WECAN SmartStart in Cancer Patient Advocacy

WECAN MASTERCLASS in Cancer Patient Advocacy

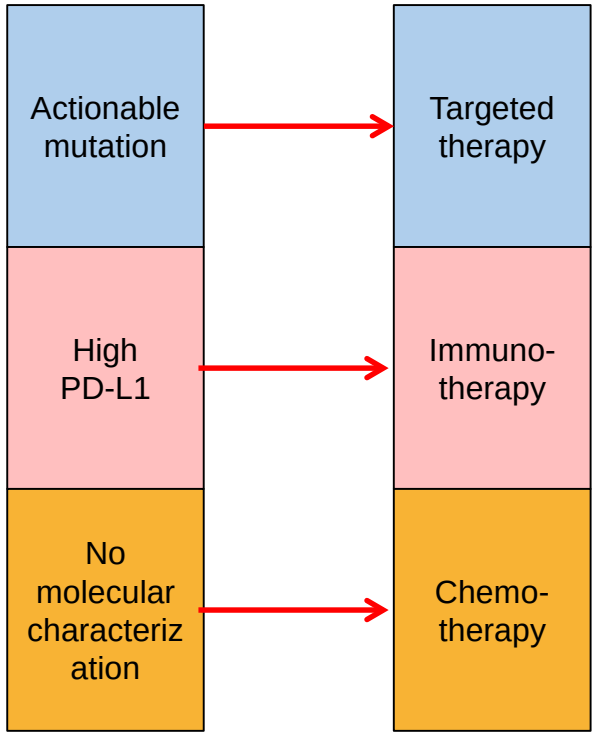
Precision medicine and immuno-oncology

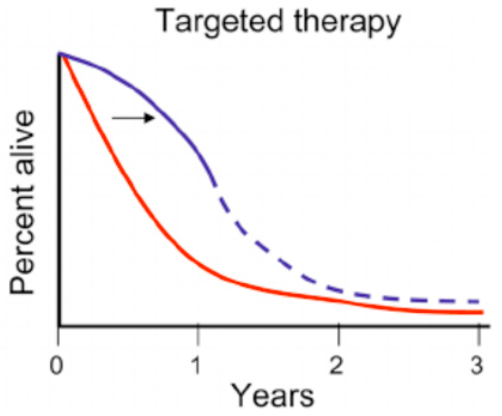
Luca Mazzarella, MD PhD

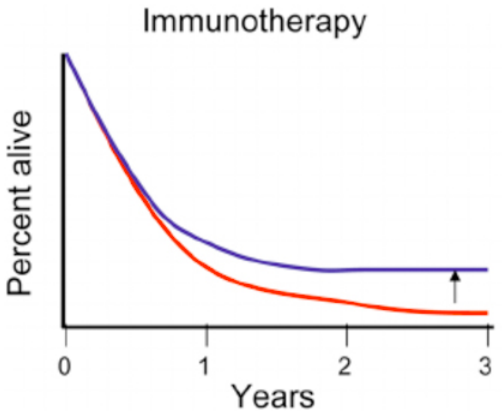
European Institute of Oncology, Milan

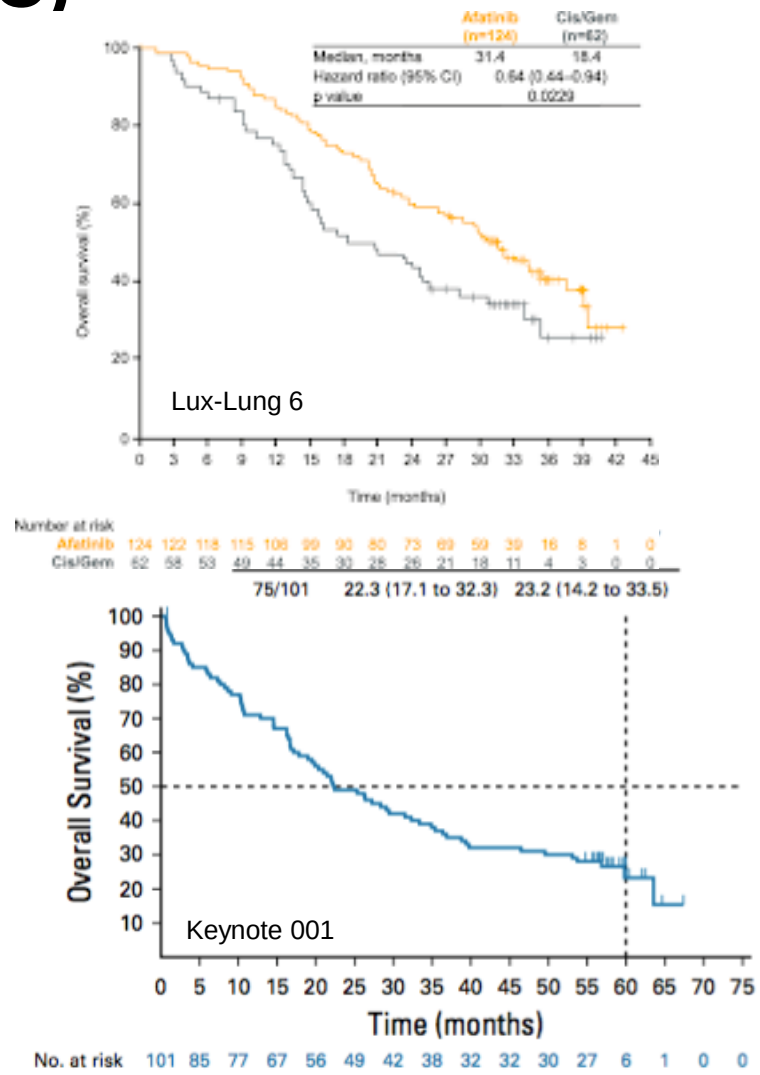
An overview of major advancements in oncology. Non-Small Cell Lung Cancer (NSCLC)

