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ONCOLOGY

Genomics: El Futuro del Cancer

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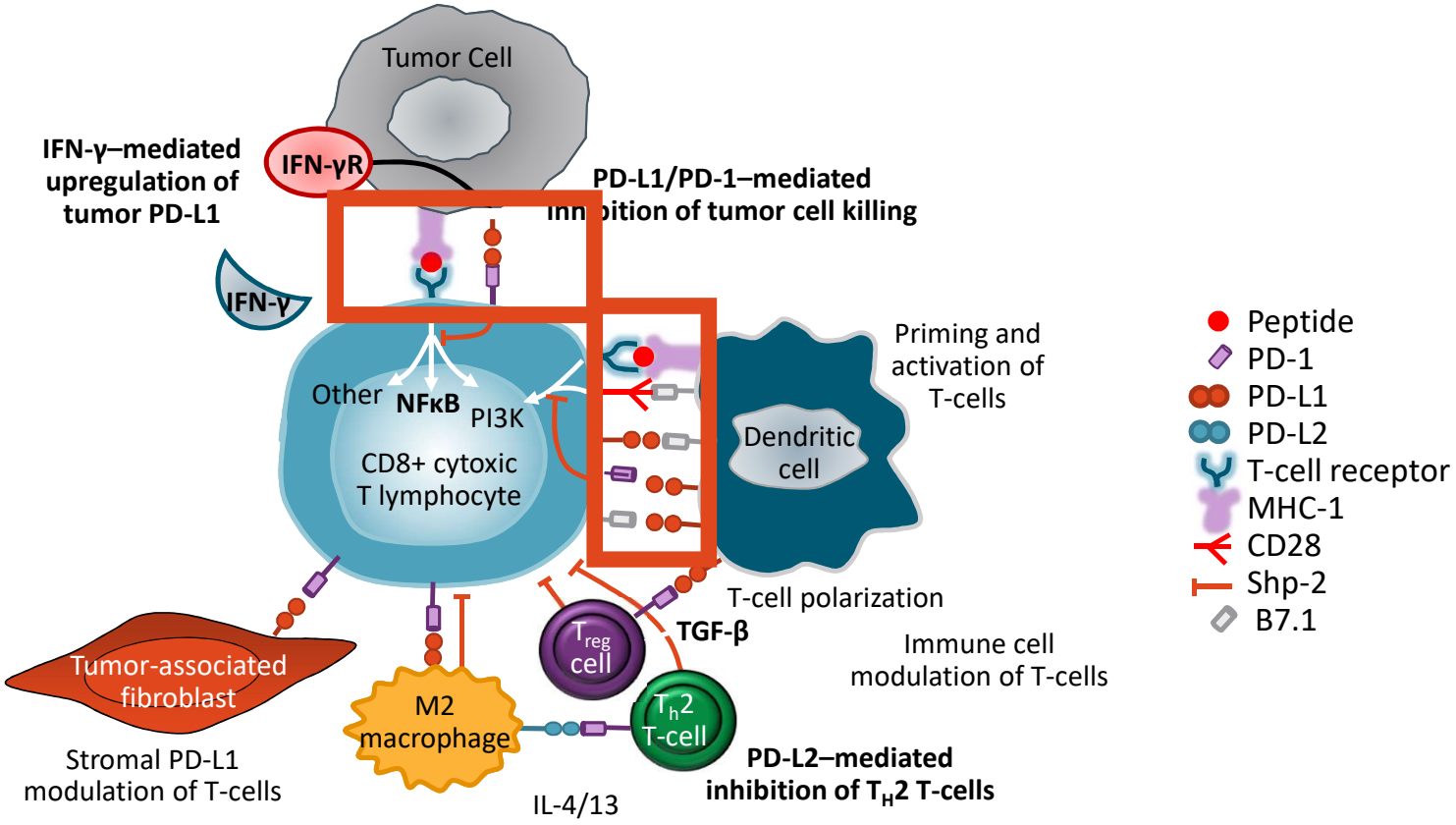
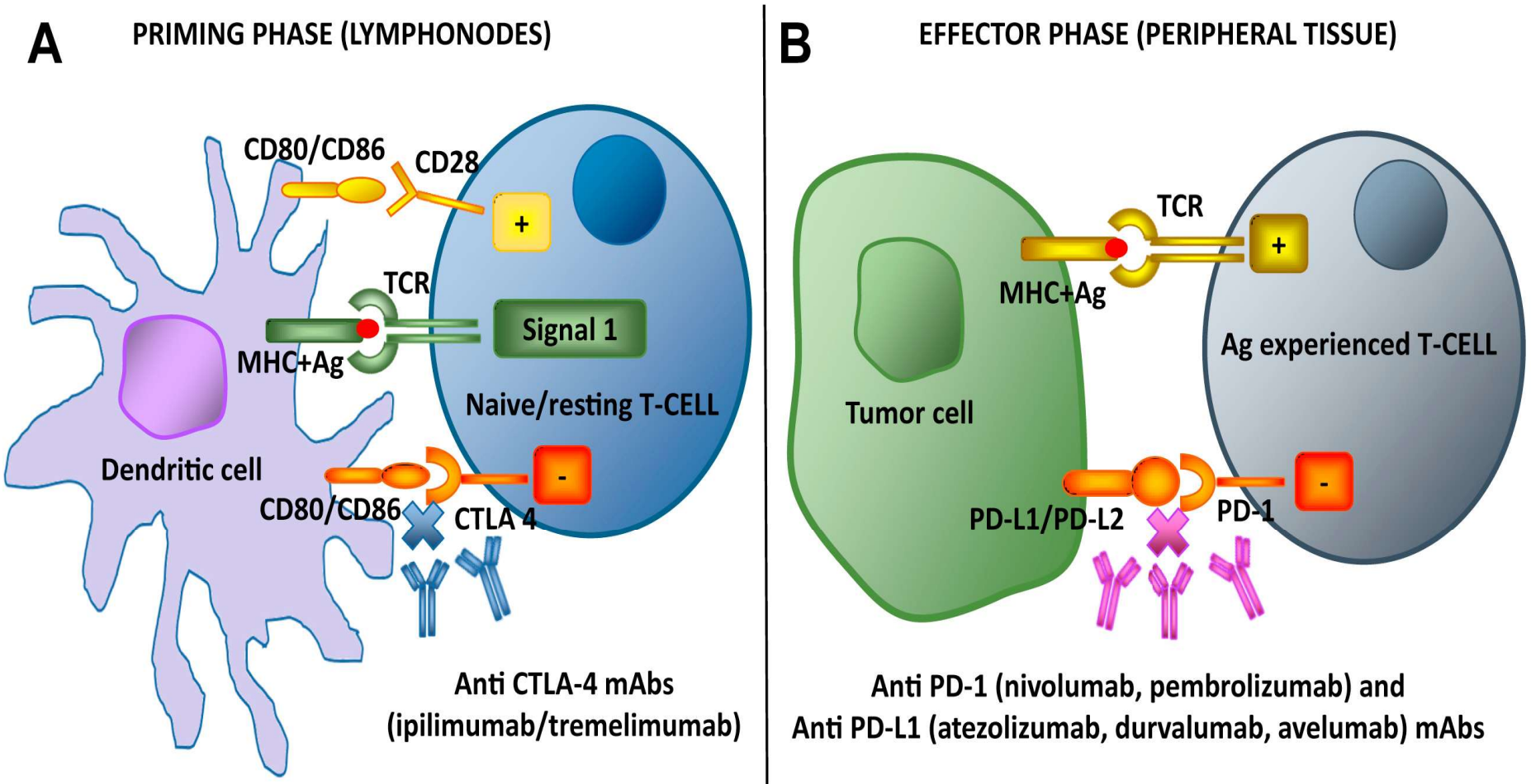
Overview

