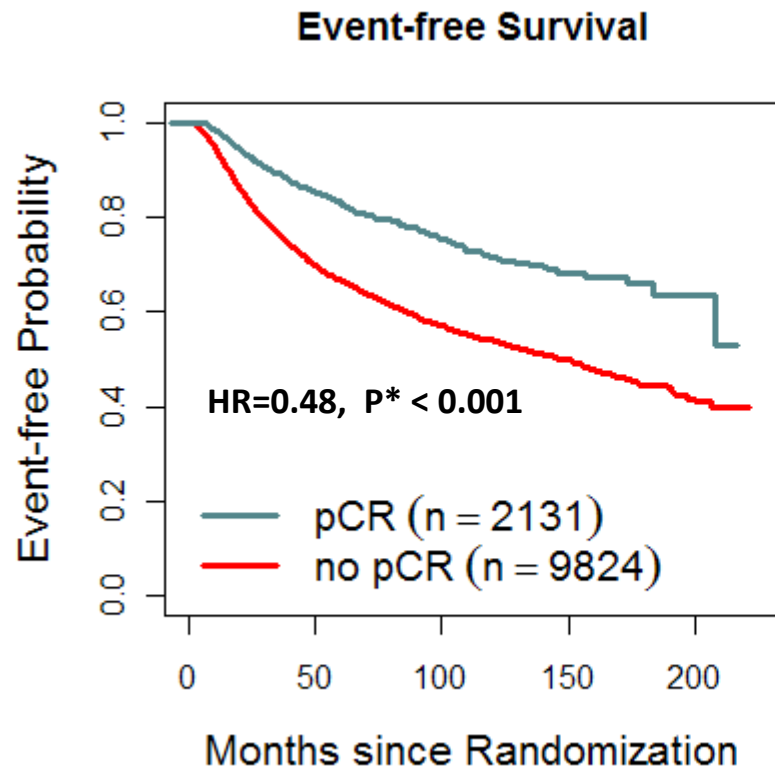
Tatiana M. Prowell, M.D., and Richard Pazdur, M.D.

The FDA may grant accelerated approval on the basis of a surrogate endpoint that is

**“reasonably likely to predict clinical benefit.”**

**For neoadjuvant breast cancer treatment, the rate of pathological complete response is used as this surrogate.**

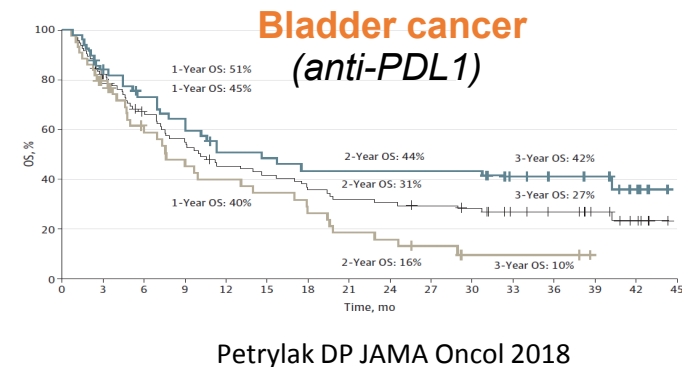
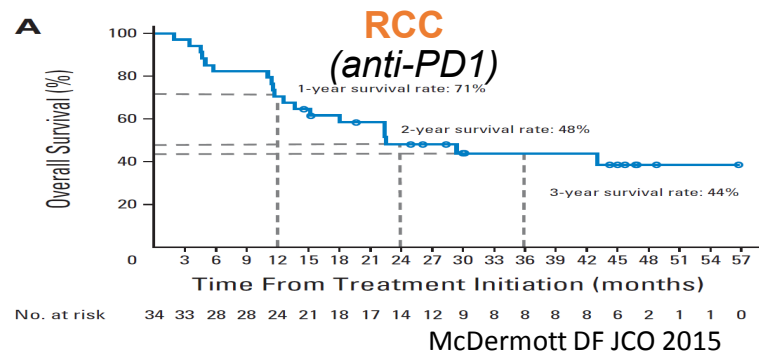
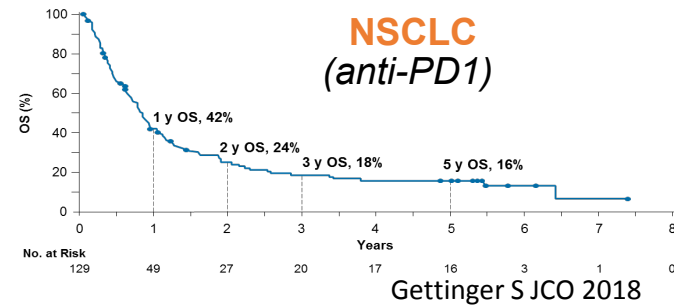
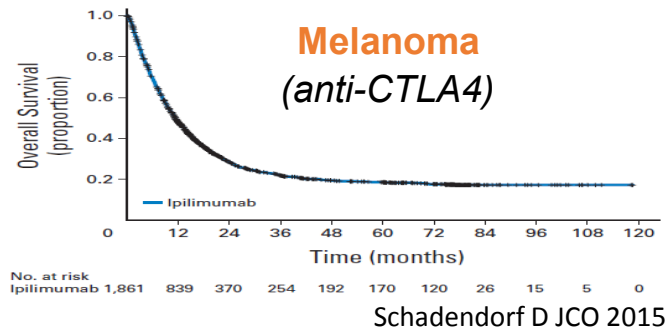
# Association of pCR on EFS and OS in the CTNeoBC meta-analysis