Diagnosis Treatment







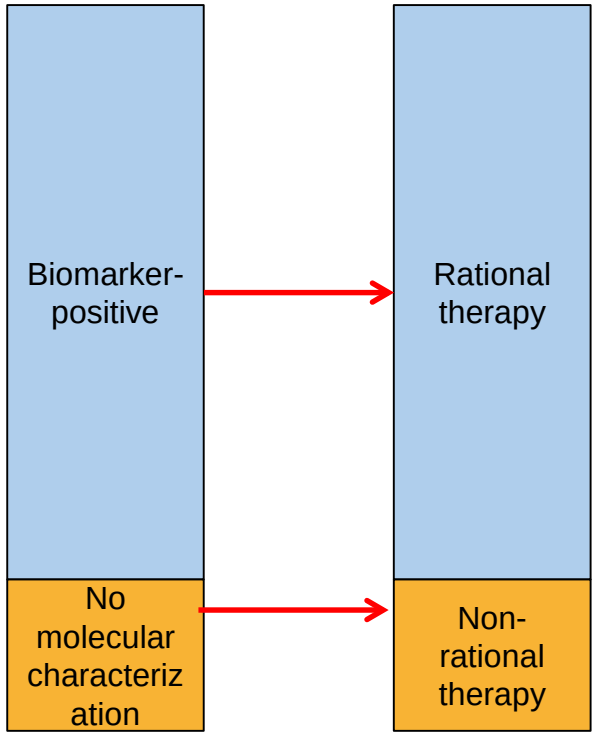


Wu et al Lancet Onc 2014

Garon JCO 2019

Outstanding questions

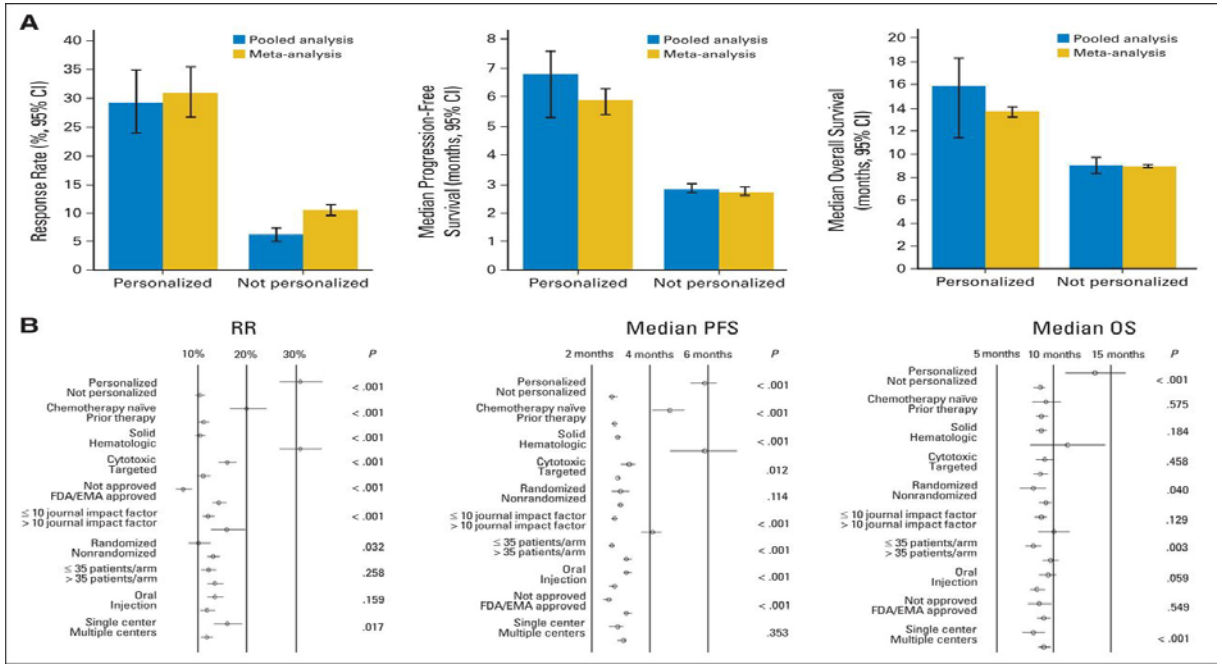
Diagnosis Treatment



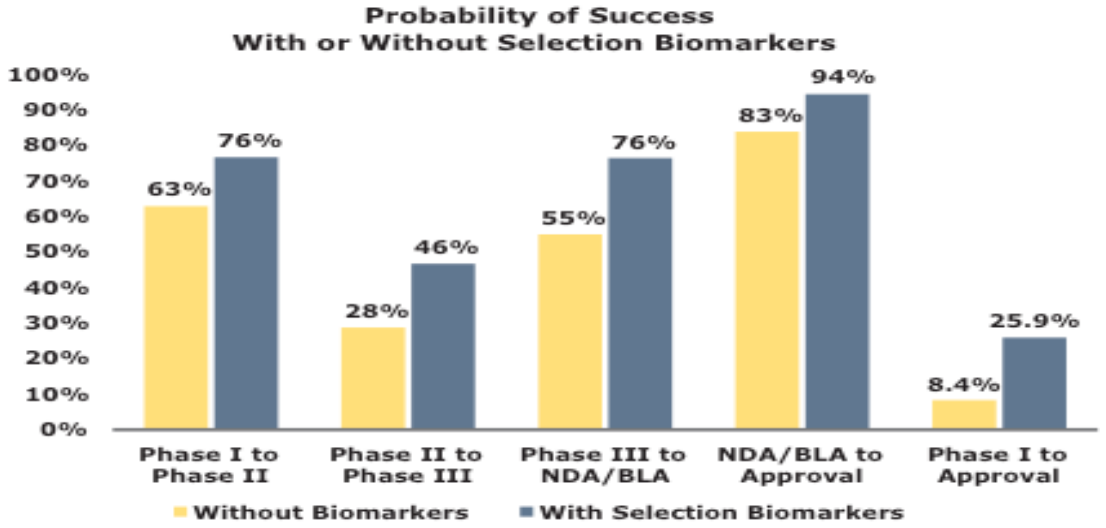
1. **How do we expand the population that can be treated rationally?**
   - Increase the number of targeted drugs

Targeting therapy improves efficacy

Benefit for patients



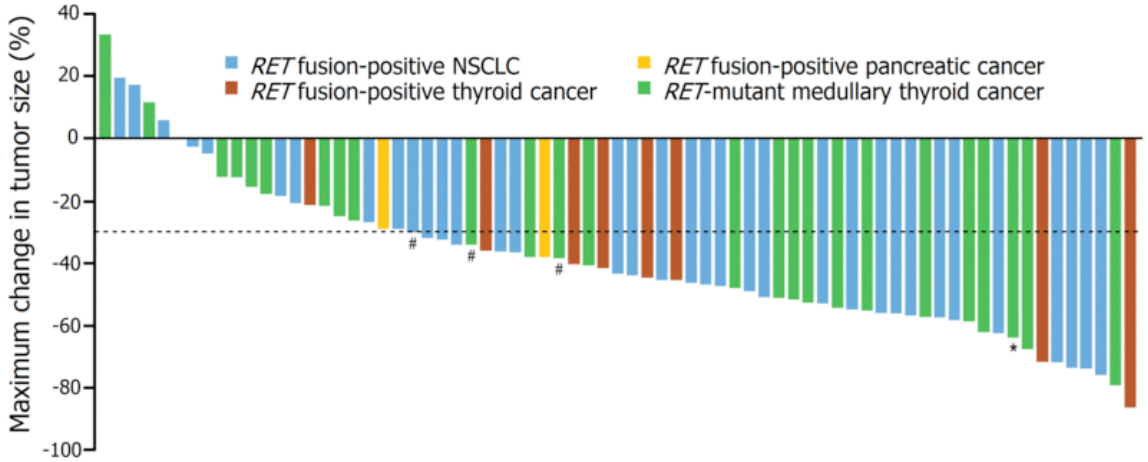
Benefit for drug development



Published in: Maria Schwaederle; Melissa Zhao; J. Jack Lee; Alexander M. Eggermont; Richard L. Schilsky; John Mendelsohn; Vladimir Lazar; Razelle Kurzrock; *JCO* **2015,** 33, 3817-3825.
DOI: 10.1200/JCO.2015.61.5997

Two recent examples of biomarkers for exceptionally active drugs: RET and NTRK

Efficacy of LOXO-292 in RET-Altered Cancers



Patients enrolled as of April 2, 2018. Follow-up as of July 19, 2018
Note: 7 patients not displayed; 4 due to treatment discontinuation prior to first post-baseline response assessment, 3 due to nonmeasurable disease at baseline (2 stable disease, and 1 complete response).
**Complete response; #Unconfirmed response awaiting confirmatory response assessment. NSCLC, non-small cell lung cancer.*