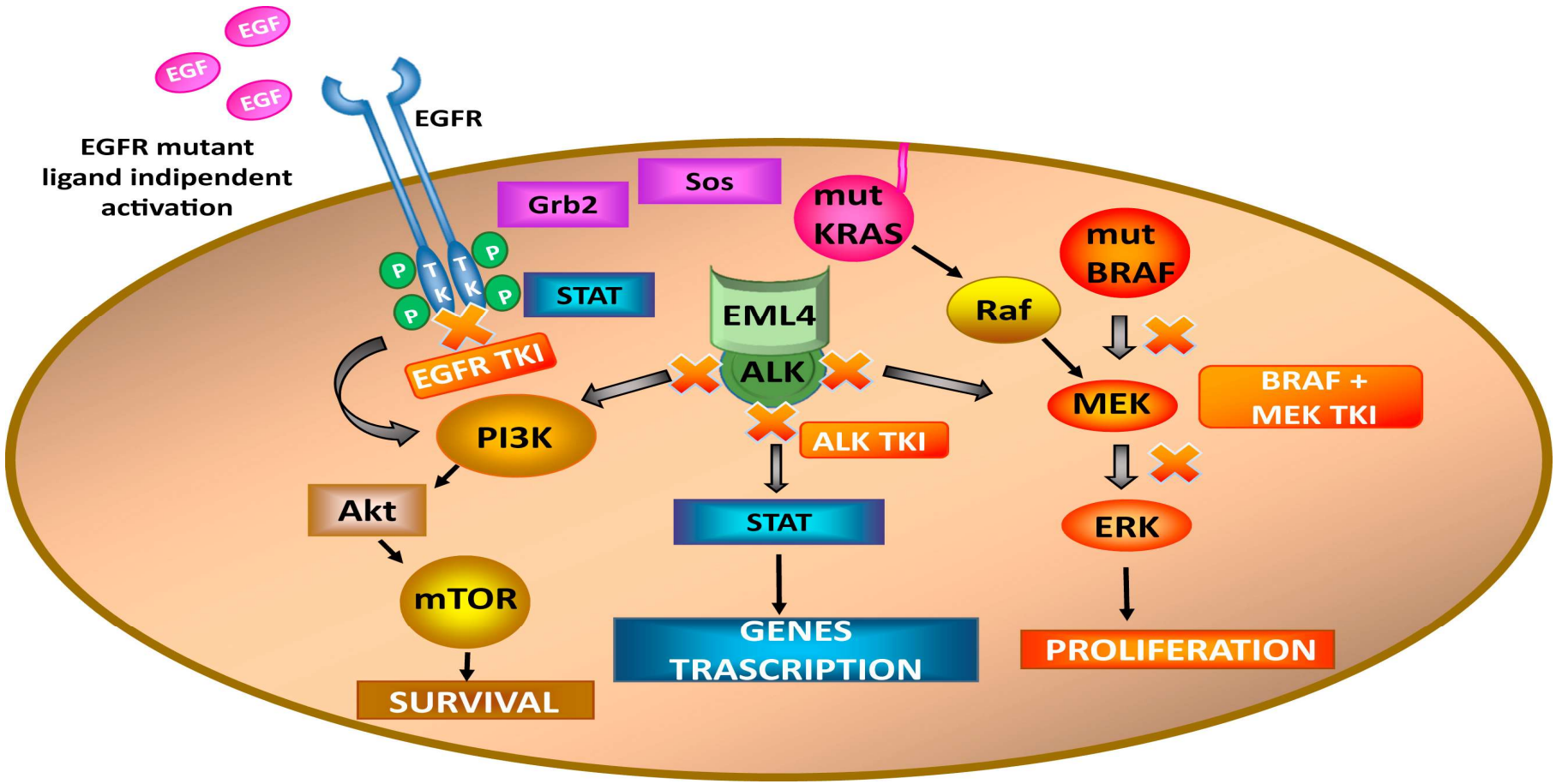
- Background
- Tumor Mutational Burden (TMB)
- Microsatellite Instability (MSI)
- Potential New Biomarkers in Lung Cancer: Immunogenic Neoantigen Burden
- Advanced NSCLC: Is PD-L1 Testing Enough?

Immunologic Synapses Within the Tumor Microenvironment

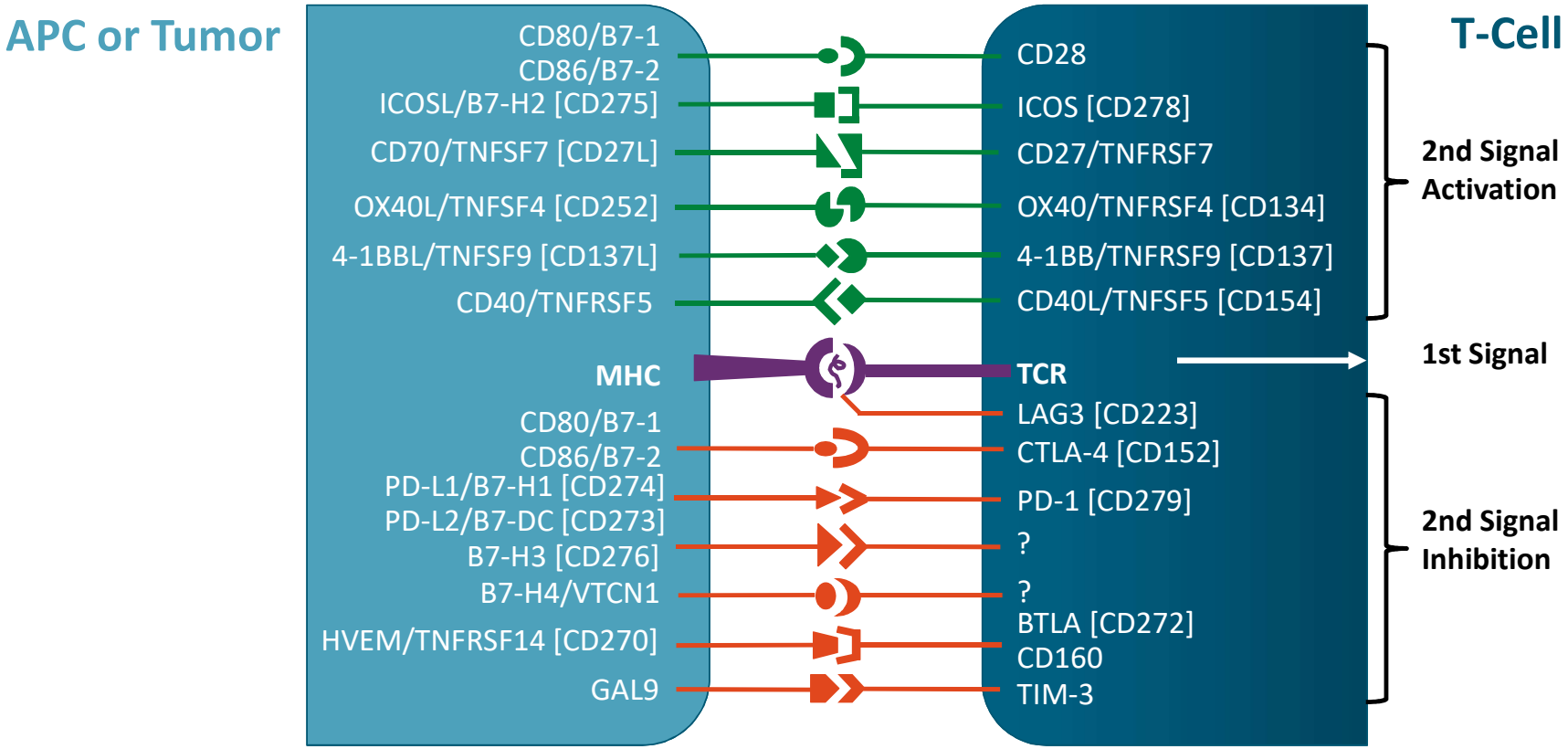


Sznol. Clin Cancer Res. 2013;19:1021. Ziani. Front Immunol. 2018;9:414. LaFleur. J Immunol. 2018;200:375.
Taylor. Immunology. 2006;117:433. Arasanz. Oncotarget. 2017;8:54936.





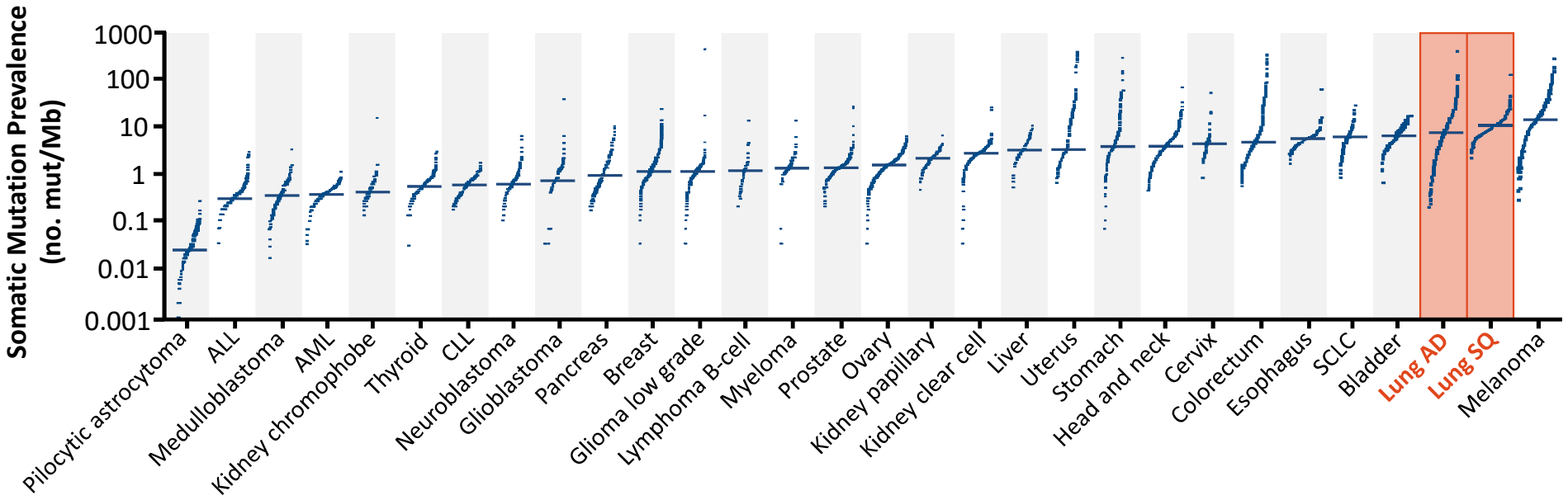
T-Cell Responses Are Regulated by Multiple Ligand-Receptor Interactions With APCs or Tumor Cells



Adapted from Pardoll. Nat Rev Cancer. 2012;12:252.