pCR=ypT0/is ypN0

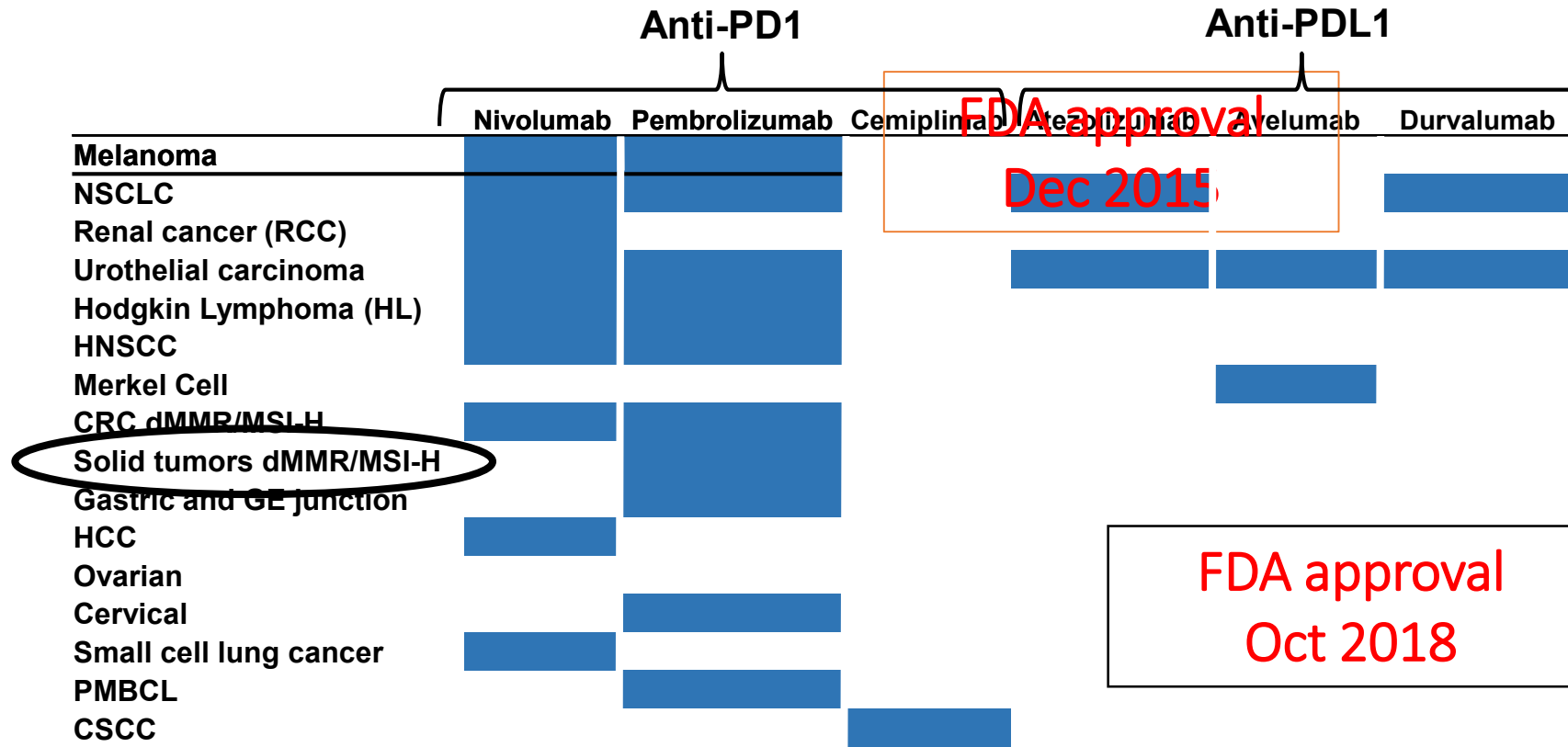
\* Nominal p-value

# Immunotherapy: the promise of cure



Immunecheckpoint inhibitors provide, in several advanced incurable diseases, the chance of cure

# FDA approvals for anti-PD1/PDL1



Abbreviations: CSCC, Cutaneous Squamous Cell Carcinoma; HCC, Hepatocellular carcinoma; PMBCL, Primary mediastinal large B-cell lymphoma