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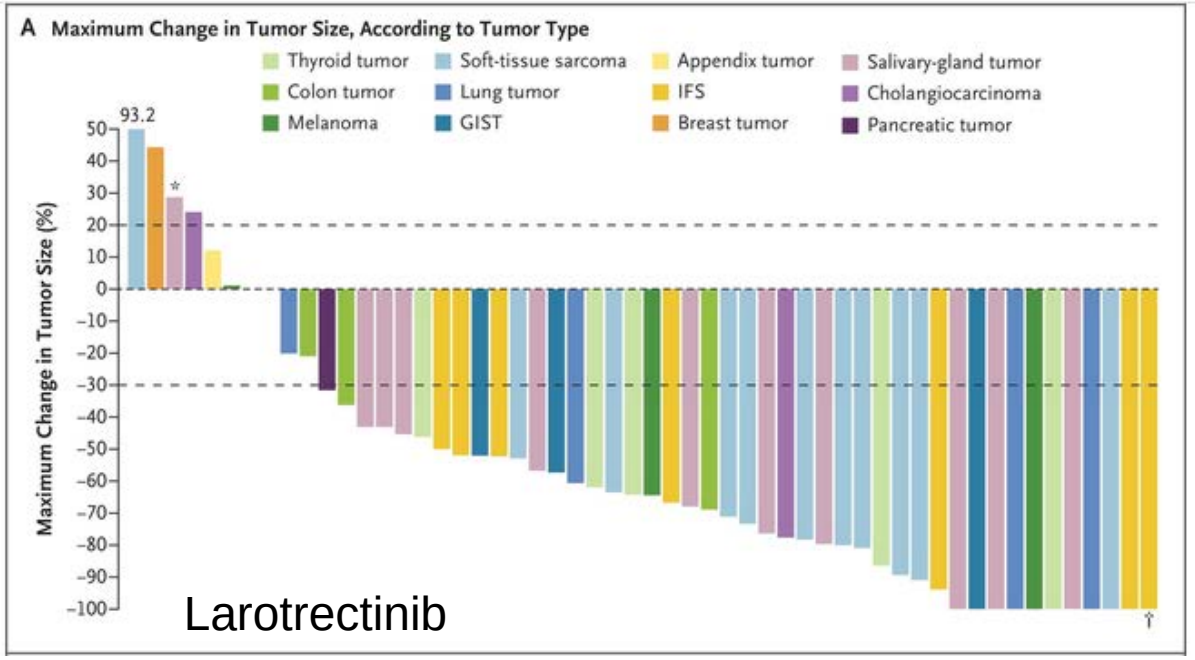
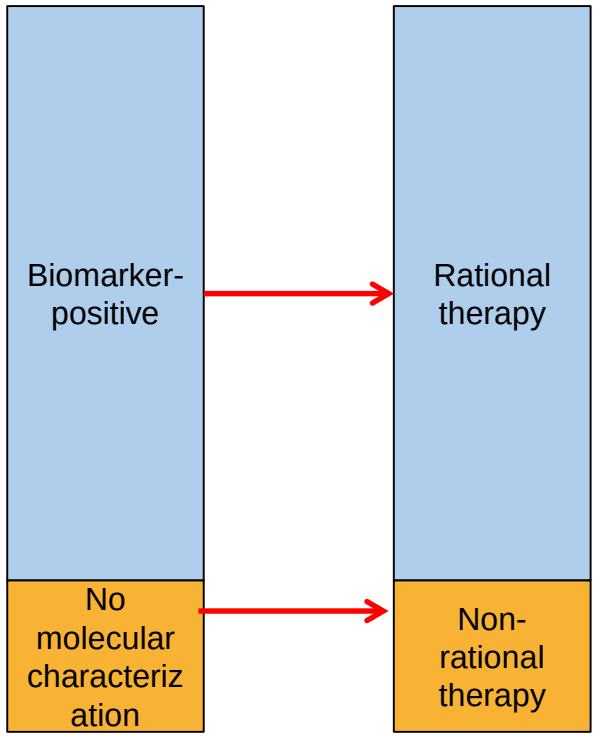


Larotrectinib

Outstanding questions



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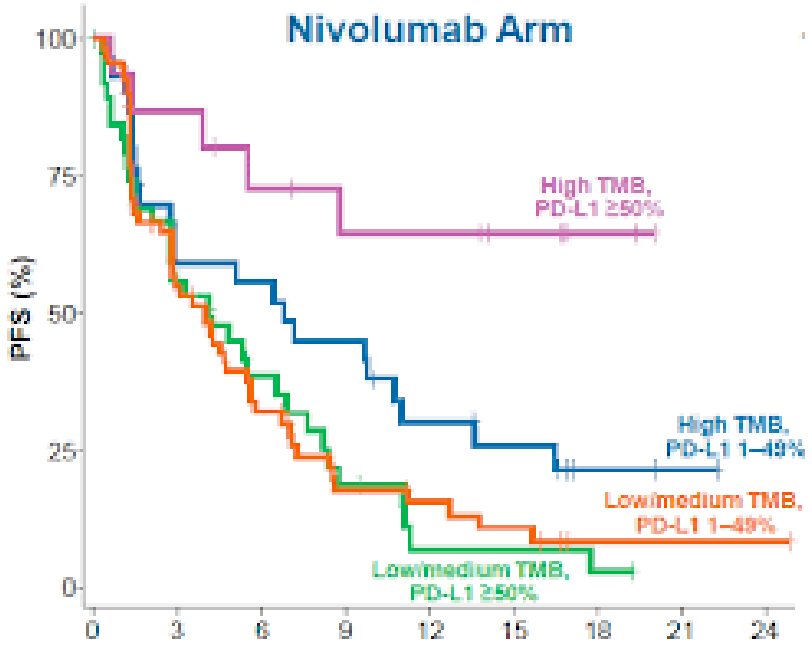
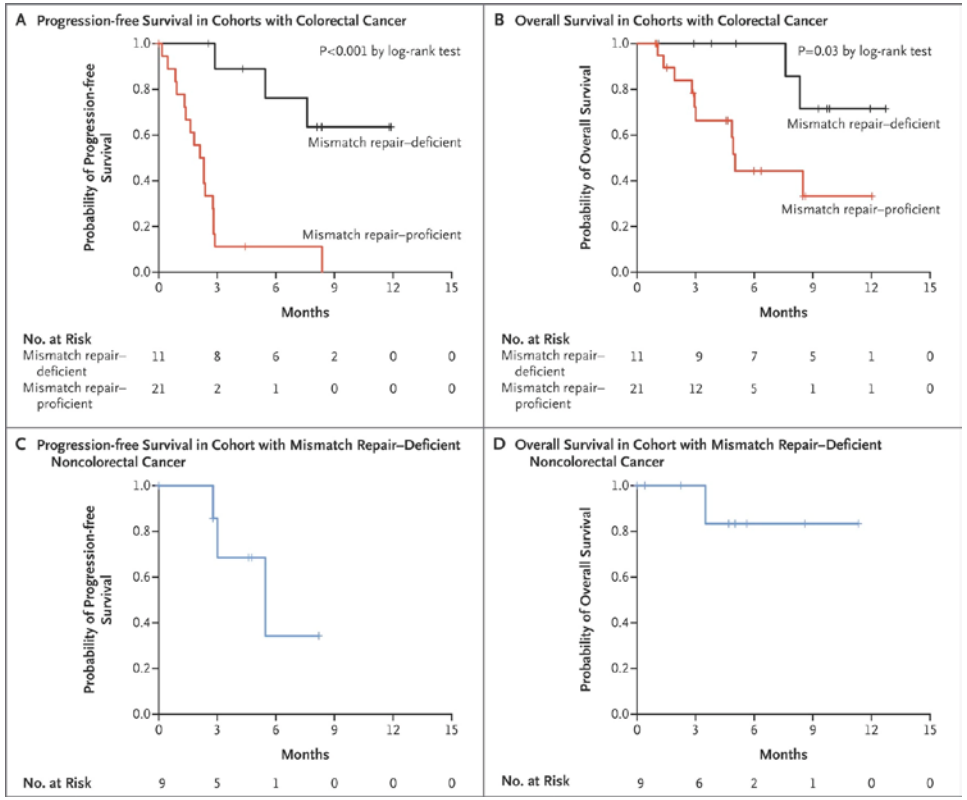
   - Increase the number of biomarkers