Tumor Mutational Burden (TMB)

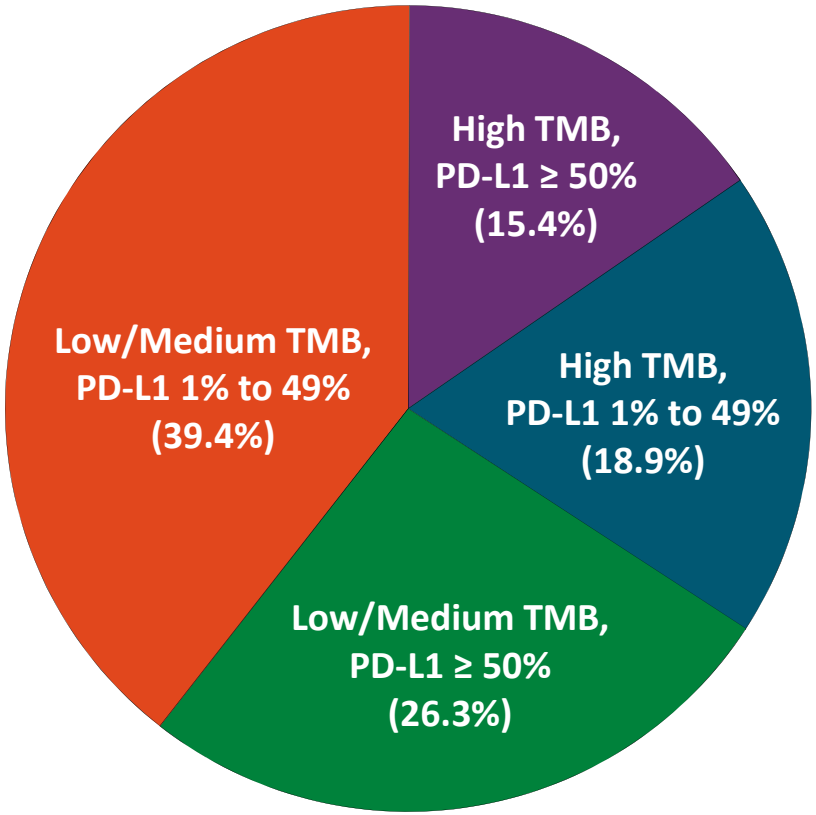
Prevalence of Somatic Mutations Across Tumor Types



- NSCLC has among the highest prevalence of somatic mutations: 0.1-100 mut/Mb

Alexandrov. Nature. 2013;500:415. Lawrence. Nature. 2013;499:214.

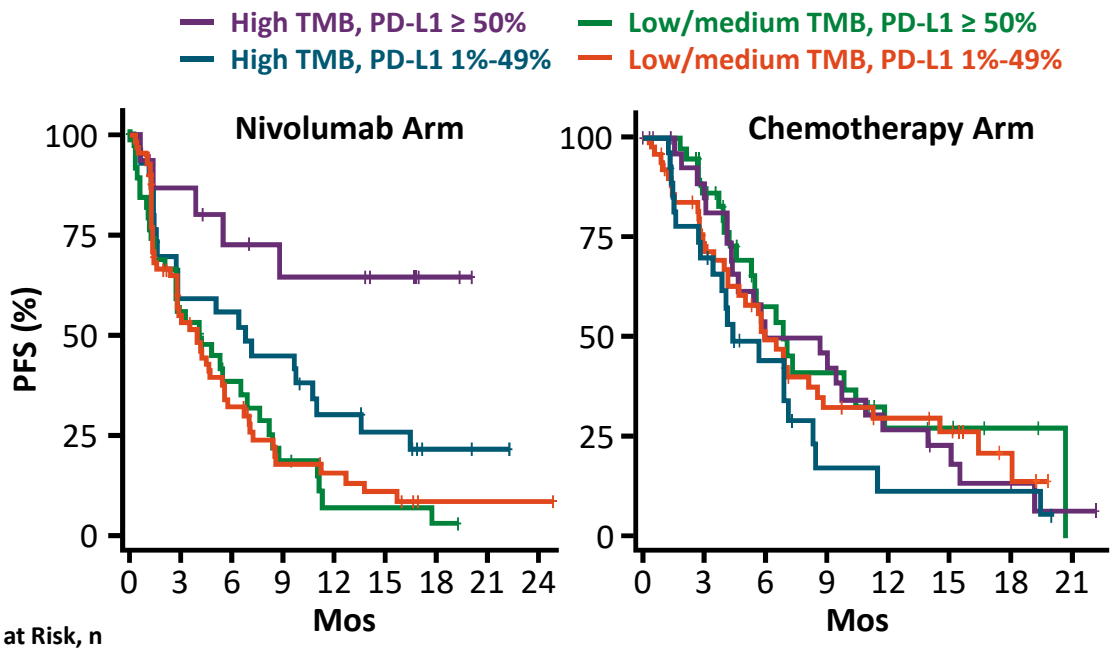
No Association Between TMB and PD-L1 Expression in Advanced NSCLC



Carbone. NEJM. 2017;376:2415. Adapted by Peters. AACR 2017. Abstr CT082.

CheckMate 026: PFS by TMB Subgroup and PD-L1 Expression With Nivolumab in First-line NSCLC

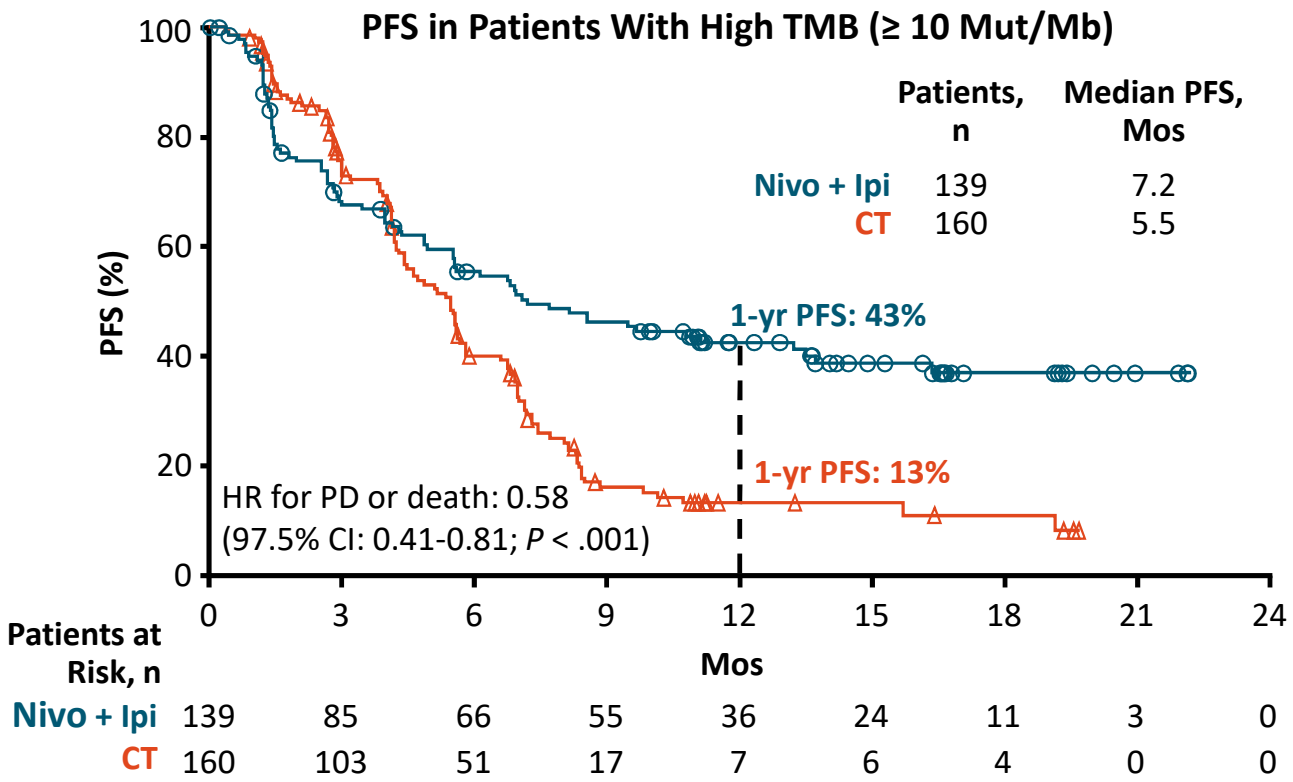
- Exploratory analysis of patients from phase III CheckMate 026 evaluating single-agent nivolumab vs CT for advanced NSCLC
- Patients with high TMB/ high PD-L1 had best outcomes with nivolumab
- Trend toward patients with high TMB/int PD-L1 doing better than those with low/int TMB/high PD-L1



Patients at Risk, n																
High TMB, PD-L1 ≥ 50%	16	13	10	8	8	6	2	0	0	32	24	13	12	7	5	2	1
High TMB, PD-L1 1%-49%	31	17	16	13	8	6	2	1	0	28	18	9	3	2	2	2	0
Low/medium TMB, PD-L1 ≥ 50%	41	21	12	6	2	2	1	0	0	41	30	14	10	5	4	2	0
Low/medium TMB, PD-L1 1%-49%	70	33	18	9	7	5	1	1	1	53	35	23	13	10	8	3	0

Peters. AACR 2017. Abstr CT082.