# FDA approves first cancer treatment for any solid tumor with a specific genetic feature

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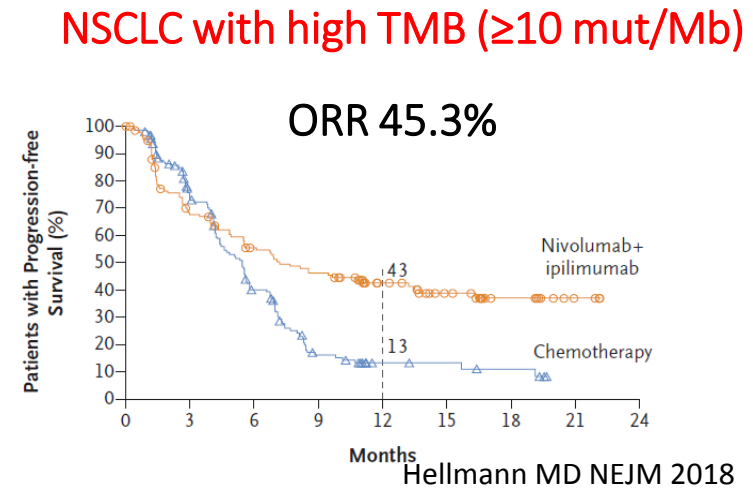
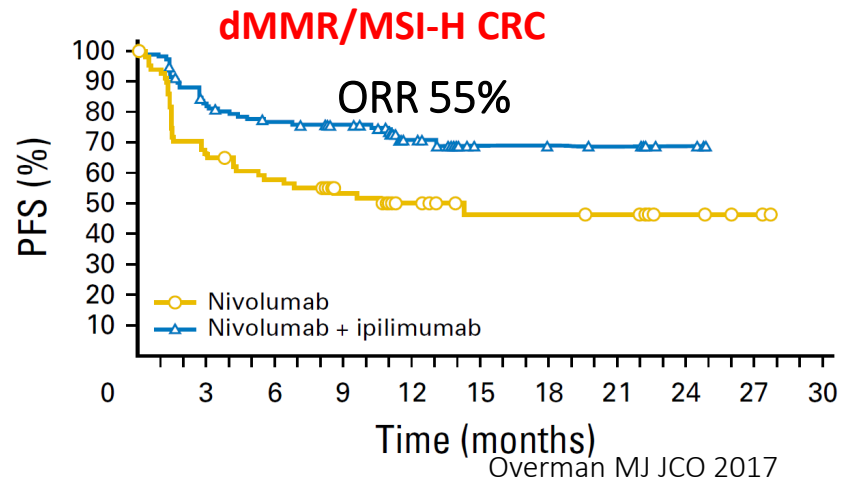
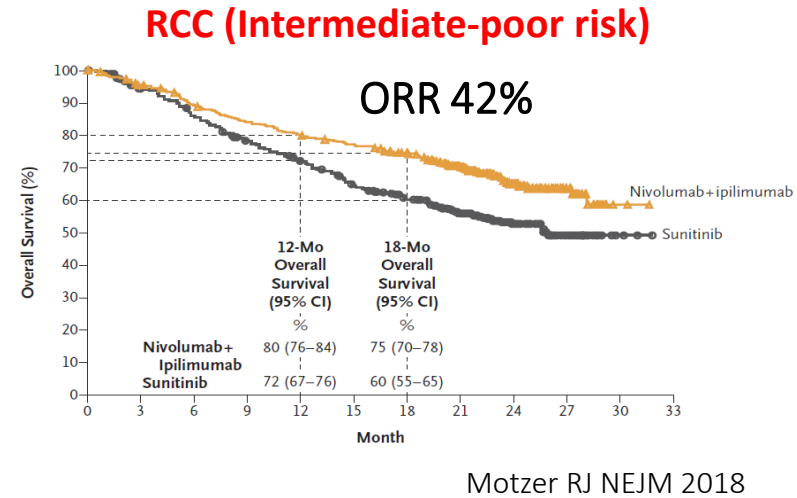
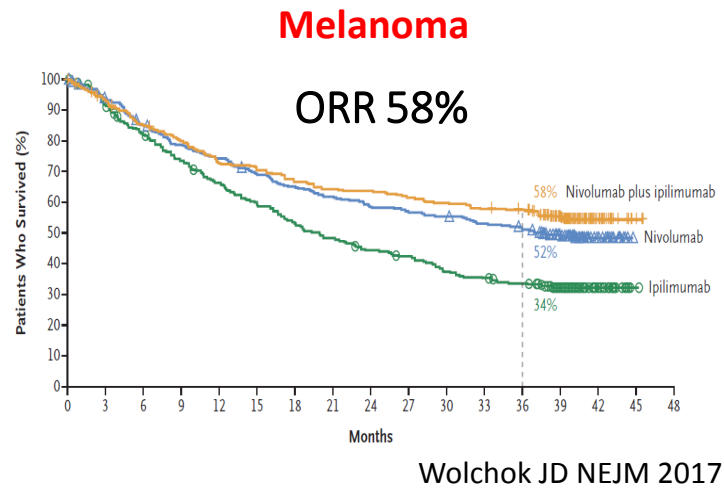
For Immediate Release