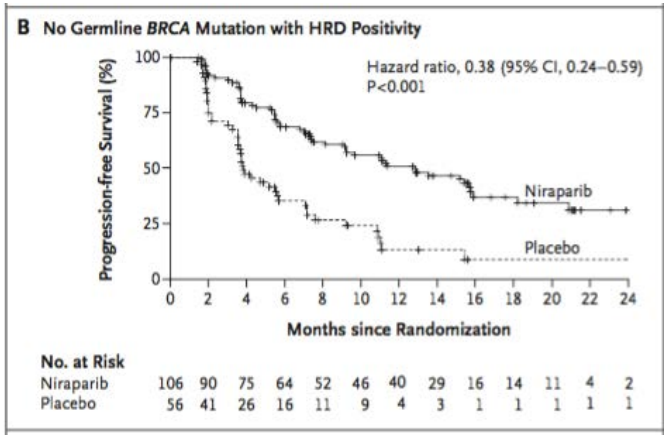
Examples of novel complex biomarkers: Tumor Mutational Burden (TMB), MisMatch Repair Deficiency (dMMR) and Homologous Recombination Deficiency (HRD)



Peters S AACR 2018

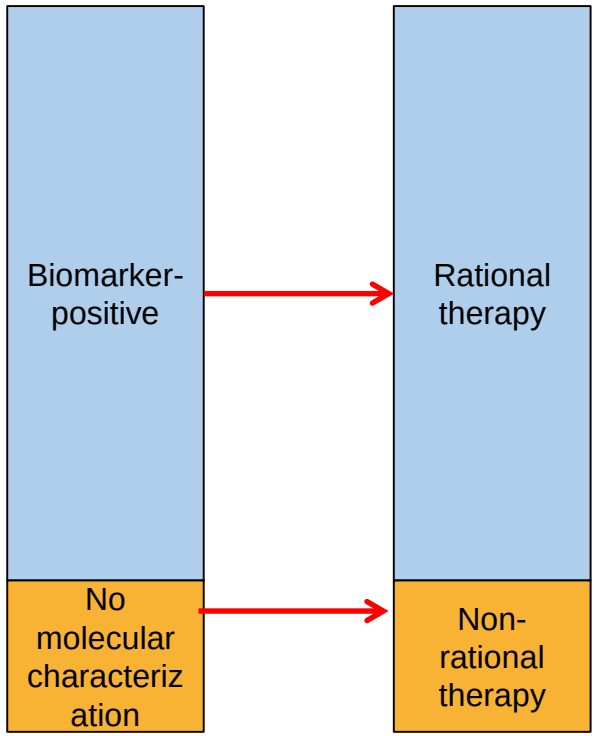


Le et al NEJM 2015



Mirza et al NEJM 2016

Outstanding questions



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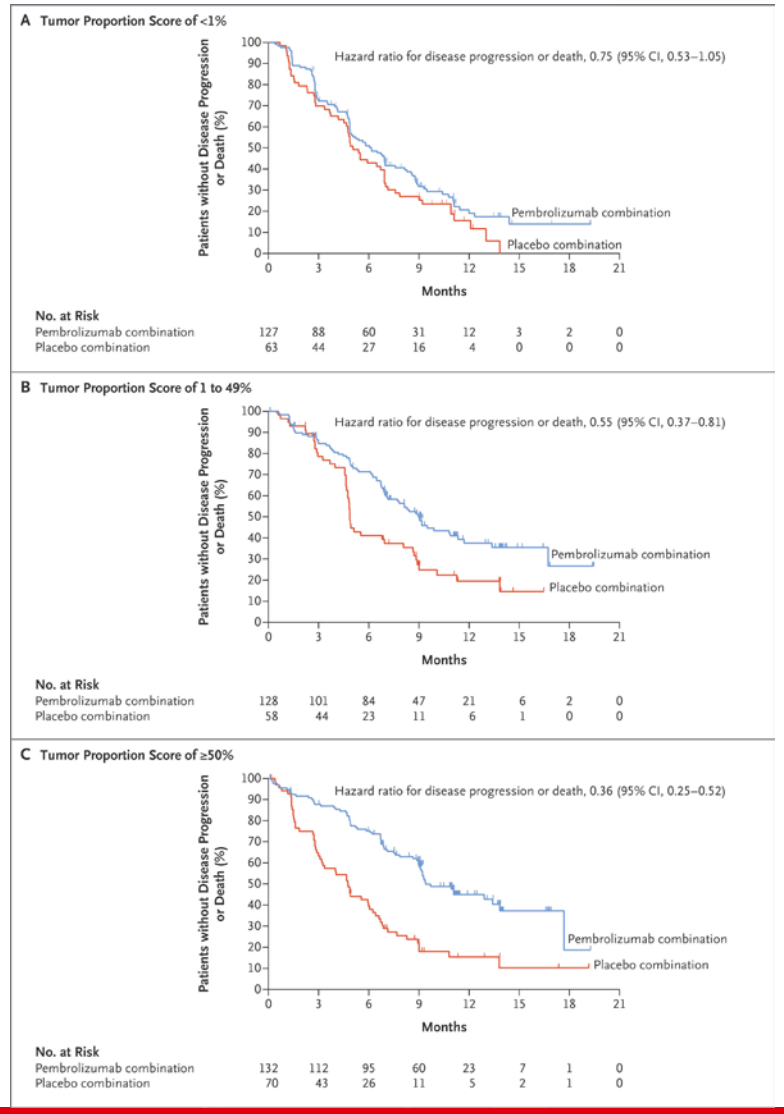
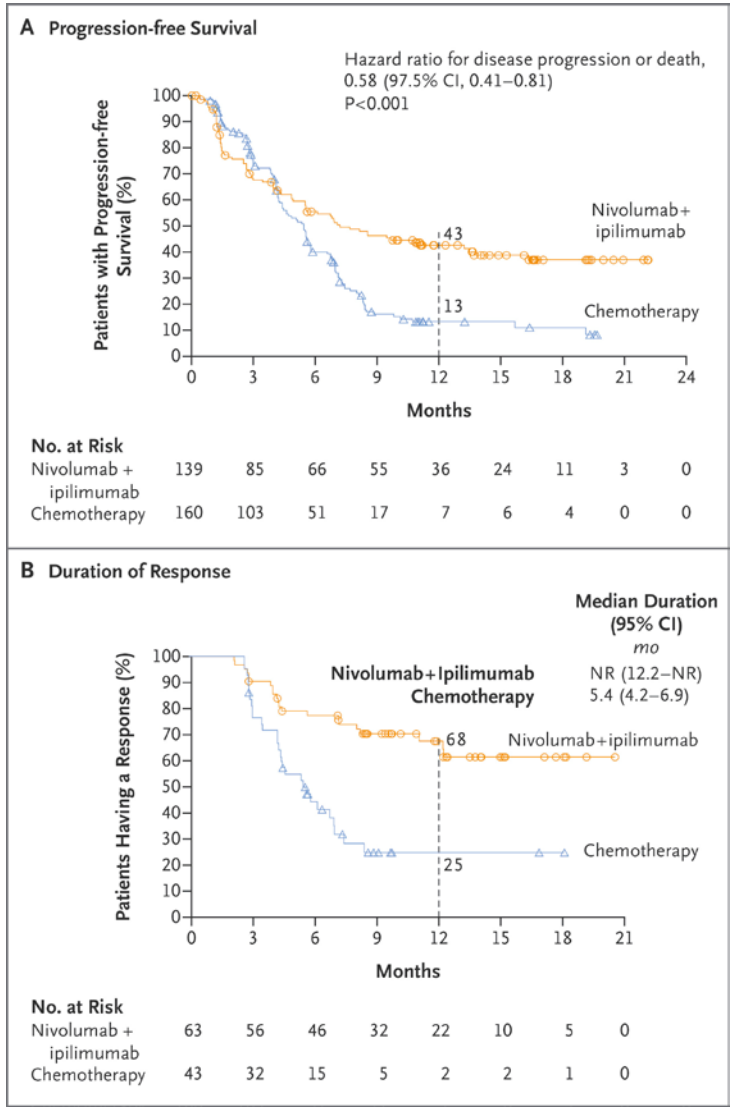
   - Combinations
     - PD(L)1 + CTLA4
     - Chemotherapy
     - Novel Immune Modulators
     - Targeted therapy