CheckMate 227: Nivolumab + Ipilimumab in Patients With Advanced NSCLC and High TMB (≥ 10 Mut/Mb)



- Press Release (July 2019): CheckMate 227 met its coprimary endpoint of significantly improved OS with first-line nivolumab + ipilimumab vs CT in patients with ≥ 1% PD-L1 expression
- Data and results to be submitted to the FDA and presented at an upcoming medical meeting

In patients with TMB < 10 mut/Mb treated with nivo + ipi vs CT, the HR was 1.07 (95% CI: 0.84-1.35; *P* = .0018).

Hellmann. AACR 2018. Abstr CT077.

TMB in NSCLC: Summary to Date

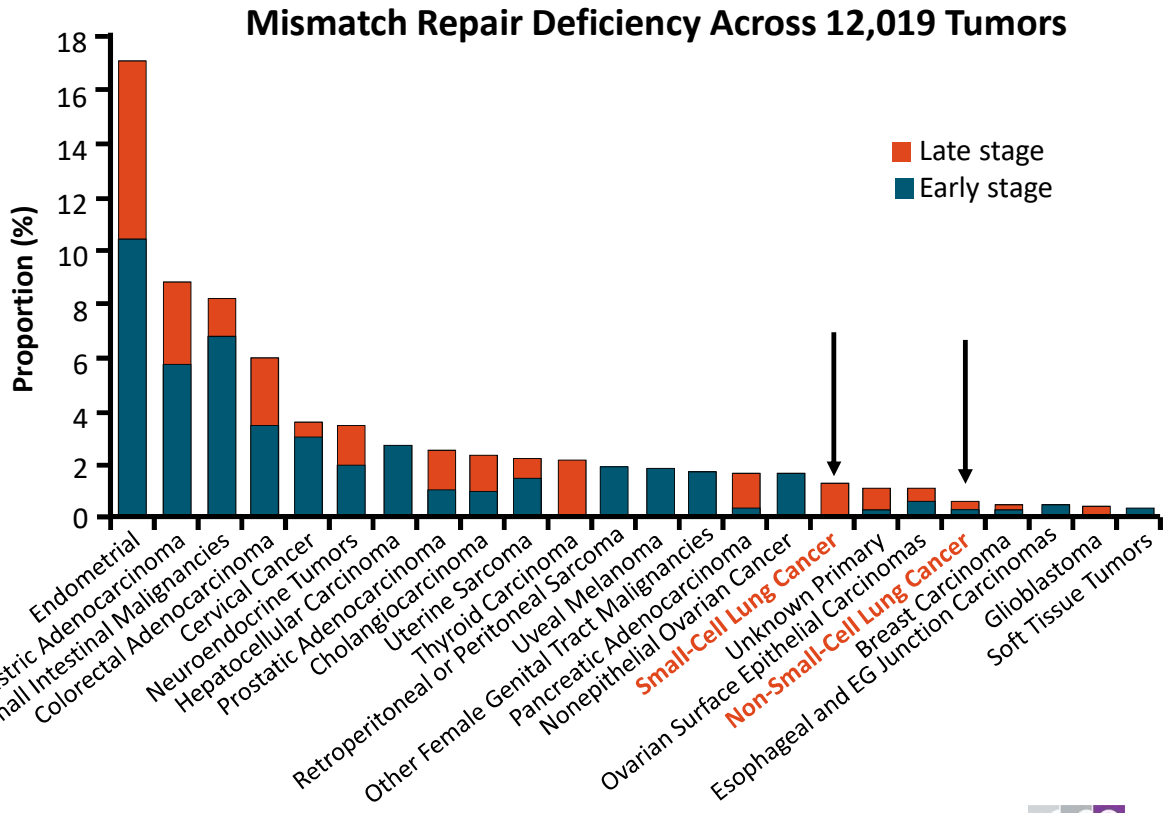
- Unclear clinical role for TMB given lack of FDA-approved therapy for TMB-high NSCLC to date
- Multiple issues with TMB
  - Standardization across assays (tumor normal vs tumor only, genomic coverage)
    - Efforts ongoing to address standardization of TMB calculation and reporting
  - Appropriate cutoff
  - Tissue input requirements
    - Tissue vs cfDNA
    - Tissue heterogeneity and tumor purity
  - Expensive and slower test than IHC
    - However, forces clinicians to wait for driver mutation results before treating with anti–PD-1 therapy

Slide credit: clinicaloptions.com

Microsatellite Instability (MSI)

MSI/dMMR in Lung Cancer

- MSI is distinct from TMB
  - MSI is specific type of frameshift mutation associated with MMR deficiency
  - TMB can be any type of mutation (eg, point, frameshift, fusion)
- MSI is commonly tested for in GI, GU cancers
- However, it is not worth testing independently for MSI-H in lung cancer
  - Uses up tissue that should be saved for driver mutation assessment
  - Would not change management for first-line ES-SCLC or NSCLC in 2019



Le. Science. 2017;357:409.

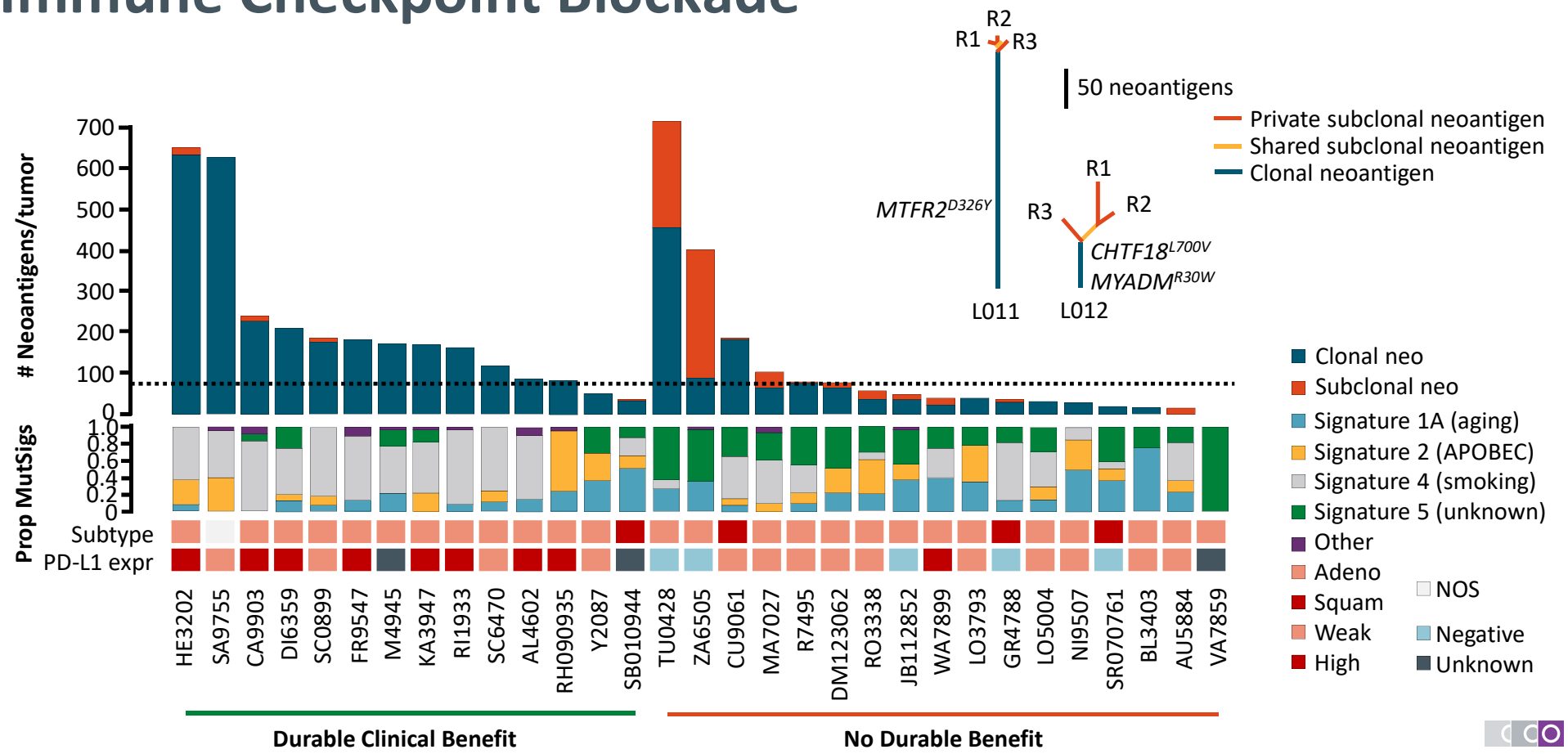
Potential New Biomarkers in Lung Cancer: Immunogenic Neoantigen Burden

Immunogenic Neoantigen Burden

- TMB represents the number of “lotto tickets” the cancer gives your immune system to recognize it and kill it
- However, typically only 1 (or rarely a few) specific neoantigen drives the entirety of the immune response; this is what is known as the **immunogenic neoantigen burden**
  - Depends on HLA type of patient
    - HLA homozygotes only have 1 opportunity to present each “lotto ticket”; heterozygotes can present twice
  - Is ideally clonal (ie, present in all cancer clones)
- **If you can identify it and stimulate an immune response to it, you have the perfect biomarker, as well as the perfect immunotherapeutic target**

Chowell. Science. 2018;359:582.