May 23, 2017

The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

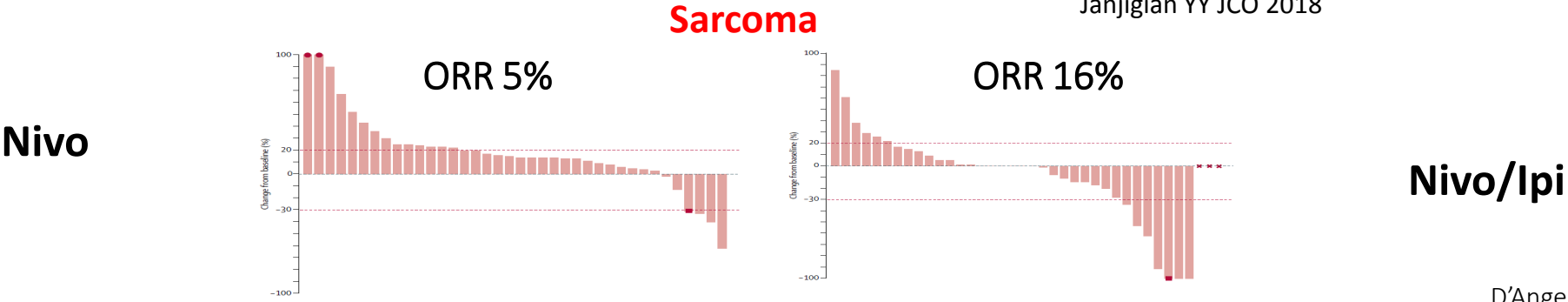
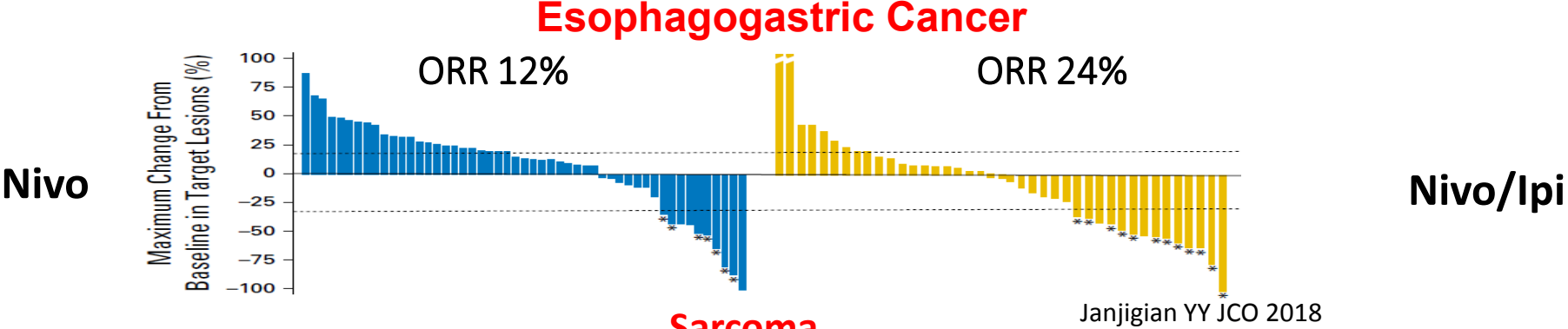
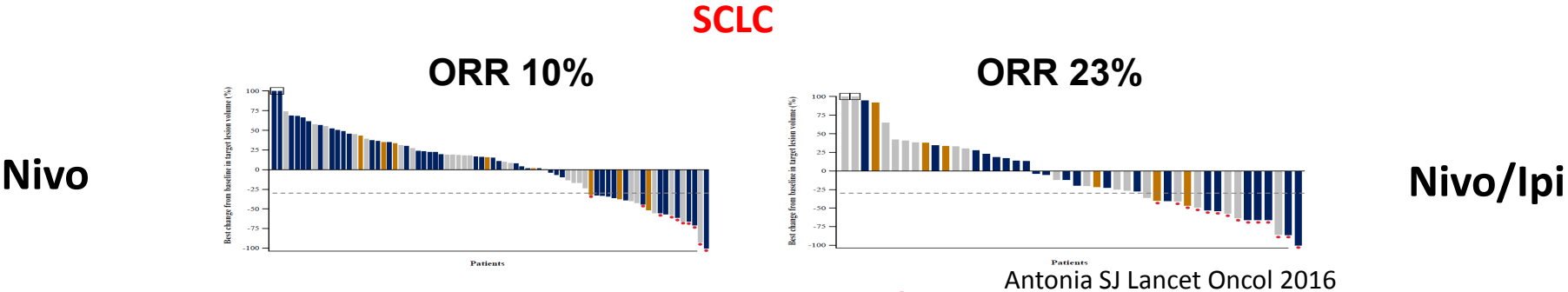
Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.<sup>1</sup>

