Genotype-driven NSCLC : what first, targeted therapies or immunotherapy ?

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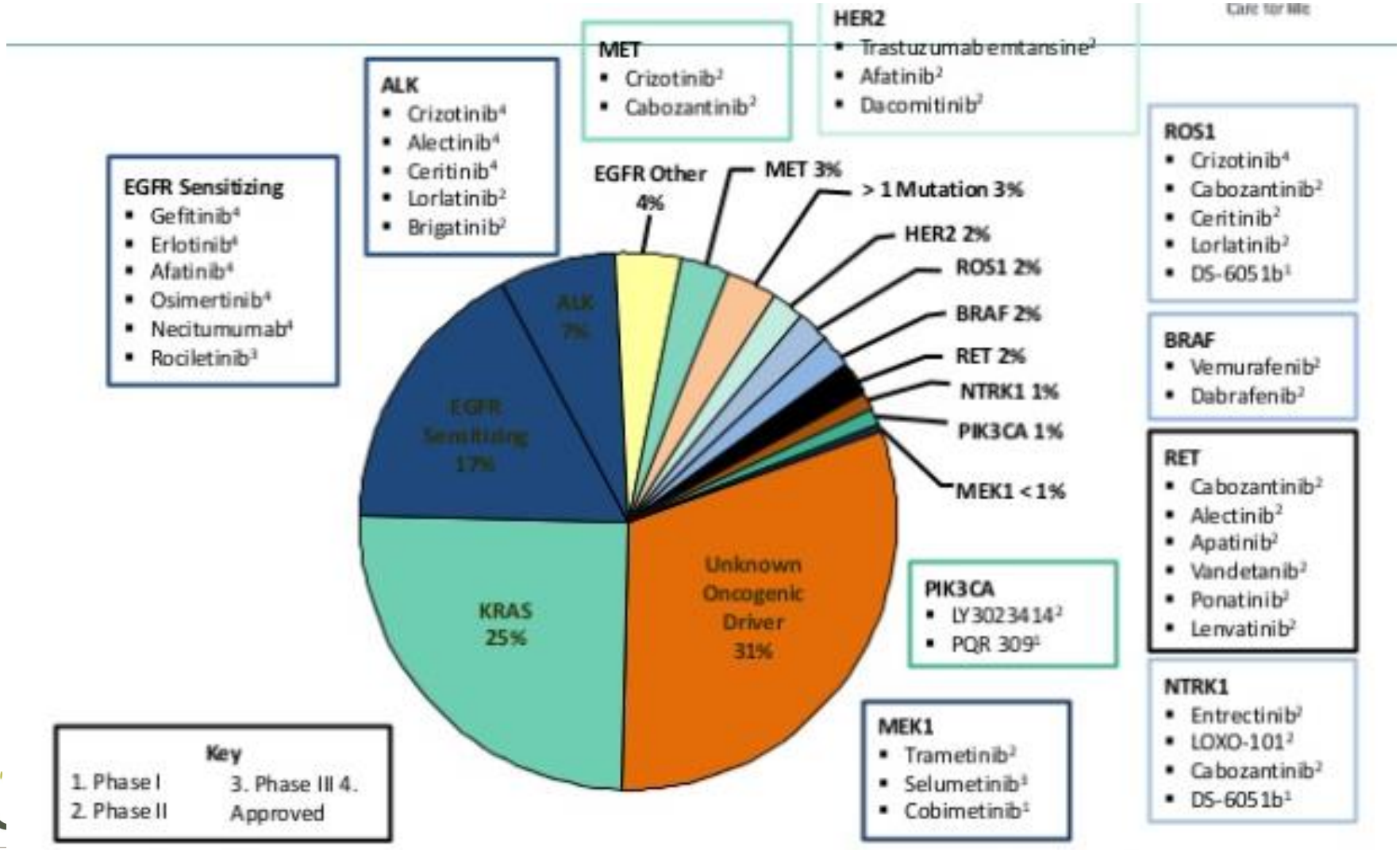
BSMO-Bordet meeting
November 22, 2019

Therapies in NSCLC

Molecular targets in lung cancer



Targeted therapies

- In non-smoking: main drivers
  → EGFR, HER2, ALK, ROS1, RET, NTRK, METex14del, BRAF, RAS

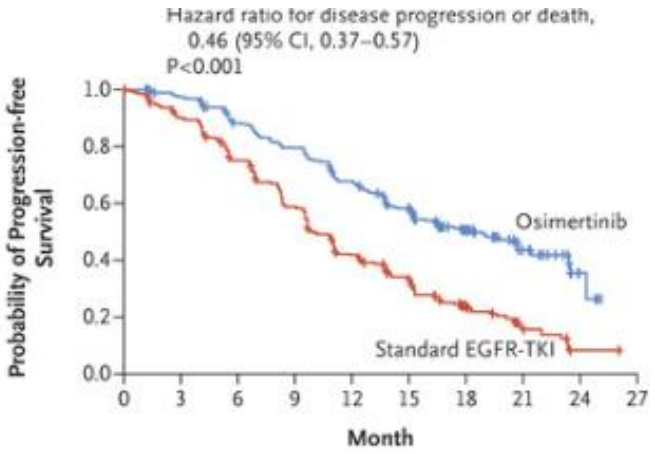
- In smokers: co-drivers
  → BRAF, RAS, METex14del
    - BRAF V600 < BRAF non-V600 (75%)*
  → Many high mutational profile

*Noeparast A, et al.. Oncotarget. 2016):60094-60108.

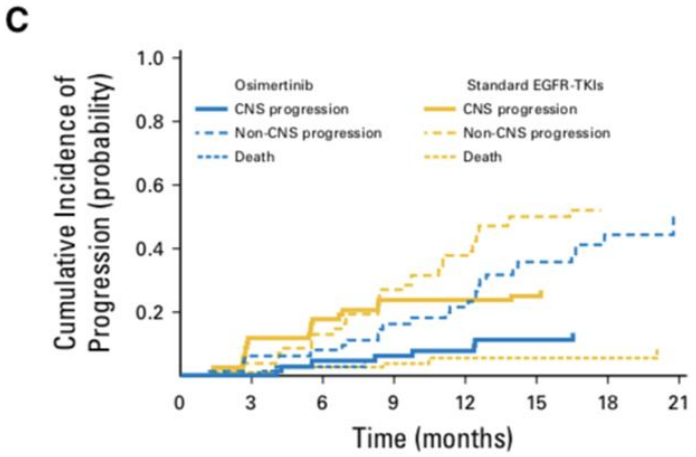
Targeted therapies: EGFR

Osimertinib first-line (FLAURA)