Neoantigen Clonal Architecture and Clinical Benefit of Immune Checkpoint Blockade



McGranahan. Science. 2016;351:1463.

Advanced NSCLC: Is PD-L1 Testing Enough?

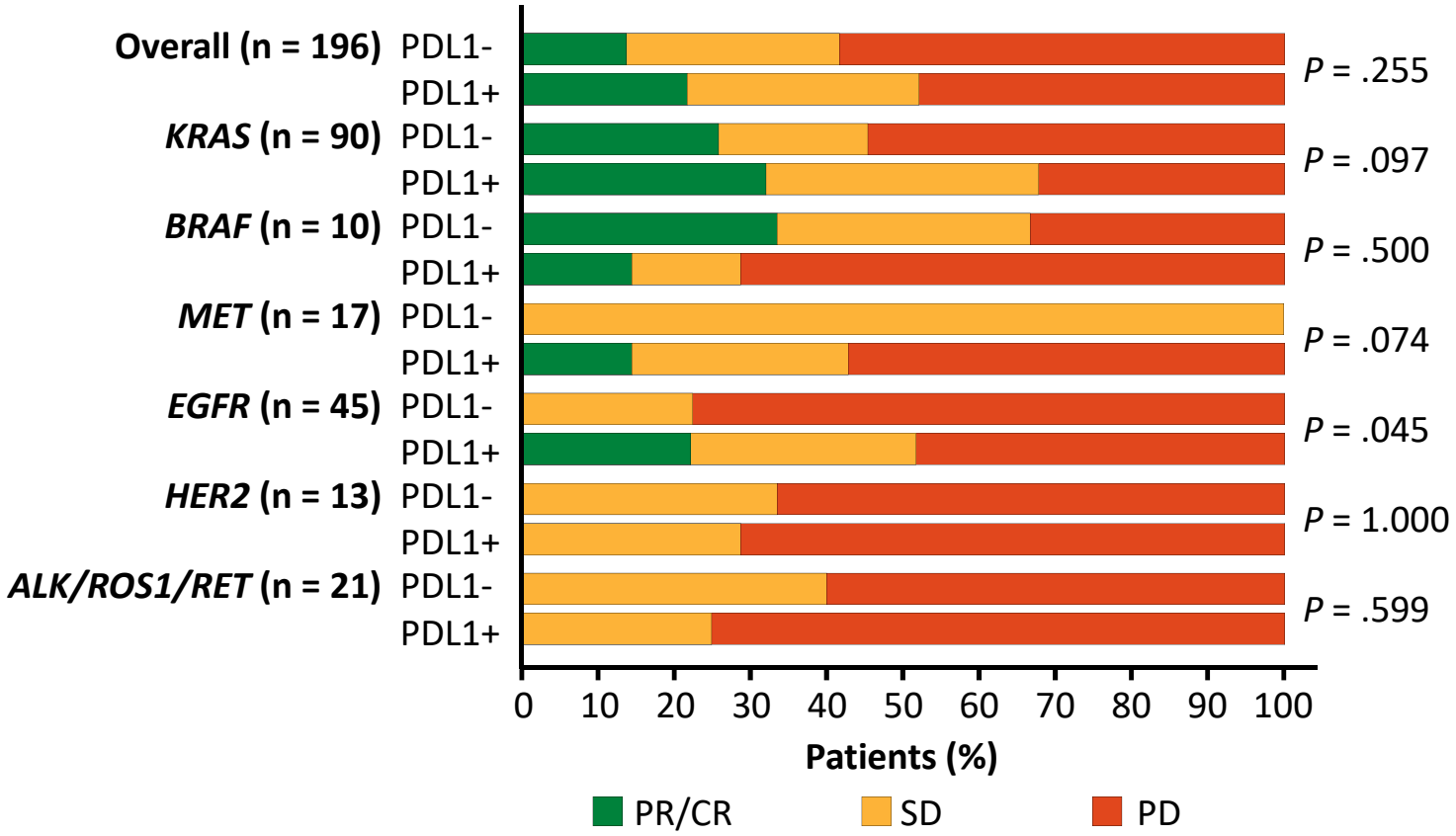
Targeted Therapy for Patients With Actionable Driver Mutations, Chemoimmunotherapy for Everyone Else

- Retrospective IMMUNOTARGET registry study of patients with advanced NSCLC and ≥ 1 driver mutation receiving single-agent ICI

Primary Oncogenic Driver	n	Median PFS, Mos	Percentage of PD-L1 Staining of Tumor Cells, n (%)		
			≥ 50%	< 50%	Missing
ROS1	7	--	3 (60)	2 (40)	0
BRAF	43	3.1	5 (55.6)	4 (44.4)	1
RET	16	2.1	3 (50)	3 (50)	2
MET	36	3.4	7 (46.7)	8 (53.3)	5
ALK	23	2.5	4 (40)	6 (60)	1
KRAS	271	3.2	26 (32.5)	54 (67.5)	15
EGFR	125	2.1	11 (28.9)	27 (71.1)	11
HER2	29	2.5	0	13 (100)	2

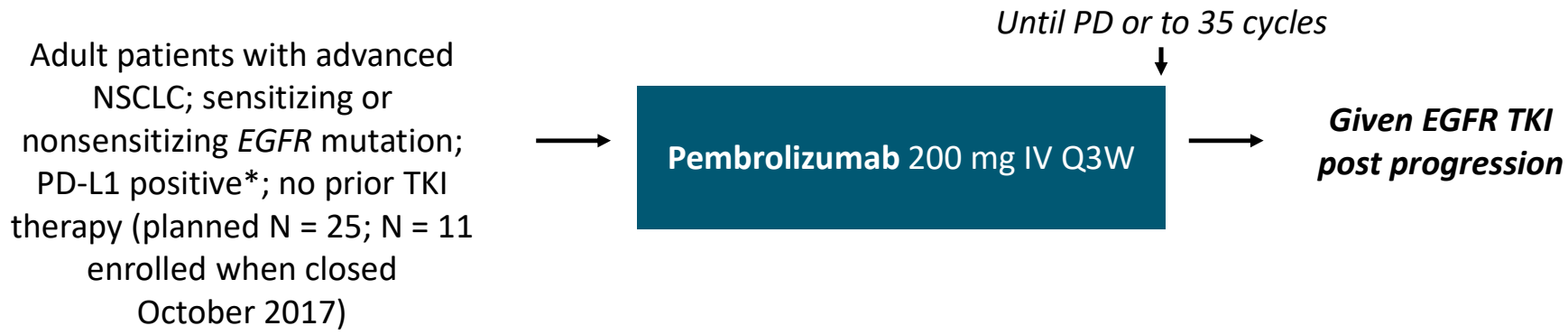
Mazières. Ann Oncol. 2019;[Epub].

IMMUNOTARGET: Association Between PD-L1 and Response to Immunotherapy by Genetic Aberration



Gautschi. WCLC 2018. Abstr MA04.03.

Phase II Study of Pembrolizumab in Patients With PD-L1–Positive *EGFR*-Mutated Advanced NSCLC



*PD-L1 positivity defined as ≥ 1% tumor membranous staining per 22C3 pharmDx IHC assay.

- Primary endpoint: ORR per modified RECIST v1.1
- Secondary endpoints: safety, PFS, OS, and safety and efficacy of subsequent EGFR TKI

Lisberg. J Thorac Oncol. 2018;13:1138. Lisberg. ASCO 2018. Abstr 9014.

Potentially Fatal Pneumonitis With EGFR TKI Following Anti–PD-1 Therapy

- Study stopped for futility at 11 patients
- **Only 1/11 patients (9%) achieved an objective response to pembrolizumab**
  - . . . and the response was in a patient where report of *EGFR* mutation was in error
  - . . . and despite 8/11 patients (73%) having PD-L1 ≥ 50%
- 1/7 patients (14.3%) died within 6 mos of enrollment due to treatment-related pneumonitis

Lisberg. J Thorac Oncol. 2018;13:1138. Lisberg. ASCO 2018. Abstr 9014.