# Nivolumab/ipilimumab efficacy across many tumor types



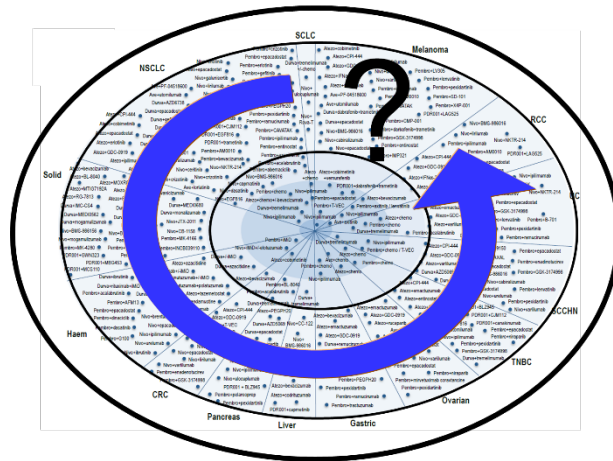
Note: indirect comparison with CheckMate-142 (\*) and KEYNOTE-164 (†)

# Nivolumab/ipilimumab promising activity across many tumor types



# Prioritization of effective combinations

- The consistent benefit of anti-CTLA4/anti-PD1 combination among several tumor types suggests that the mechanisms of immune escape, which are overcome by this combination, are - at least to some extent - general and tumor type independent («agnostic»).



# Immune combinations: a challenge for conservative regulatory authorities?

26 July 2018 The Committee for Medicinal Products for Human Use (CHMP) gave a negative opinion for the use of nivolumab/ipilimumab combination as first-line therapy in RCC because ***“there was no evidence showing if Ipilimumab contributed to these results and if so, how much”***