- → PFS benefit: 18.9 vs 10.2 months (vs. erlo/gef), HR 0.46
- → Better toxicity profile
- → Better QOL
- → CNS activity



PFS 18.9 vs 10.2 mo; HR 0.46



Probability of CNS progression 24 vs 35% at 1 year

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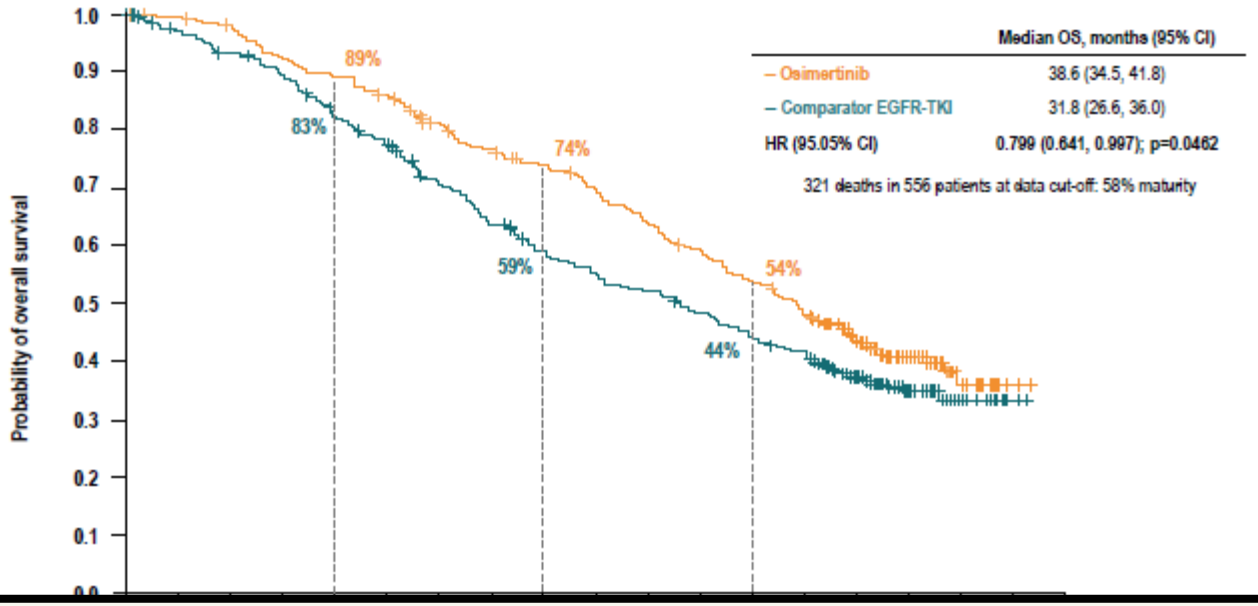
Soria et al. N Eng J Med 2018, Reunwetwattana T et al. J Clin Oncol 2018

Targeted therapies: EGFR

- Osimertinib survival benefit
  - → ESMO 2019: FLAURA: update on survival data
  - → Median OS: 38.6 vs 31.8 mo; HR 0.799; p=0.05



Of interest: 1/3 of patients did not receive subsequent treatment in both arms

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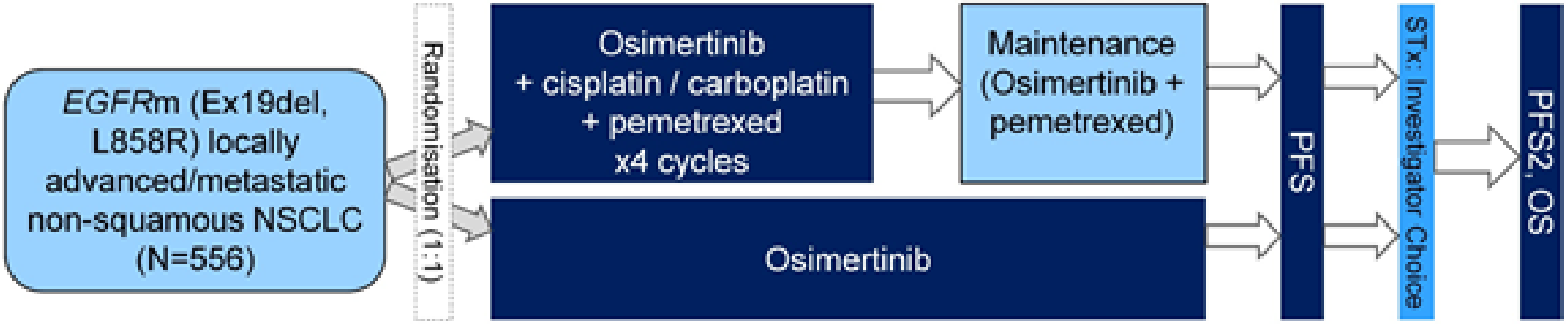
Ramalingam S et al. ESMO 2019

Targeted therapies: EGFR

- Future perspectives:
  → FLAURA 2 study: osimertinib + chemotherapy



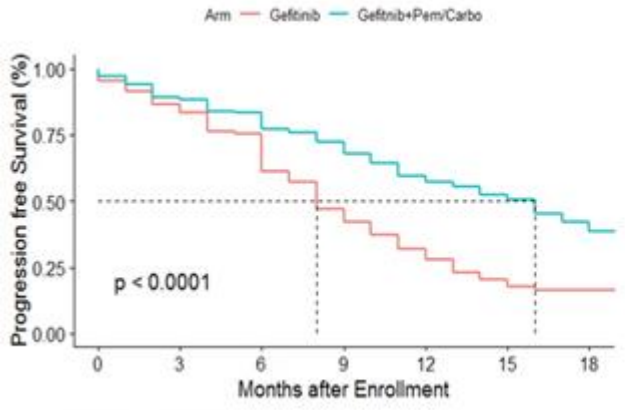
- Osimertinib given at a dose of 80 mg QD during induction and maintenance
- The osimertinib dose can be reduced to 40 mg QD for management of AEs; chemotherapy dose interruption/reduction is to be prioritised over reduction/interruption of osimertinib
- Randomisation will be stratified by race, WHO PS (0 vs 1), and tissue *EGFR* mutation test at enrolment
- Planned to involve approximately 248 sites in 27 countries