Advanced NSCLC: Before You Treat

- **Radiographic diagnosis:** CNS imaging and CT CAP (or PET)
- **Pathologic diagnosis** AND **stage** by biopsy of highest-stage nonbone lesion
  - Ensure at least 4 passes of a larger bore needle for molecular analyses
- **Molecular diagnosis**
  - cfDNA or tissue-based multiplex for *EGFR/ALK/ROS1/BRAF/HER2/MET/RET/NTRK*
  - PD-L1 IHC helpful
    - Even in PD-L1 ≥ 50%, make sure to wait for NGS prior to starting treatment

Summary

- TMB is an emerging biomarker for response to immune checkpoint blockade with anti–PD-(L)1 agents (± anti–CTLA-4)
  - To date, appears to portend immunotherapeutic response
  - Patients who are PD-L1 negative by IHC but have high TMB may benefit from anti–PD-(L)1 therapy
  - Not ready for routine clinical use yet
- MSI/dMMR should not be routinely tested for in lung cancer due to rarity, use of valuable tissue, and would not change management of patient

Summary

- Ability to predict immunogenic neoantigen burden allows for a more precise predictive biomarker, but of more importance, truly personalized immunotherapy
- In metastatic NSCLC, need to test for *EGFR/ALK/ROS1* and ideally other drivers, even in PD-L1–positive patients
  - OK to start chemo alone without anti–PD-1 if need to while waiting for NGS

RET rearrangement

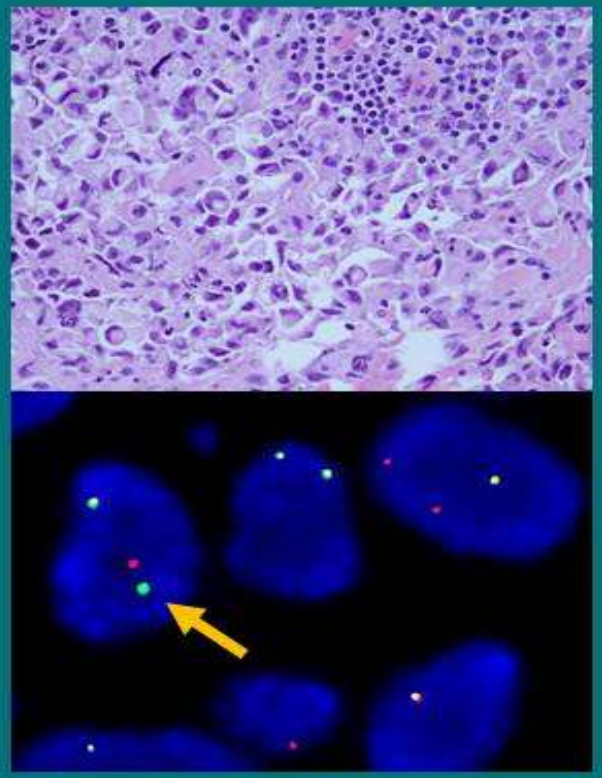
RET Rearrangements

- intact tyrosine kinase domain fused to an upstream gene partner
  - most common: *KIF5B*
  - others: *CCDC6, NCOA4, TRIM33, KIAA1468*
- result in ligand-independent dimerization and downstream growth pathway activation
- oncogenic *in vitro* and *in vivo*

Drilon AD, et al, Cancer Discov 2013;3:630-5, Kohno T, et al, Nat Med 2012;18:375-7, Saito M, et al, Carcinogenesis 2014;35:2452-6
Suehara Y, et al, Nat Med 2012;18:6599-608, Lipson D, et al, Nat Med 2012;18:382-40, Takeuchi K, et al, Nat Med 2012;18:378-81

RET-Rearranged Lung Cancers

- 1-2% of unselected non-small cell lung cancers
- clinical features
  - young, never or former light cigarette smokers
- pathology
  - lung adenocarcinoma: most common histology
  - solid subtype and signet ring cells
- diagnosis
  - break apart fluorescence in situ hybridization (FISH)
  - next-generation sequencing (NGS)



Ju YS, et al, Genome Res 2012;22:436-45 (epub Dec 2011), Wang R, et al, J Clin Oncol 2012;30:4352-9, Lee SE, Mod Pathol 2015;28:468-79
images courtesy of Lu Wang, Charles Leduc, and Natasha Rekhtman, Department of Pathology, Memorial Sloan Kettering Cancer Center

Cabozantinib

- oral multi-tyrosine kinase inhibitor with potent activity against RET
  - inhibits growth of *RET*-rearranged lung cancers *in vitro* and *in vivo*
  - FDA-approved for progressive metastatic medullary thyroid cancers
- minimal activity in unselected non-small cell lung cancers
  - phase II randomized discontinuation trial
  - 60 patients with advanced NSCLCs
  - ORR 10%, median PFS 4 months

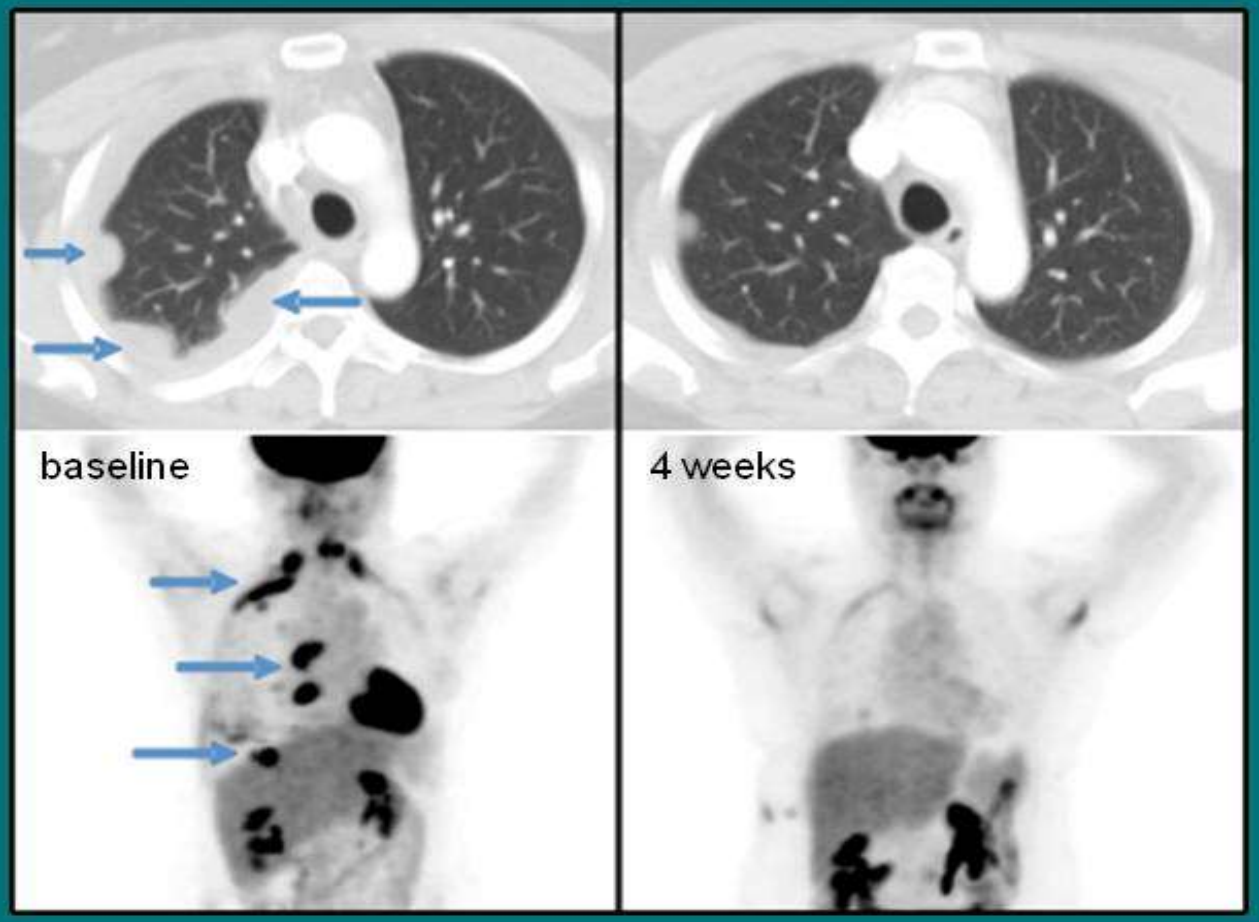
Kinase	IC_{50} (nM)
VEGFR2	0.035
MET	1.3
RET	5.2
KIT	4.6
AXL	7.0
FLT3	11.3
TIE2	14.3

ORR – overall response rate, PFS – progression-free survival, NSCLCs – non-small cell lung cancers

Yakes FM, et al, Mol Cancer Ther 2011;10:2298-308, Kodama T, et al, Mol Cancer Ther 2014;13:2910-8, Hellerstedt BA, et al, J Clin Oncol 2012;(suppl; abstr 7514)