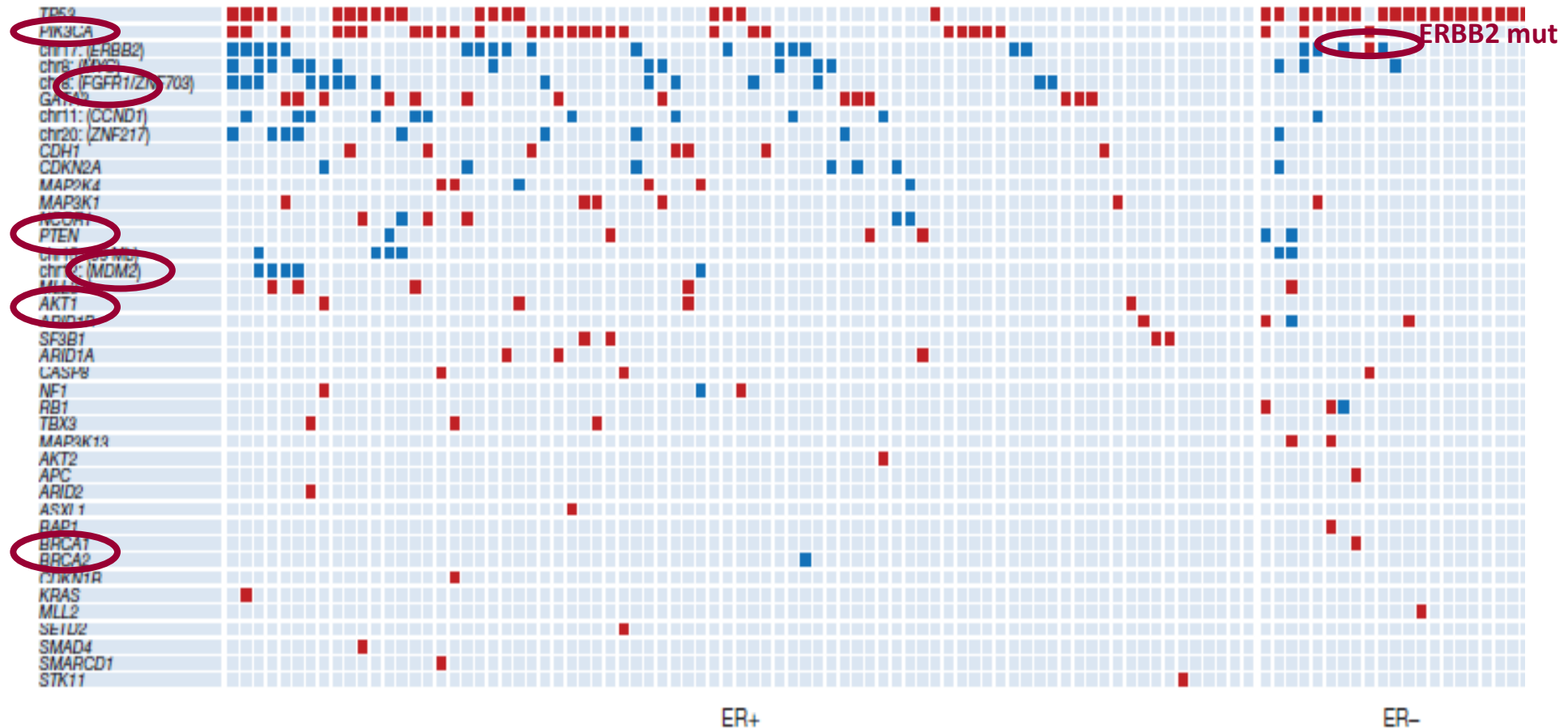
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## Research Letter

**A Joint Statement from the European Association of Urology Renal Cell Cancer Guidelines Panel and the International Kidney Cancer Coalition: The Rejection of Ipilimumab and Nivolumab for Renal Cancer by the Committee for Medicinal Products for Human Use Does not Change Evidence-based Guideline Recommendations**

“..... regardless of the outcome of additional research, it still has no bearing on the conclusion of the trial, which shows that the ***immunotherapy combination is significantly more active and better tolerated than sunitinib.***”