Chemotherapy and CTLA4+PD1

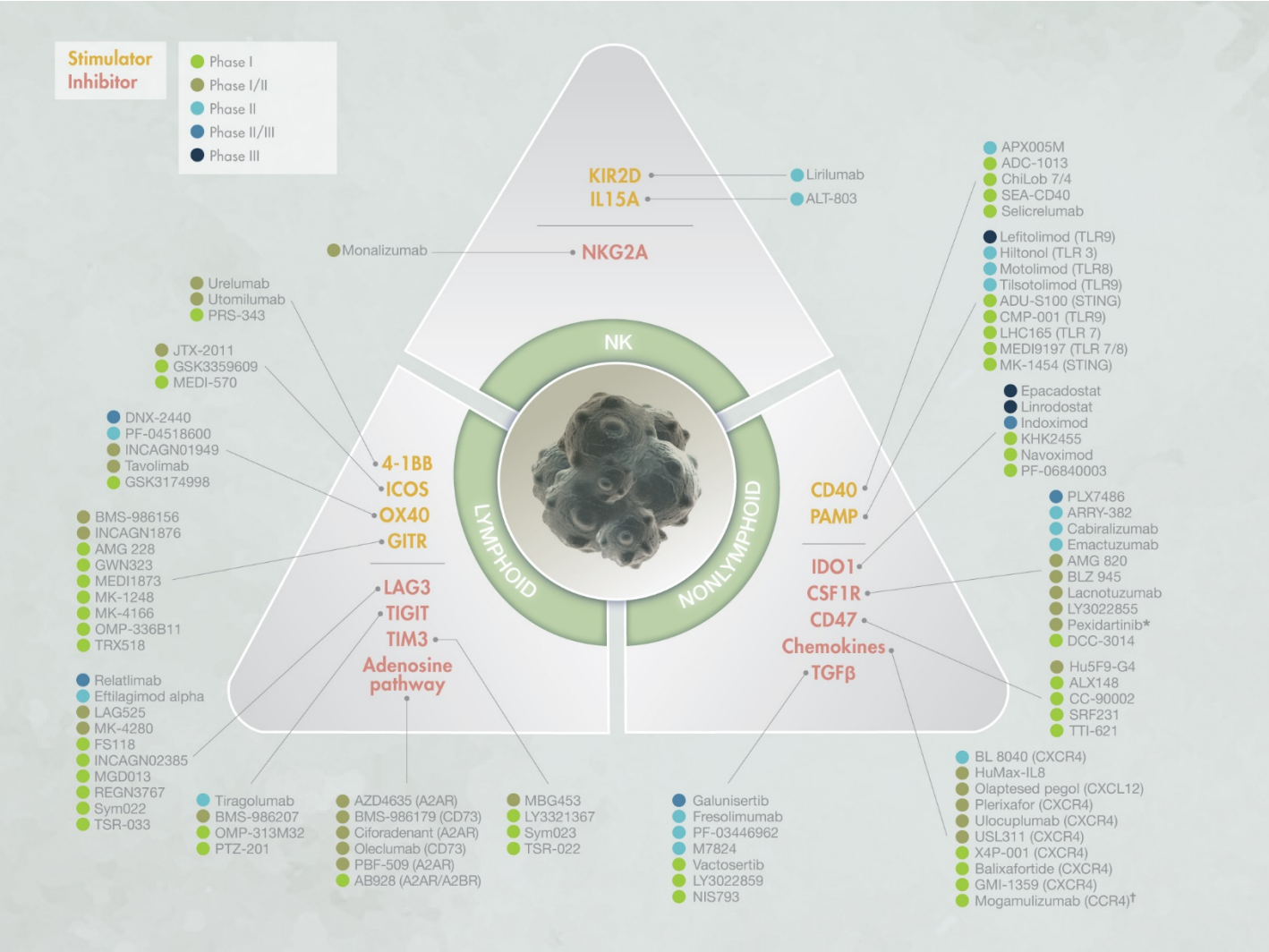


Keynote 189
Gandhi et al NEJM 2018



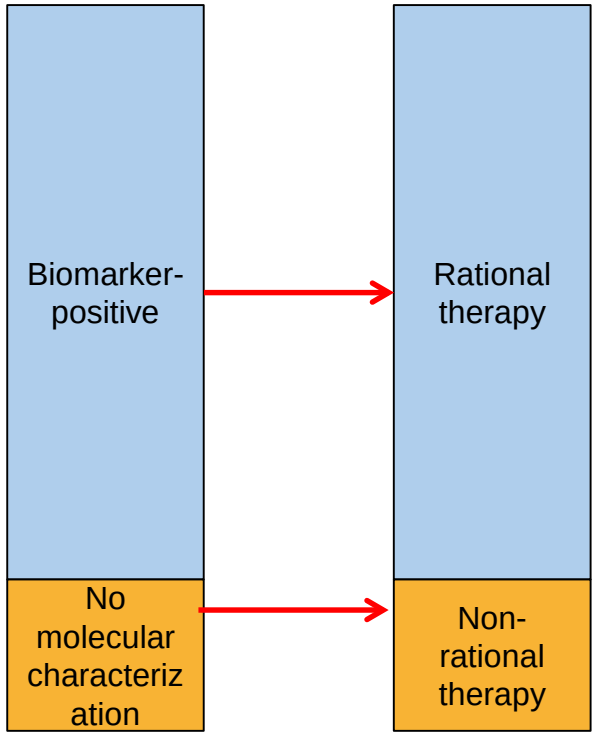
Checkmate 227
Hellman et al NEJM 2018

The evolving landscape of Next Generation Immune Modulators (NGIM)