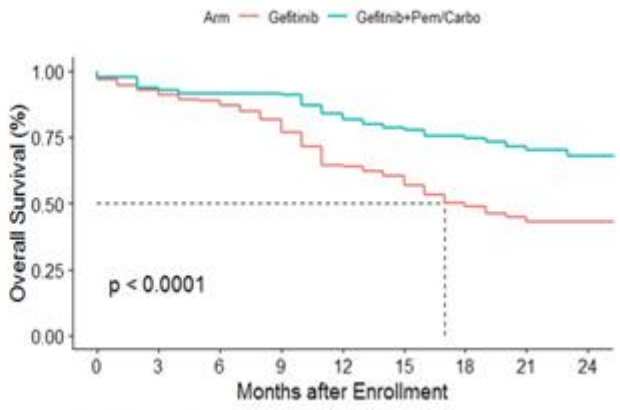
Janne et al. WCLC 2019

Targeted therapies: EGFR

- Gefitinib + Carboplatinum/Pemetrexed vs Gefitinib

	Gefitinib + chemo	Gefitinib	
ORR	75.3%	62.5%	
mPFS	16 m	8 m	HR 0.51
mOS	NR	17 m	HR 0.45





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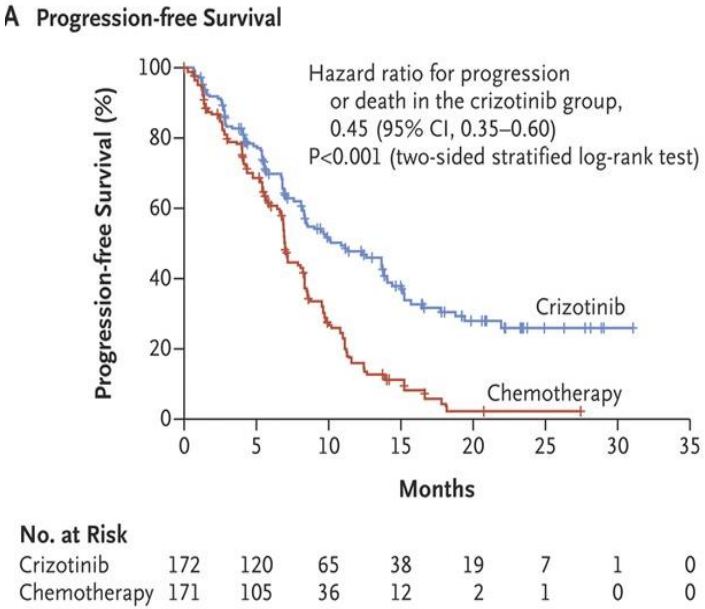
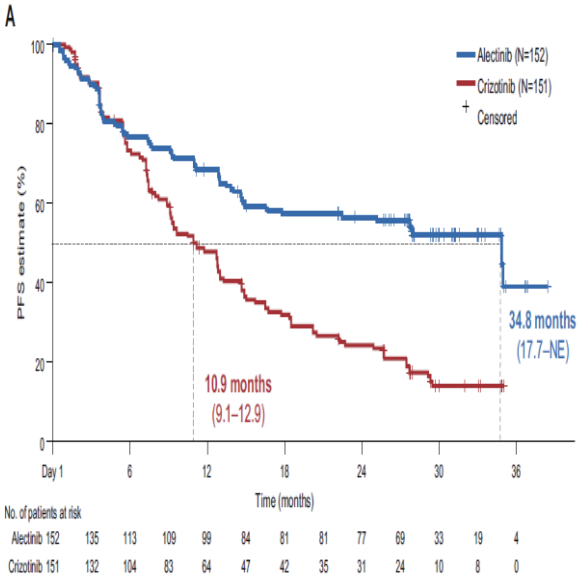
Toxicity issue: G3/4 75% vs 49% (p<0.001)

Noronha et al ASCO 2019

Targeted therapies: ALK





Crizotinib superior to chemotherapy

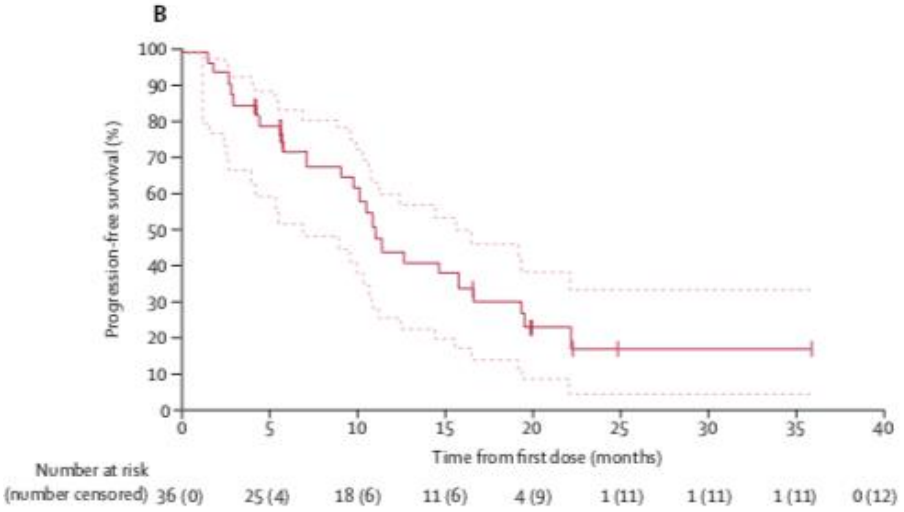
Alectinib superior to crizotinib

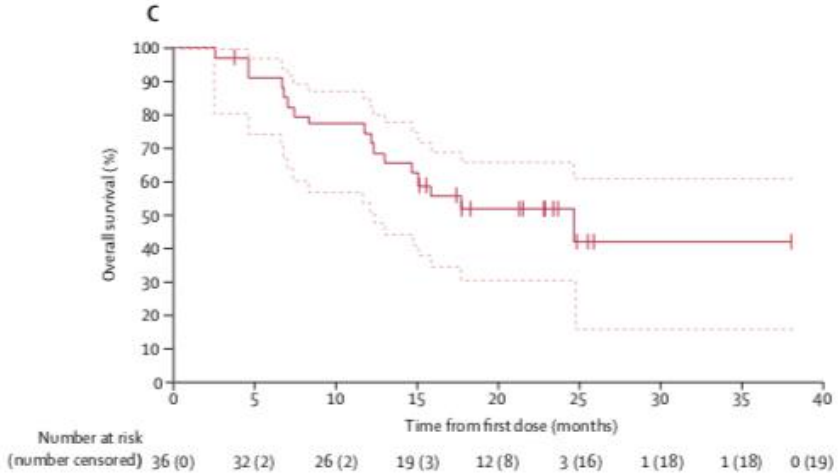
ORR (82.9% vs 75.5%, p=0.09)
PFS (34.8 vs 10.9 months; HR, 0.43)
(ALEX trial)