# Drug Development in Rare Genomic Segments



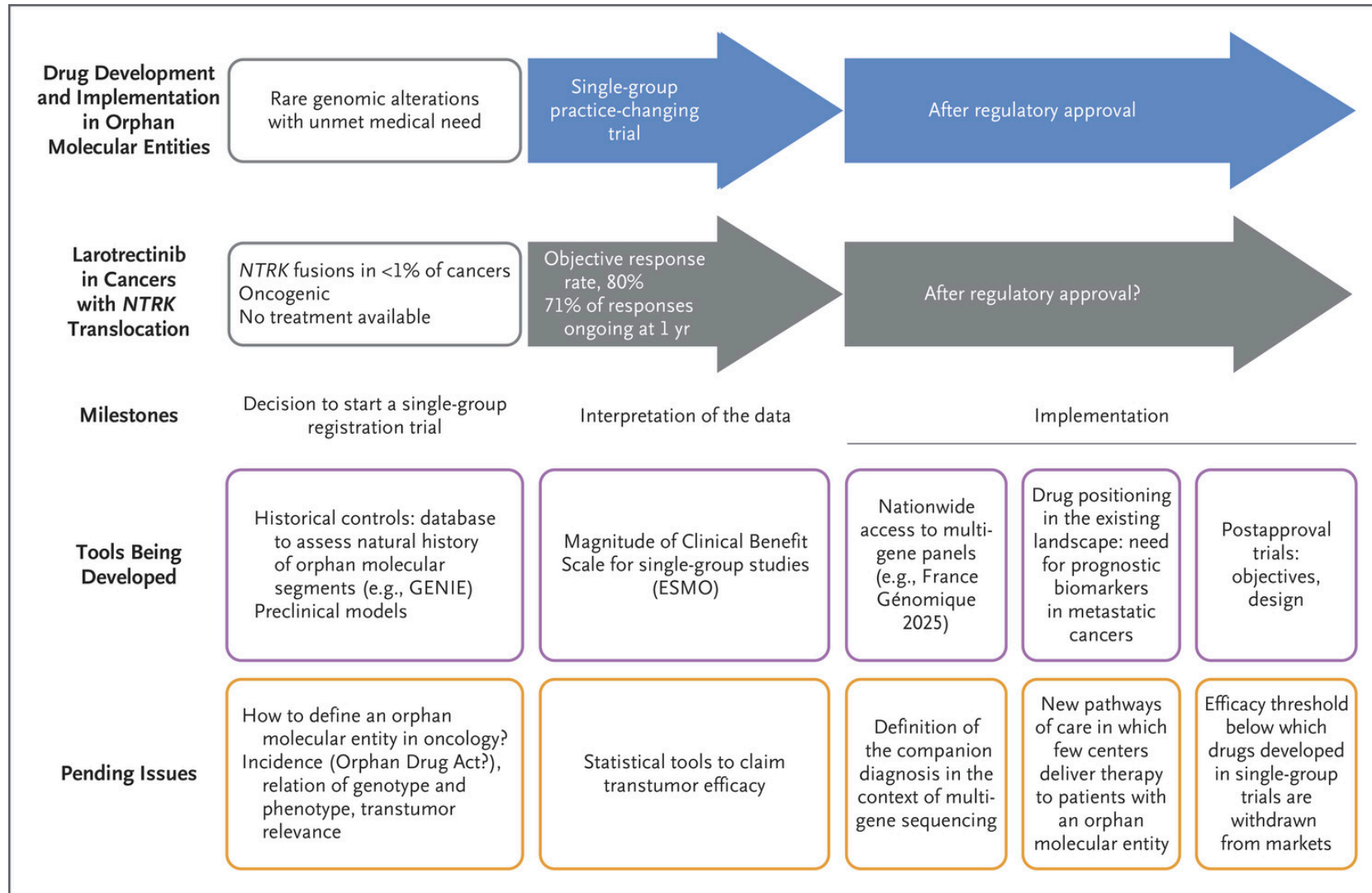
What are the current challenges to develop drugs in a rare genomic segment?

- There is a large number of rare genomic segments
- Genomic segments are too rare to deserve a drug development

# Challenges for drug development in rare genomic segments

- Some oncogenic alterations occur at very low frequency and are shared across tumor types
- Single- group trials are particularly adapted to rare clinical scenarios with well-established natural histories. The low incidence of these genomic segments makes randomized trials challenging.
- Rare genomic segments are defined by a genomic alteration that drives cancer progression, hence they usually have high sensitivity to targeted therapies.
- **Example: a single-group trial led to the regulatory approval of dabrafenib and trametinib combo in patients with NSCLC expressing a BRAF V600E mutation, an alteration observed in 1% of lung adenocarcinomas**