Mazzarella et al Eur J Can 2018

Outstanding questions



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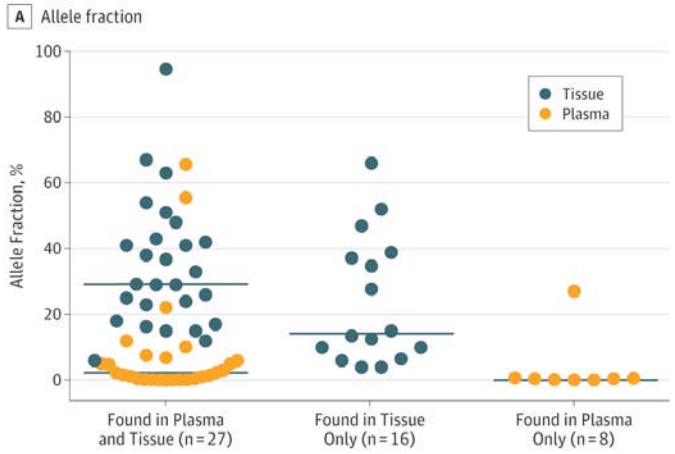
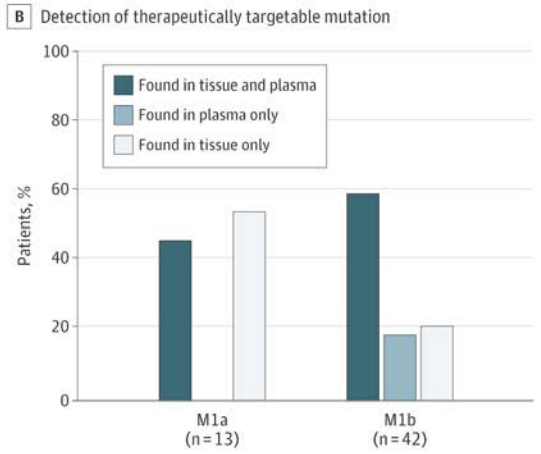
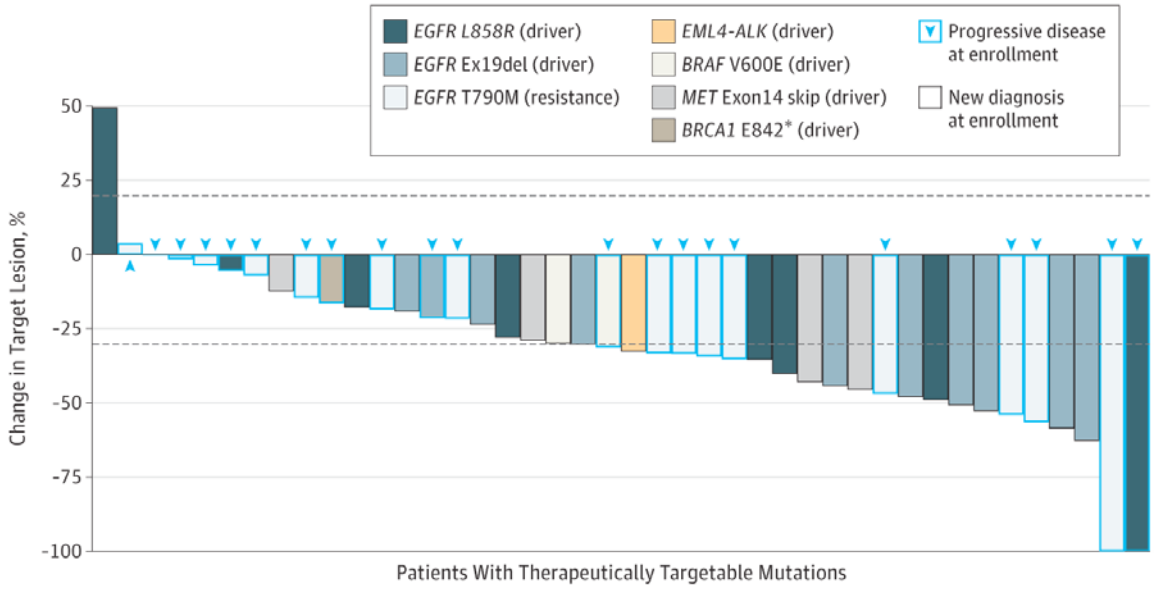
Treatment based on liquid biopsy only is effective