Camidge et al. 2019

Targeted therapies: BRAF

- Phase 2
- ORR 64%
- mPFS 10.9 mo
- mOS 24.6 mo, 2yOS 51%



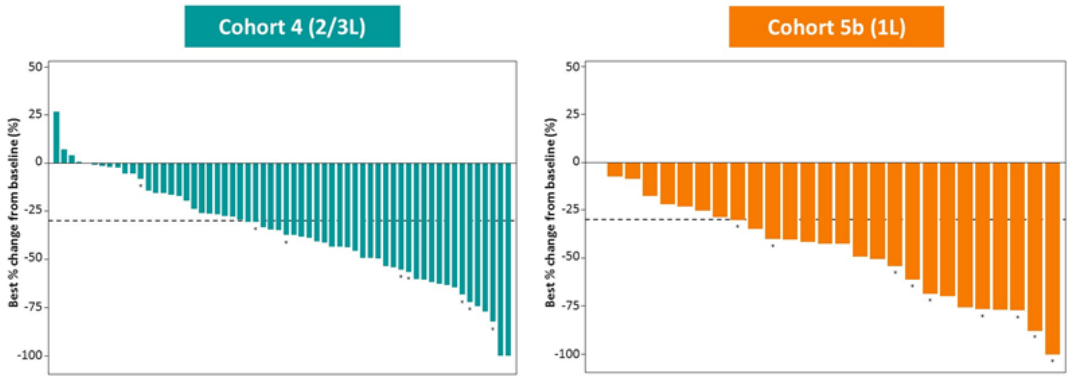


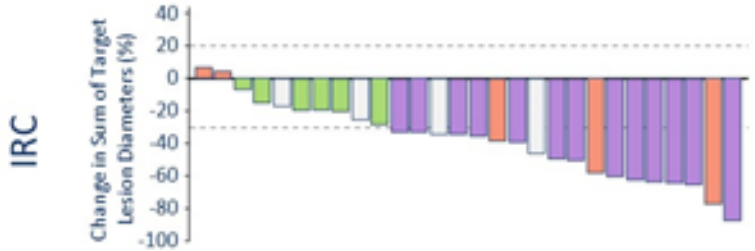
Planchard et al. Lancet Oncol 2017

Emerging targets: MET exon 14

- 3-4 % of NSCLC (8-32% sarcomatoid lungCA)
- Two selective MET inhibitors

	Capmatinib	Tepotinib
ORR	68% (1L) 41% (2/3L)	59% (1L) 45% (2/3L)
mPFS	9,7 m (1L) 5,4 m (2/3L)	10.8 m (all lines)