# Anticancer Drugs in Orphan Molecular Entities





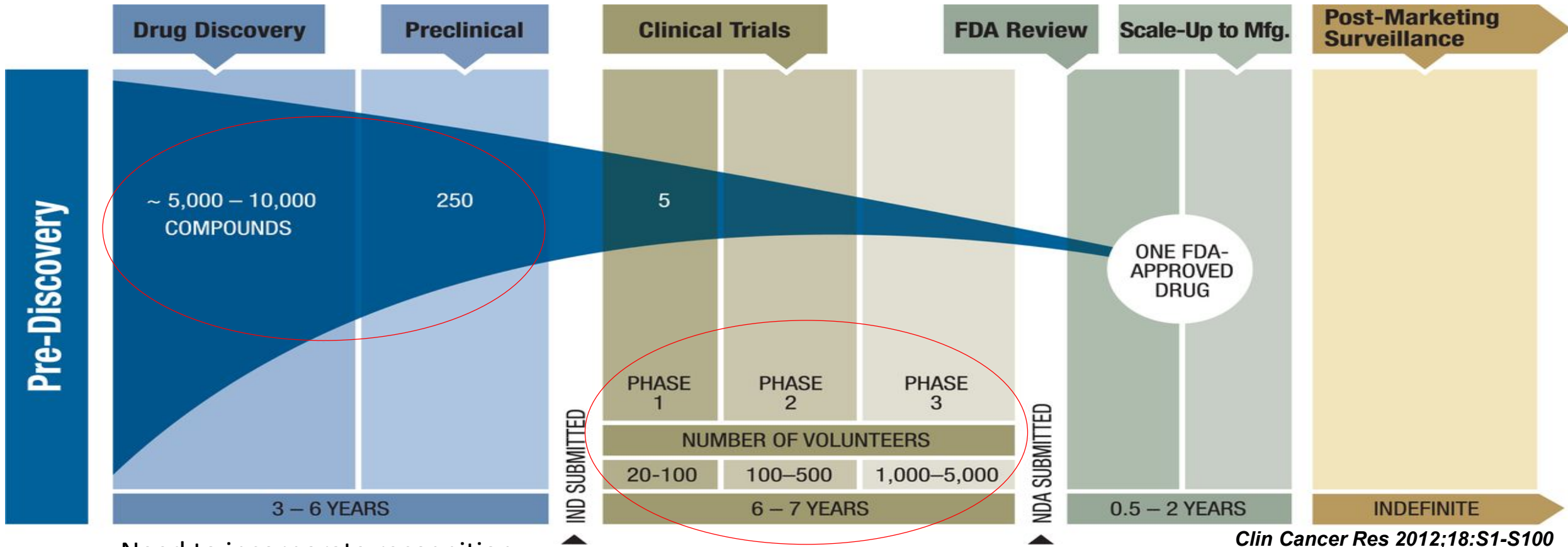


The US FDA has approved a new cancer treatment in an unconventional way: not by tumor type, but rather by the genetic mutation the drug targets. It's only the second time the FDA has approved a cancer drug's use based on a certain mutation rather than a particular tumor type.

“ The FDA approval of larotrectinib marks an important milestone in how we treat cancers that have an *NTRK* gene fusion. ”

- David Hyman, Memorial Sloan Kettering Cancer Center (NY, USA)

# The Long and Winding Road



*Clin Cancer Res 2012;18:S1-S100*

Need to incorporate recognition of tumor heterogeneity early

Predictive factor determination

How long if only relevant for 1% of cancers?

# Challenges of trans-tumors trials

- Trans-tumor approach successful in the case of *NTRK* fusions with larotrectinib, or in the case of mismatch repair–microsatellite instability with anti-PD1, BUT some failures as well, notably BRAF inhibitors.
- Develop statistical tools to support a claim that a drug works across tumor types
- Knowledge of the biology
- To reconcile the concept of companion diagnostic testing with the use of multigene panels.

# Conclusions

- When the clinical development is successful, this leads to the creation of new entities that are defined according to biomarkers and no longer according to histologic classification.
- Screen the highest number of patients for the highest number of genomic alterations  
→ more patients included in genomic driven trials
- A framework to rank genomic alterations as targets for cancer precision medicine: The ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)
- In line with new pathway for approval from regulatory agencies, ESMO has developed a Magnitude of Clinical Benefit Scale that is dedicated to single- group trials.
- According to this scale, studies that show ORR > 60% and a median PFS >6 months are considered to have the highest magnitude of clinical benefit
- Need to consolidate efficacy data in post-approval studies with large sample sizes
- In diseases for which conventional and effective treatments are available, need to define the appropriate positioning of the precision medicine strategies in the treatment landscape

# ACTIONABILITY + CLINICAL BENEFIT + RISK → APPROVAL

- clinical trial data
- Efficacy
- Antitumor activity
- Safety
- Magnitude of benefit
- Evidence for the match in other tumor types
- Evidence for the match for other biologically similar mutations

- FDA/EMA registration status
- Not aiming to judge pathogenicity of mutations (biological relevance)
- Not based the drug alone but in the match

Thank you