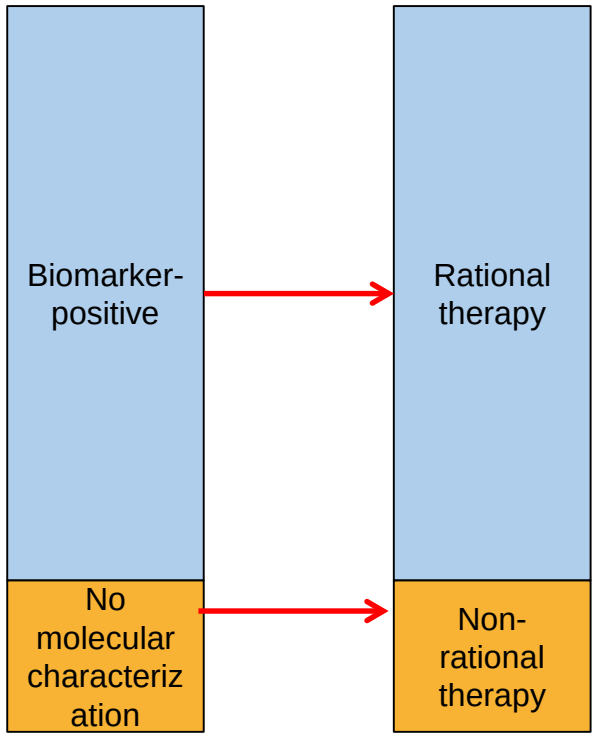






Aggarwal et al JAMA onc 2019

Outstanding questions



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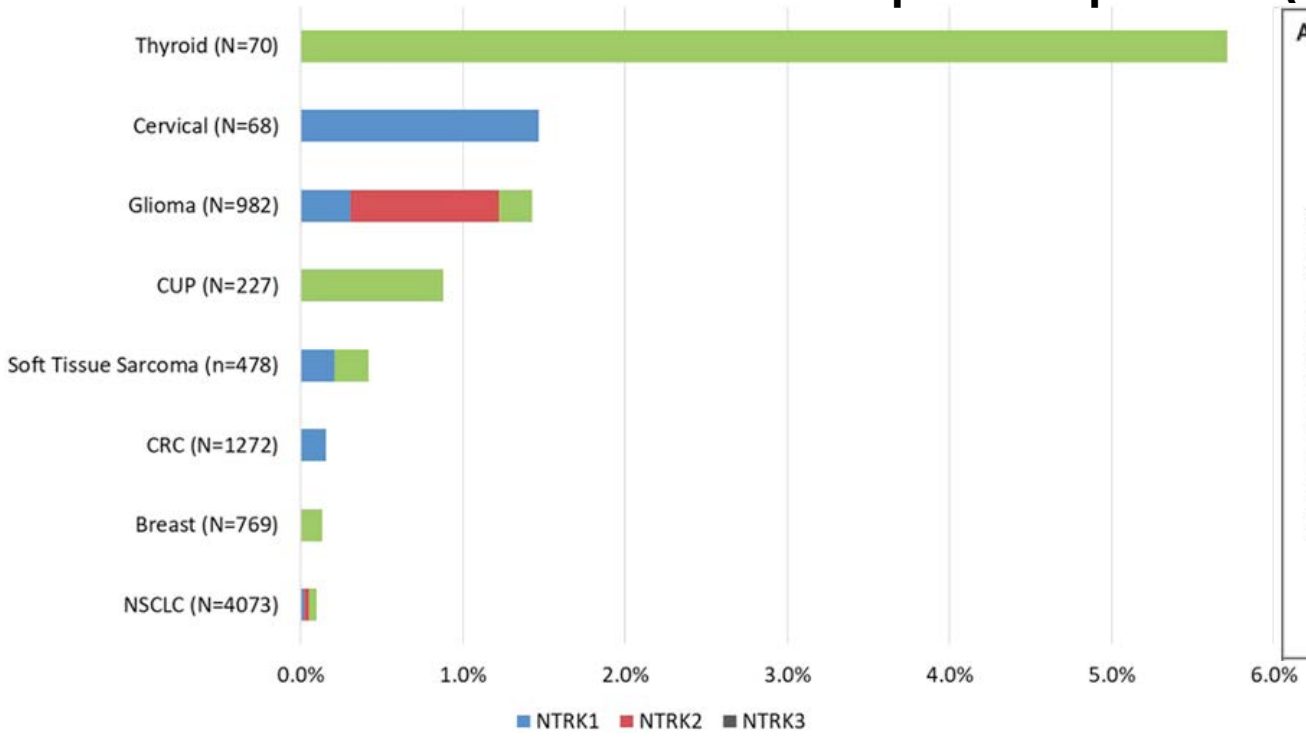
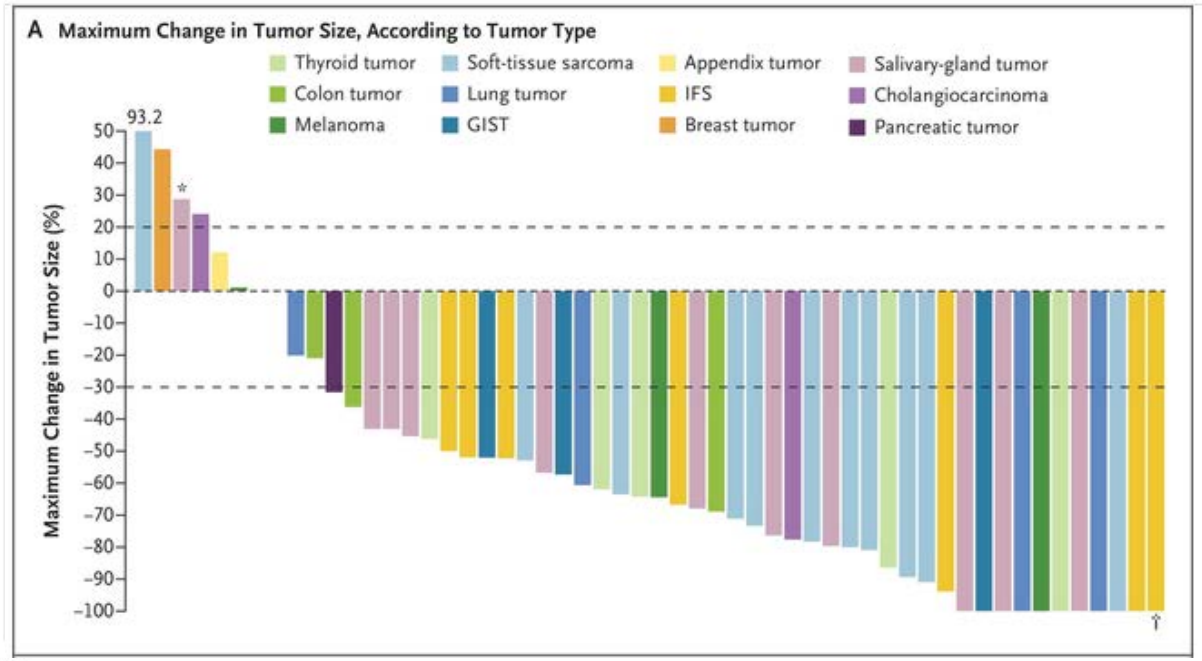
   - Build a statistical and regulatory consensus for trials on hyperfragmented population

More biomarkers means rarer biomarkers!
An extreme example: NTRK

31 out of 11.502 patients positive (0.27%!!!!!)



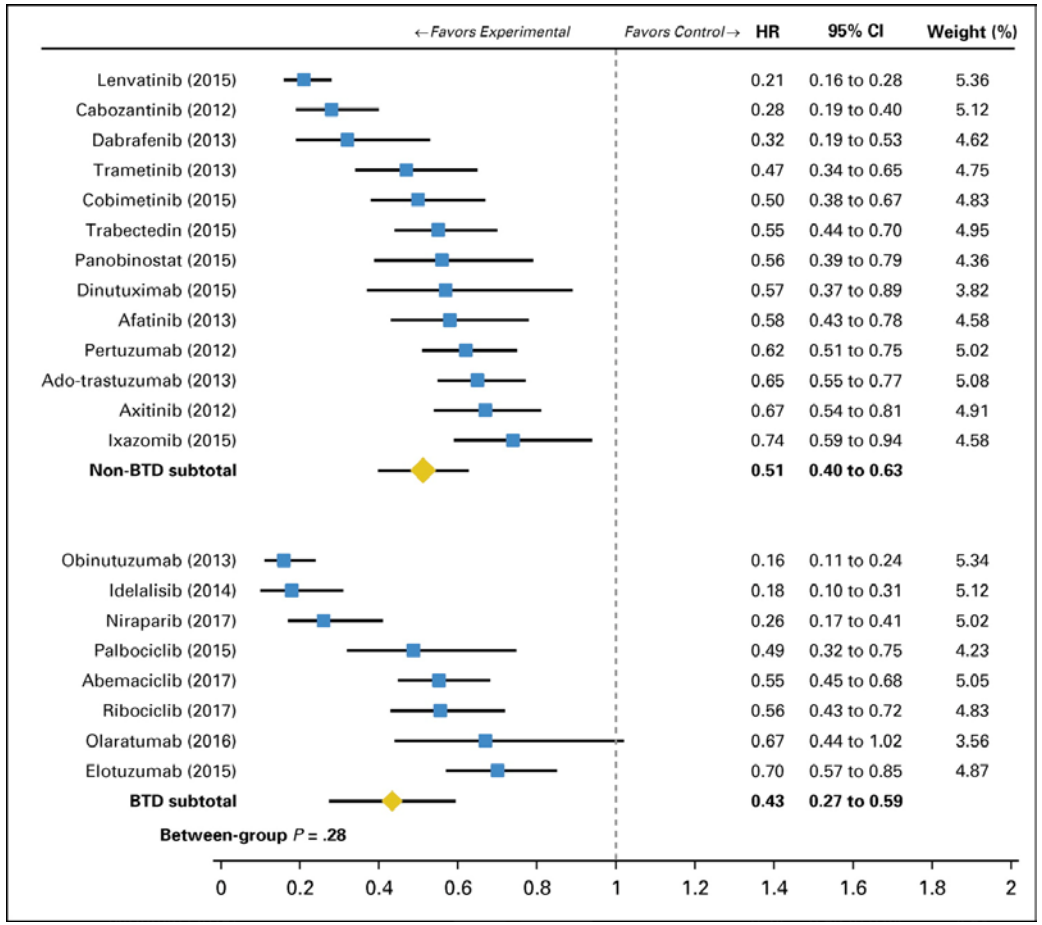


Gatalica et al Mod Path 2018

The need for a new clinical trial framework

- Difficult to conduct randomized controlled trials with hyperfragmented population
- Larger phase 1-2 trials than phase 3
- Emphasis on early biomarker implementation
- Novel trial designs (basket, umbrella, platform, adaptive)
- Include real world data
- Regulatory approval should be granted even without RCTs
- However this should be regulated and explicit criteria for trial conduct should be identified

Access vs evidence. A hamletic tradeoff



Outcome parameters and safety are not different between breakthrough (BT) and non-breakthrough (nBT)-approved drugs

Expectedly, BT drugs were approved 2 years earlier than nBT

How should we interpret these data?