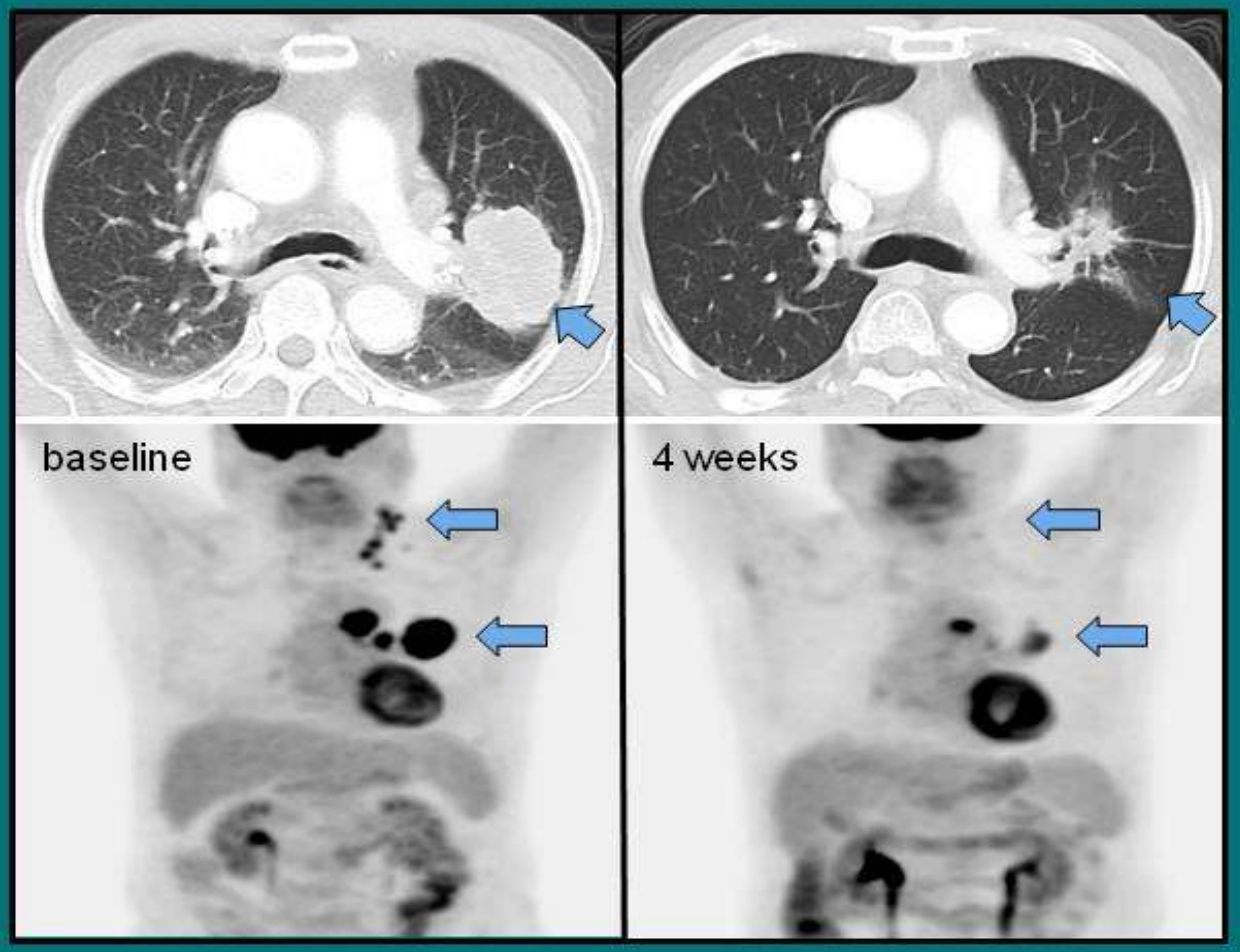
Response to Cabozantinib

- 46-year-old female never smoker with *CLIP1-RET*-rearranged lung adenocarcinoma
- received cabozantinib as first-line therapy
- confirmed partial response lasting 19 months



Response to Cabozantinib

- 80-year-old male never smoker with *KIF5B-RET*-rearranged lung adenocarcinoma
- received cabozantinib after progression on chemotherapy (carboplatin and pemetrexed followed by maintenance pemetrexed)
- confirmed partial response lasting 5 ½ months

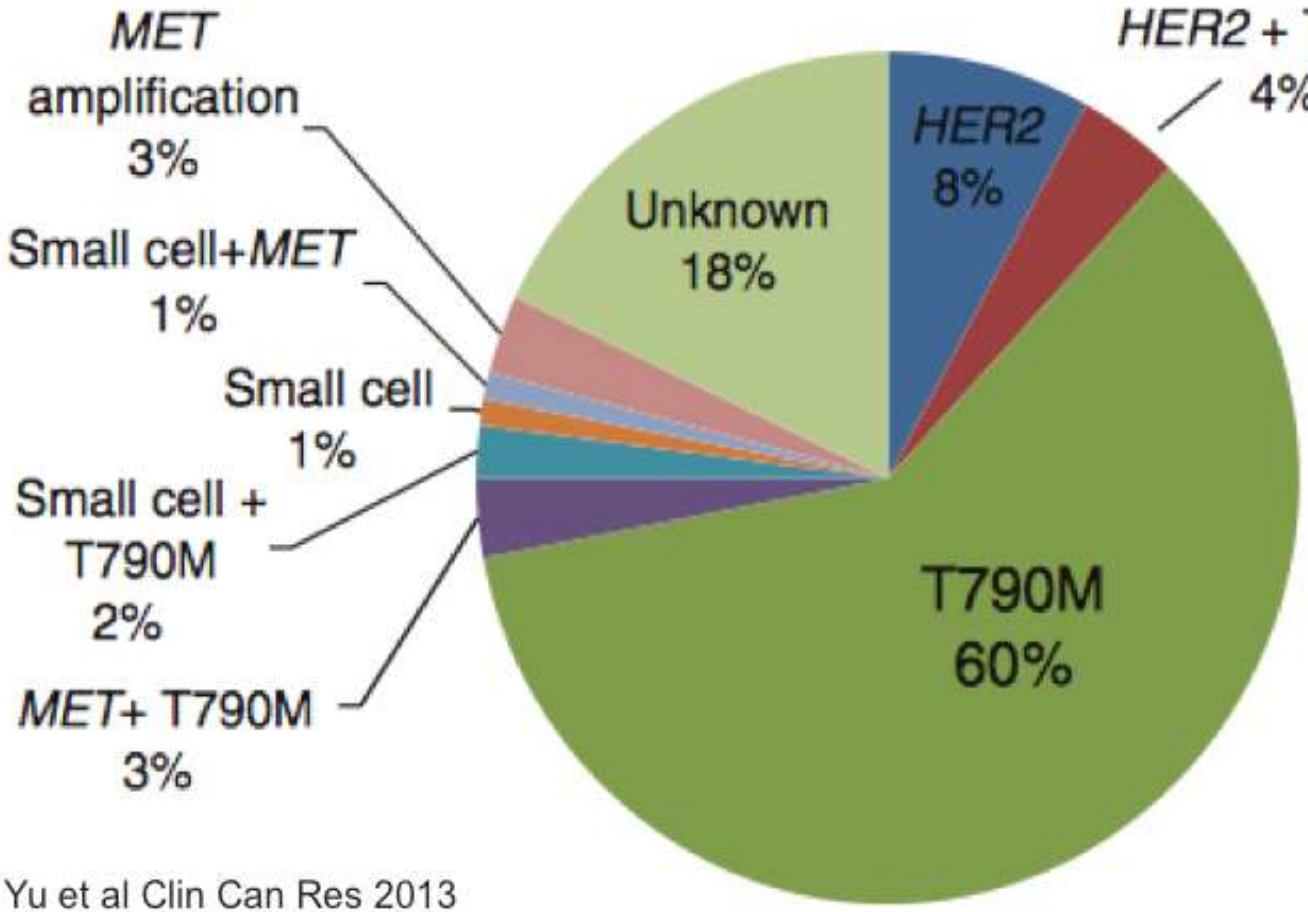


Summary

- Cabozantinib is active in patients with *RET*-rearranged lung adenocarcinomas.
  - stage 1 completed
    - ORR 38% (95% CI 15%-65%)
    - Median PFS 7 months (95% CI 5-NA months)
    - Median OS 10 months (95% CI 8-NA months)
  - stage 2 currently accruing
- Drug-related adverse events were mostly grade 1 or 2 but were frequent.
  - at a starting dose of 60 mg daily, most patients required a dose reduction
  - clinical benefit can be maintained despite dose reduction
- This phase II trial has met its primary endpoint.
  - sufficient total responses (minimum of 5 at any stage surpassed) to meet primary endpoint
  - a larger, confirmatory trial is warranted