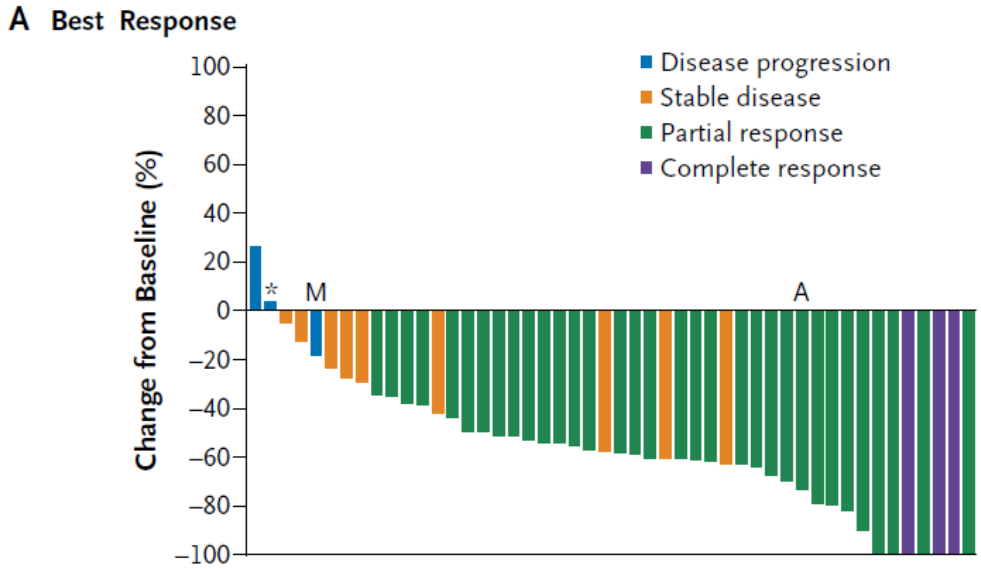
Intracranial activity reported

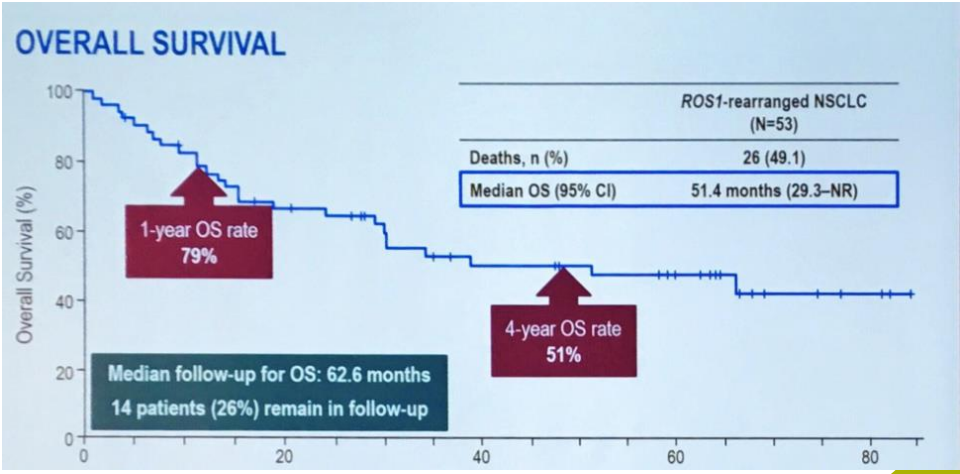
Wolf et al. AND Paik et al ASCO 2019

Targeted therapies: ROS1

Crizotinib

- RR 72%
- mPFS 19.3 mo
- mOS 51 mo
  - 1yOS 79%
  - 3y0S 51%





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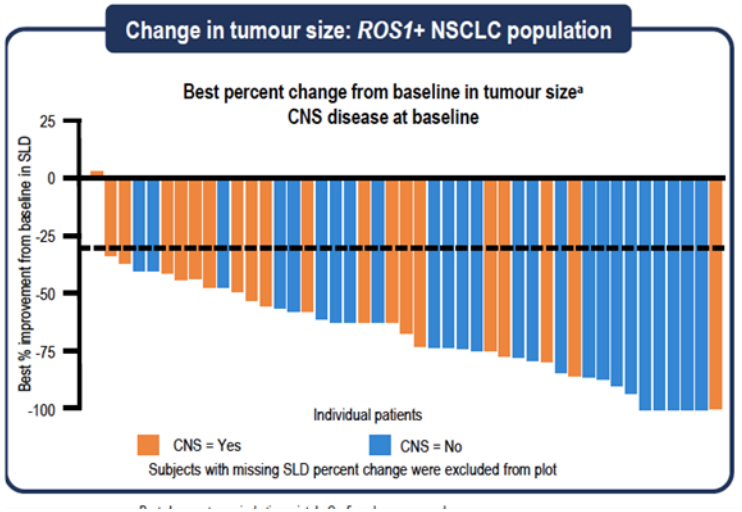
Shaw et al N Eng J Med 2014; Shaw et al ELCC 2019

Targeted therapies: ROS-1

- Entrectinib
  - → Phase 1/2 (n=53 pts)
    - ORR 77.4%
    - mPFS 19.4 mo
    - ICR 55%



- Repotrectinib
  - → Designed to overcome TKI resistance, especially ROS1 G2032R mutations
  - → Phase 1/2
    - TKI naive ROS1+ NSCLC: ORR 82%
    - TKI pretreated ROS1+ NSCLC: ORR 39%

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Barlesi et al. ELCC 2019; Cho et al. ASCO 2019

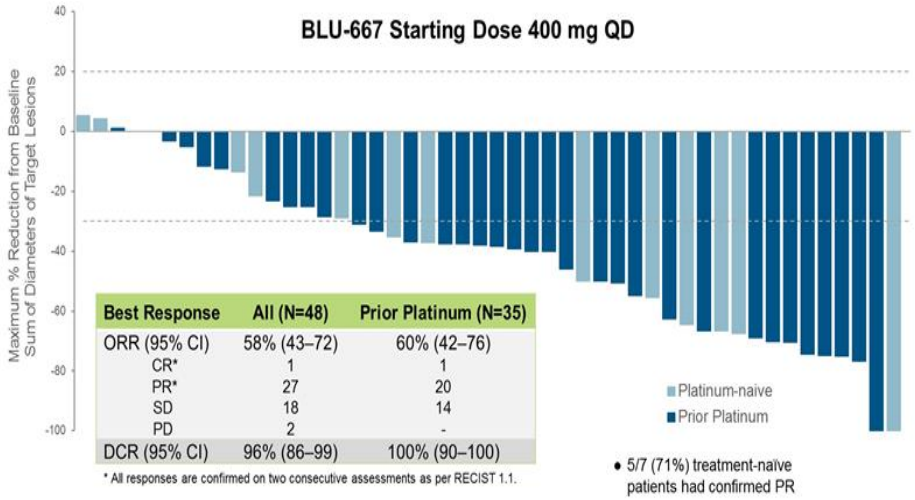
Emerging targets: RET

- 1-2% of NSCLC
- Fusion partners: KIF5B, CCDC6, other
- Multikinase inhibitors such as vandetanib, cabozantinib
  - → **RR 25% but PFS only 2-3 months**
  - → High toxicity

Emerging targets: RET

- 2 new selective RET inhibitors

BLU-667 (Pralsetinib)

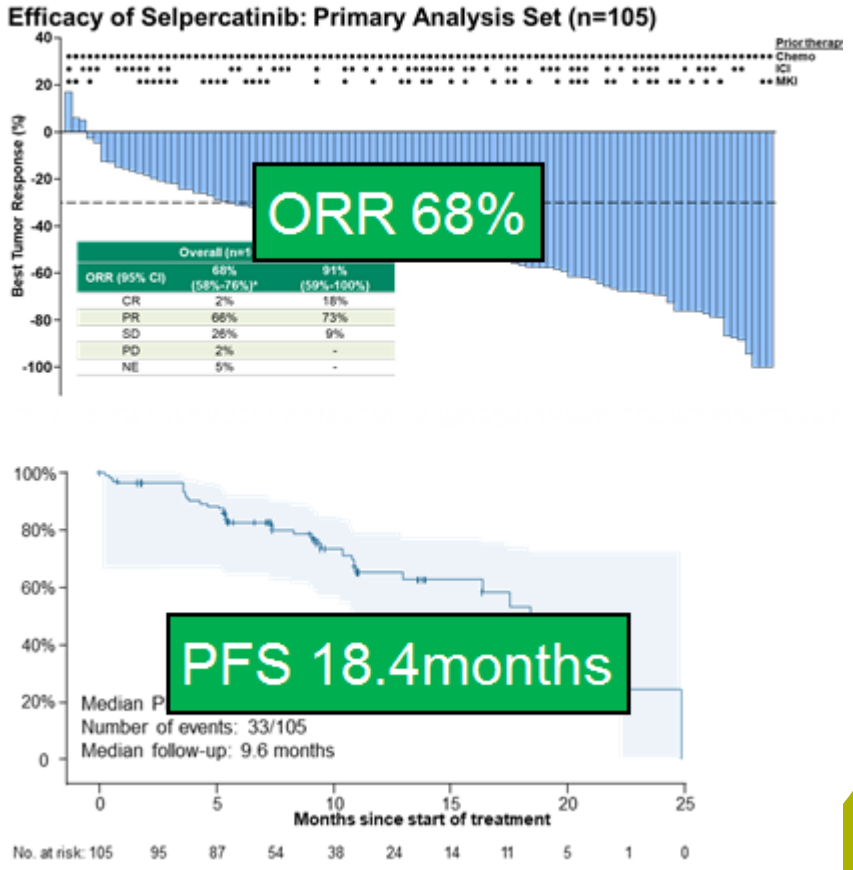


Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

ORR 58%;
70% treatment naive

LOXO (selpercatinib)



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Gainor et al, ASCO 2019; Drilon et al WCLC 2019