- No justification for granting BT approval since clinical benefit is equal to nBT (authors'perspective)

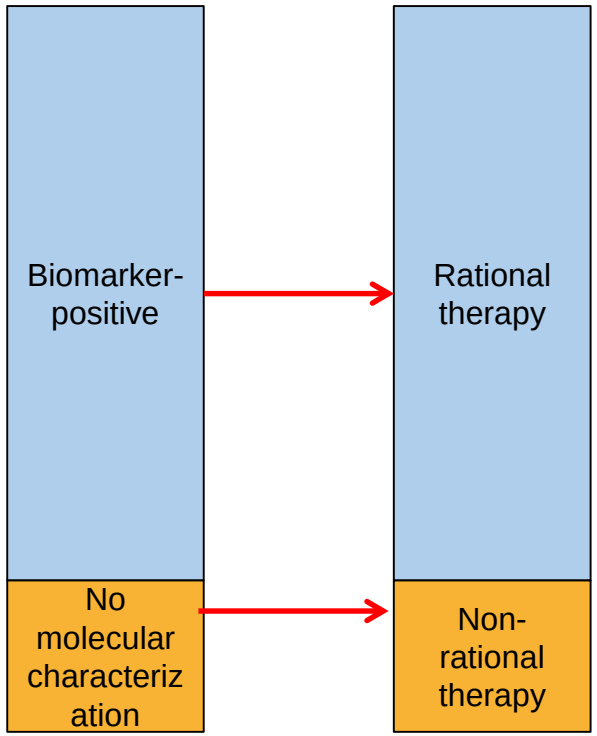
Or

- No justification for NOT granting BT approval to nBT drugs, since clinical benefit is equal (my perspective)

In general, what do we prefer: earlier access or stronger evidence?

Hwang et al JCO 2018

Outstanding questions



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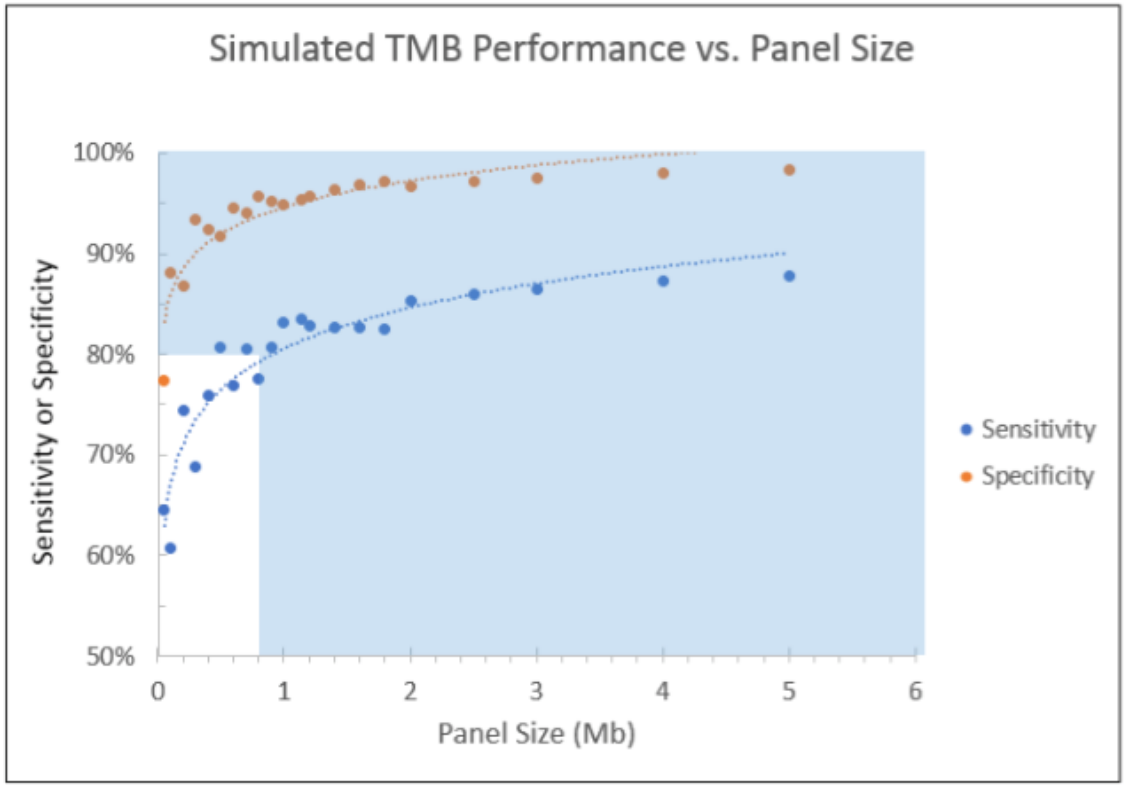
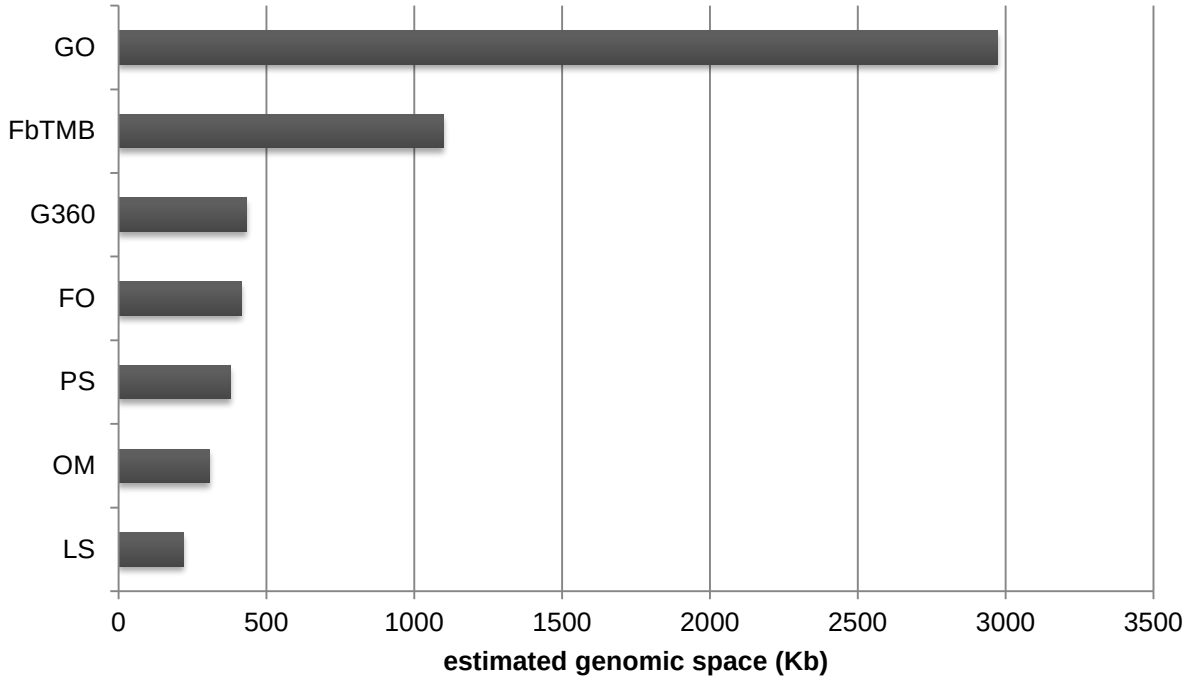
   - Decrease the need for biopsy by using circulating biomarkers
   - Build a statistical and regulatory consensus for trials on hyperfragmented population
   - Educate patients, doctors and all stakeholders on pros and cons of genetic/clinical data sharing

As the size of the sequenced genome increases, so does the chance for incidental findings or variants of unknown significance



Liquid biopsy panels are getting bigger



Gandara et al Nat Med 2018

Conclusion

- Oncology is steadily becoming
  - histology-agnostic
  - biomarker-avid
  - data-intensive
- This is causing a radical change in the way:
  - diagnosis is obtained
  - clinical research is conducted
  - patients are engaged
- **We need to educate ourselves to this new world**
  - Devise adequate statistical tools
  - Create an adequately regulated but sufficiently flexible regulatory environment
  - Engage in public debates over the utility of genetic and clinical data exchange
  - Provide adequate educational tools to all stakeholders

Thank you for your attention

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