HER-2 Inhibition

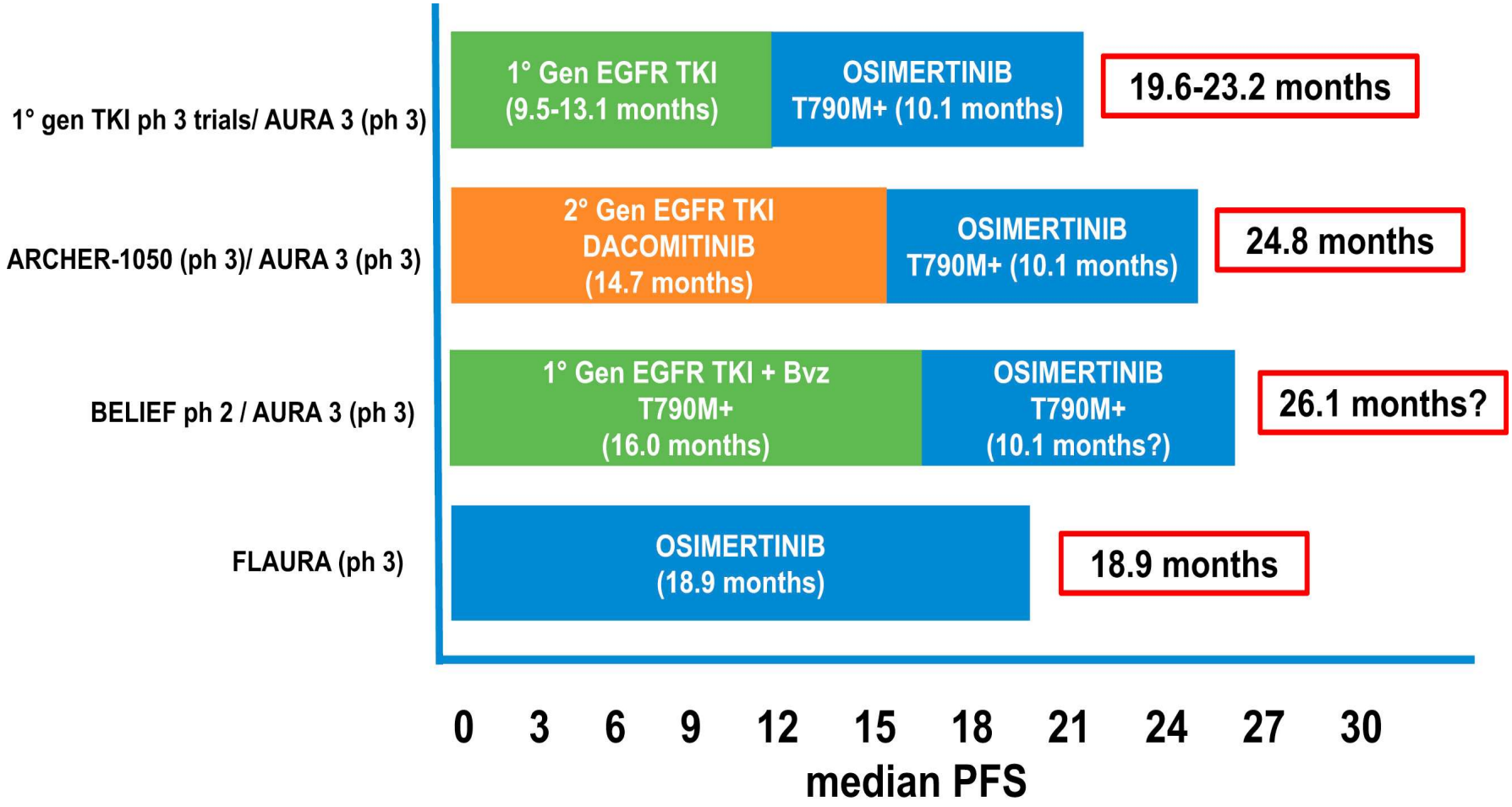
Her2-targeted therapies, such as trastuzumab, have been insufficiently powered to determine whether patients with NSCLC with Her2 gene amplification (rather than overexpression by IHCemistry) may benefit
It is unclear whether agents targeting Her2 might prove successful either with Her2 amplification or Her2 gene mutations.
The frequency of Her2 mutations in NSCLC may be too low to justify a prospective clinical trial.
The frequency of Her2 amplification (2-23%) in NSCLC and the use of FISH migth justify a study of trastuzumab monotherapy.
The most promising Her2-targeted strategy will likely prove to be combinatorial approaches using an EGFR tyrosine kinase inhibitor together with Her2 dimerization inhibitors.

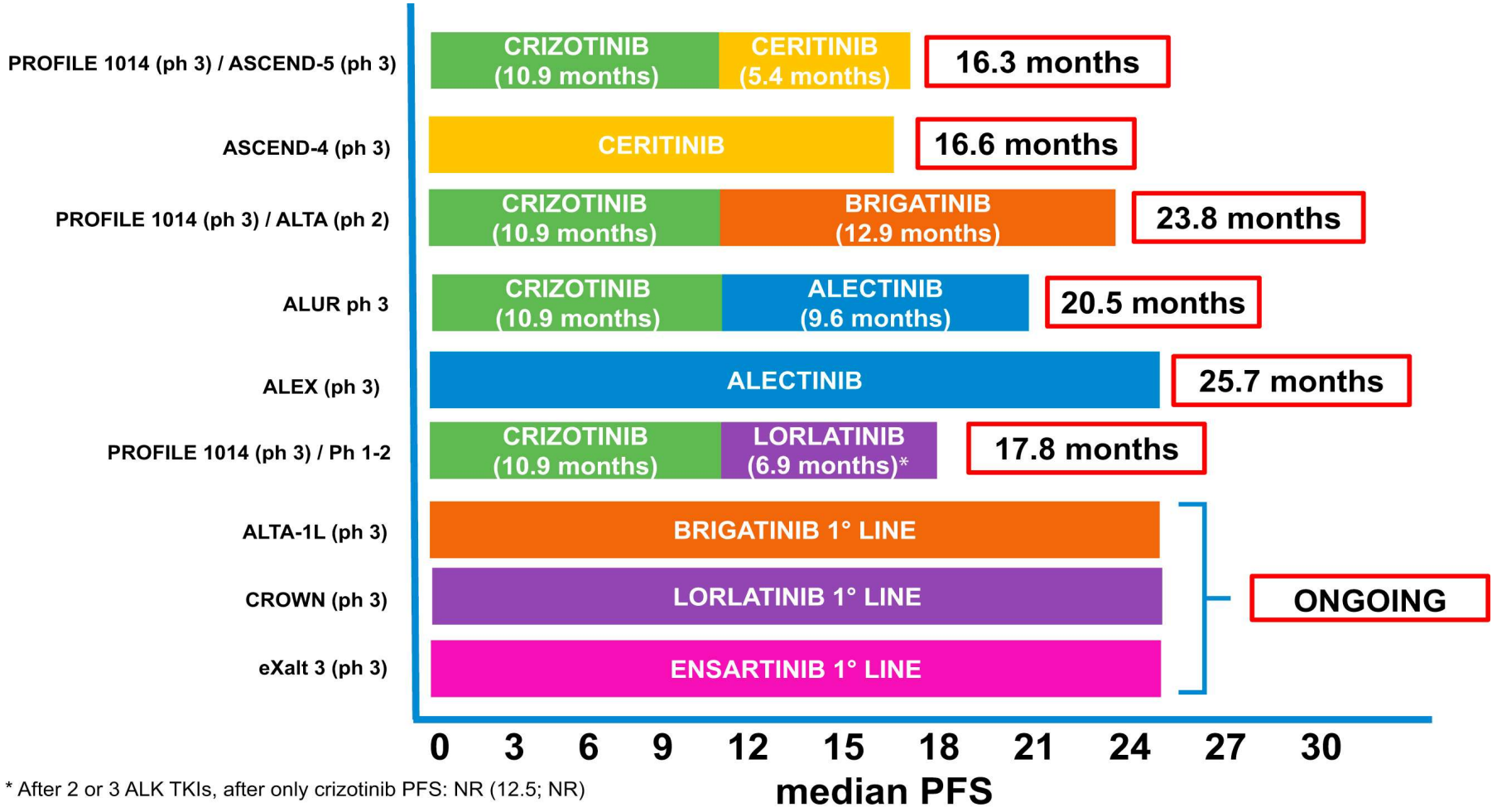


Mechanisms of Resistance:

T790M 60%
Her2 Amplification
NFkB Upregulation
MET Amplification
AXL Upregulation
Histologic Transformation

Yu et al Clin Can Res 2013





* After 2 or 3 ALK TKIs, after only crizotinib PFS: NR (12.5; NR)

Sumarry:

- Personalized medicine involves the use of an individual's genetics profile to guide decisions made regards to the prevention, diagnosis, and treatment of disease.

- All Cancer have different mutations, but also they can change during the course of the disease. Ej changes in neoantigens.

- NGS (Next generation sequencing) refers to a type of sequencing technology in which the sequence of multiple genomes fragments are determined in parallel,allowing an exponential increase in the amount of sequence data generated.

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The End

QUESTIONS ?