Emerging target: NTRK

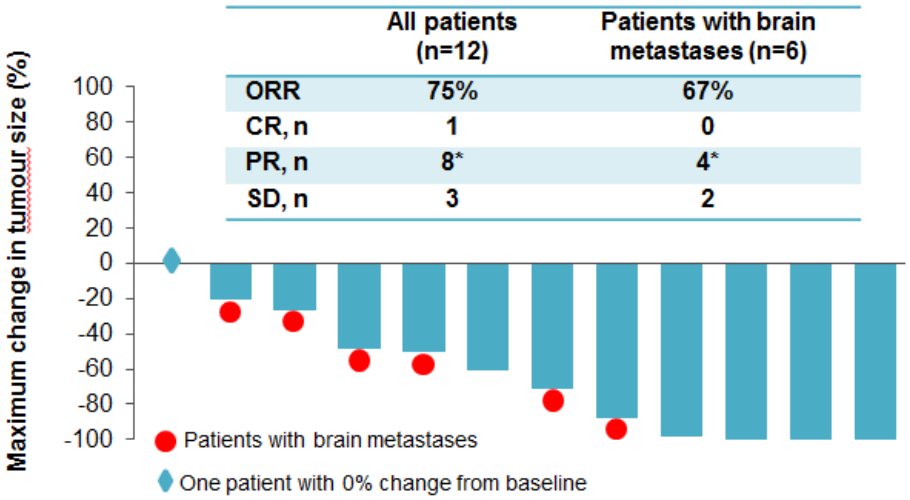
- NTRK gene fusions
  - → Neurotrophic Receptor tyrosine Kinase genes
  - → Rearrangements involving either NTRK 1,2 or 3 genes and various unrelated partners
  - → Activated kinase function with oncogenic potential

- Frequency is 0.2% in NSCLC
  - → Mutually exclusive with other oncogenic drivers
  - → Irrespective of smoking history, age and histology
  - → Diagnose with immunohistochemistry and RNA sequencing

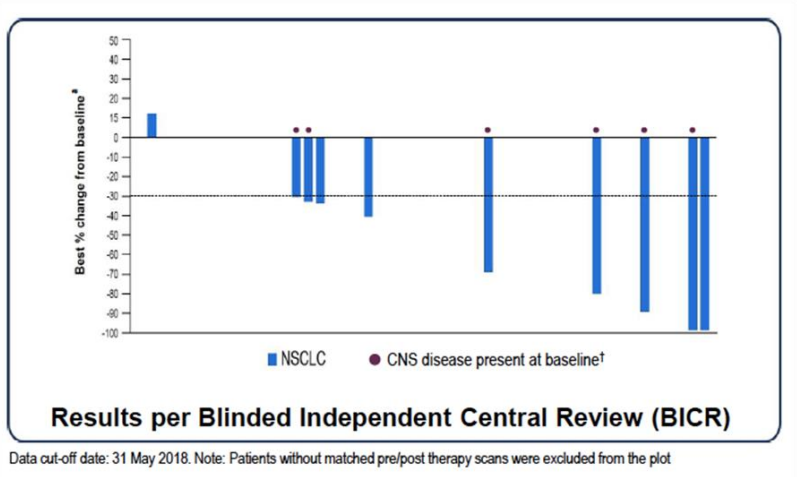
Vaishnavi et al. Cancer Discov 2015; Farago et al. JCO Precis Oncol 2018

Emerging target: NTRK

- Larotrectinib
  - → 12 NSCLC in phase I/II
  - → ORR 75%
- Entrectinib
  - → 10 NSCLC phase I/II
  - → ORR 70%



Median duration of response not reached (range 3.9+ to 25.9+ months) (median follow-up of 12.8 months)



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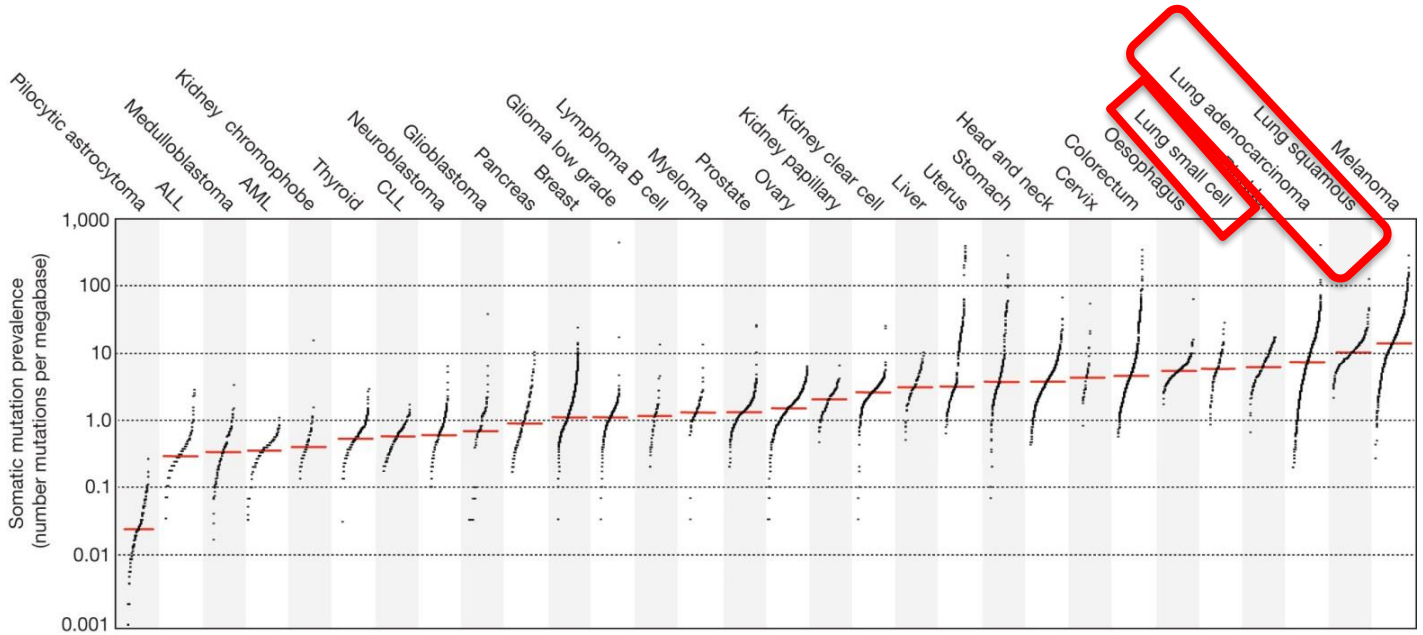
Farago AF et al. WCLC 2019; Paz-Ares et al. ELCC 2019

Immunotherapy

High mutational burden, increased neo-antigens in smokers



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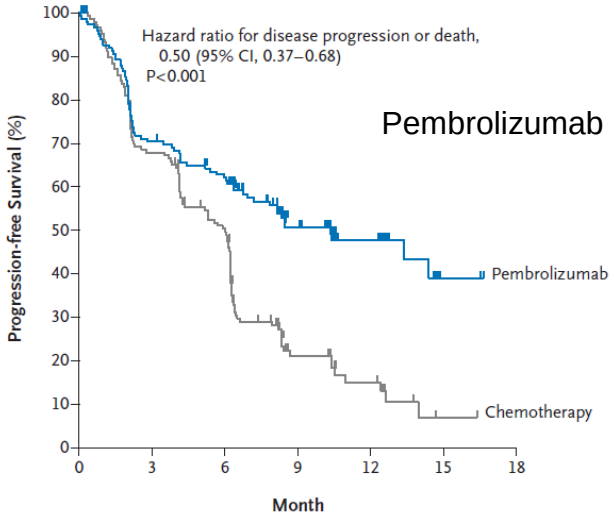
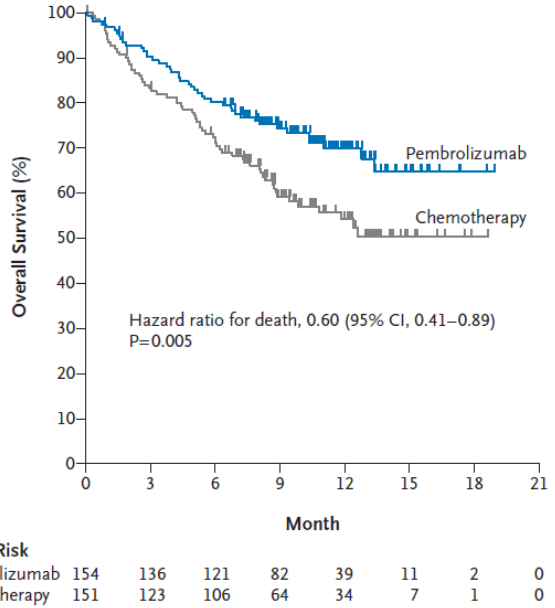
LB Alexandrov *et al. Nature* 2013

Immunotherapy

- Important improvement in metastatic and locally advanced stages in smoking-related lung cancer
- First-line standard in PD-L1 high NSCLC
- A minority of patients (15–20%) derive a durable benefit in second-line





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Herbst RS et al, Lancet. 2016;387(10027):1540–50.
Antonia S et al , N Engl J Med. 2017;377(20):1919–29.
Reck M, et al.N Engl J Med. 2016;375(19):1823–33.

Oncogene-driven NSCLC has poor immune attributes

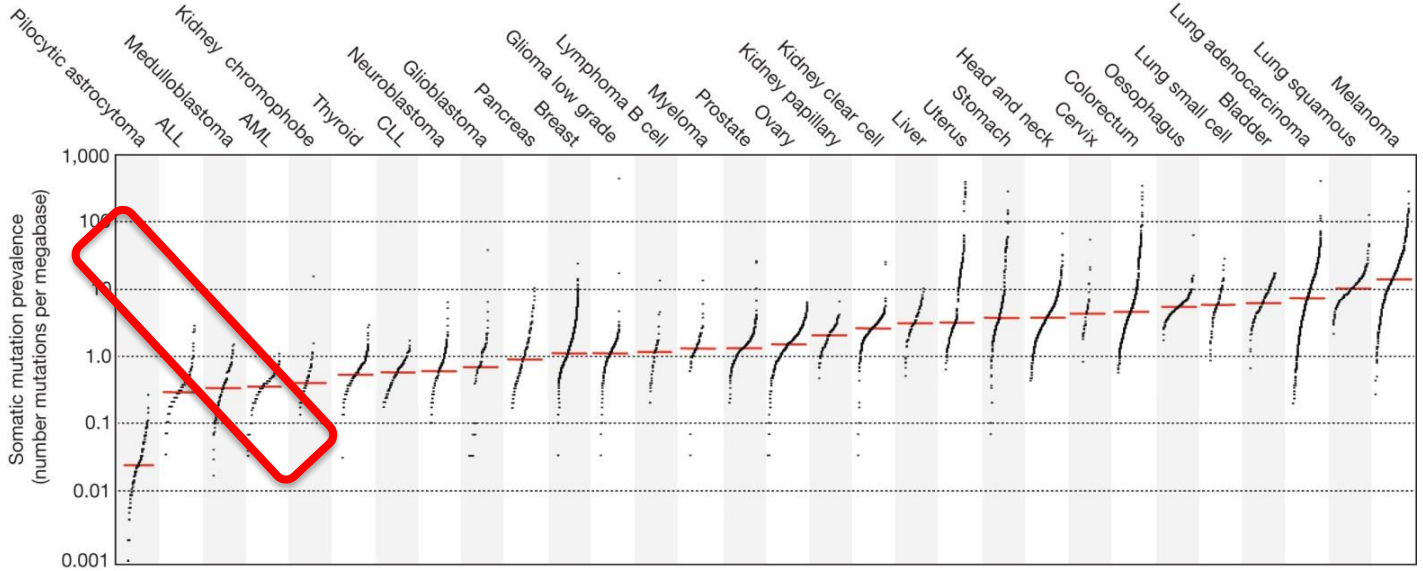
- High response rate to targeted therapies
- High response rate to chemotherapy

- In **smokers** high mutation rate, even with specified targets
  - → KRAS and BRAF non-V600E and some METex14del and some EGFR exon 20 are more likely found in smokers
  - → Can be immune sensitive

- **No or low smoking history**
  - → Low mutation rate, low TMB*
  - → Low inflamed microenvironment, low infiltrating CD8+ lymphocytes*

Dong Z-Y, Oncoimmunology. 2017;6(11):e1356145

Immunotherapy



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LB Alexandrov *et al. Nature* 2013

Inverse correlation between driver actionability and immunogenicity

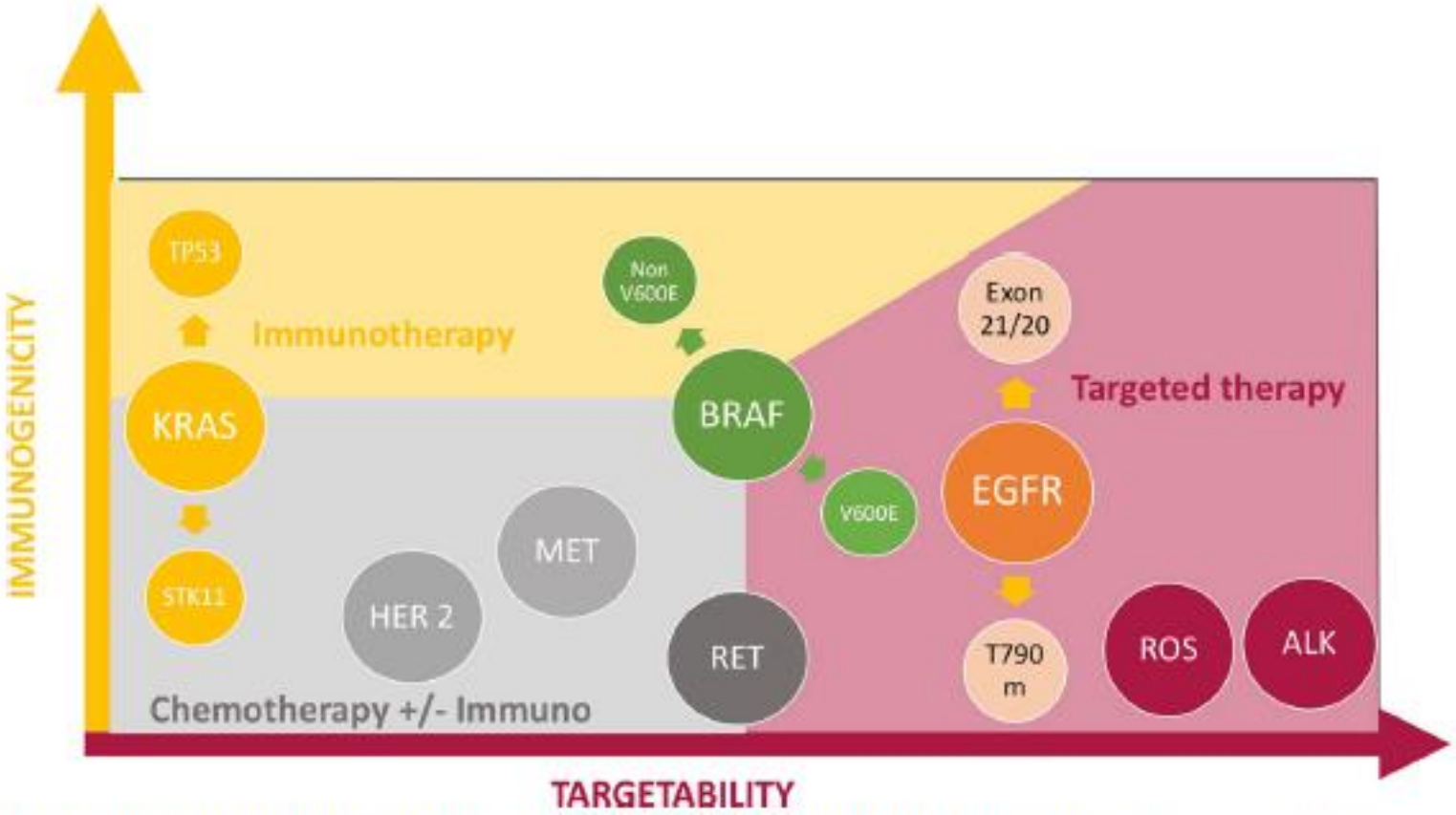

Fig. 2. Likelihood of sensitivity to ICI and/or genotype-directed agents in each oncogenic addiction setting.

EGFR mutant lung cancer

- **Very low RR (3.6%) with immunotherapy***
- OS similar to docetaxel*
  → Meta-analysis of CheckMate 057, Keynote 010, and POPLAR)
- Pembrolizumab in PD-L1 positive, TKI-naïve EGFR mutated
  → **no response, even with high (≥ 50%) PDL1** (phase 2)
- Durvalumab**
  → EGFR/ALK (Atlantic), TKI pretreated **RR 3.6%, even with high PD-L1**
  → **PFS 1.9 months** and **not influenced by PD-L1 expression**

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*Lee CK, et al. J Thorac Oncol. 2017;12(2):403–7
**Garassino MC, et al Lancet Oncol. 2018;19(4):521–36

BRAF mutant lung cancer

- Retrospective study of 39 BRAF-mutated patients*
  - → **RR of 25 and 33%, but PFS of 3.7 and 4.1 months** in patients with V600E and non-V600E*
- IMMUNOTARGET 35 BRAF-mutated patients**
  - → **ORR 24% but PFS of 3.1 months**
  - → Influenced by smoking, with **smokers better PFS**
  - → **non-V600E** mutations better response rates and PFS
- **Immunotherapy could be considered in BRAF-mutated patients, *if they are smokers***

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*Dudnik E, et al. J Thorac Oncol. 2018;13(8):1128–37
**Mazieres J, et al. J Clin Oncol. 2018;36(15_suppl):901

MET alterations

- Low TMB and poor outcome with immunotherapy*
  → **ORR 17% (4/24) but PFS 1.9 months**

- IMMUNOTARGET a median PFS of 4.7 months**

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*Sabari JK et al.: Ann Oncol 29:2085–2091, 2018
**Koyama S, et al. Cancer Res. 2016;76(5):999–1008.

Translocations much less studied, but available evidence not encouraging

- Hypothesis: also insensitive to ICI as they have same non-smoking background
- **RET rearrangements** associated with **low TMB** and **poor response to immunotherapy***
- Few studies, very few **ALK patients** and all very **poor outcome under ICI****

- IMMUNOTARGET cohort population**
  - → **ALK, ROS1, and RET** analyzed together
  - → **4.9%** ORR

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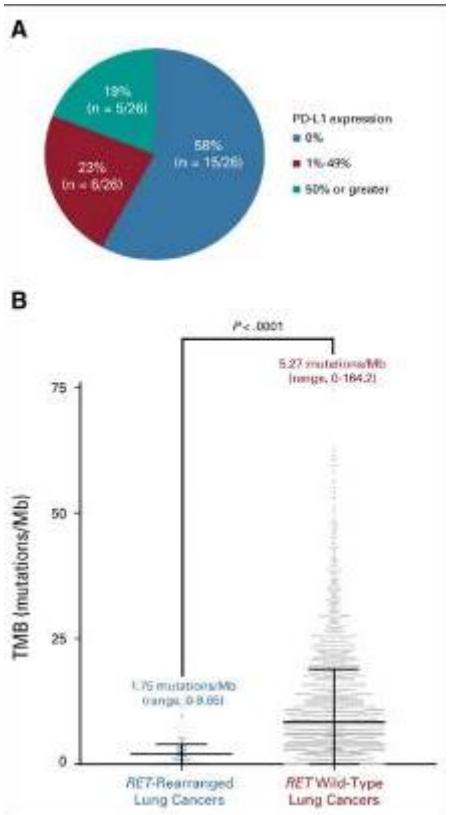
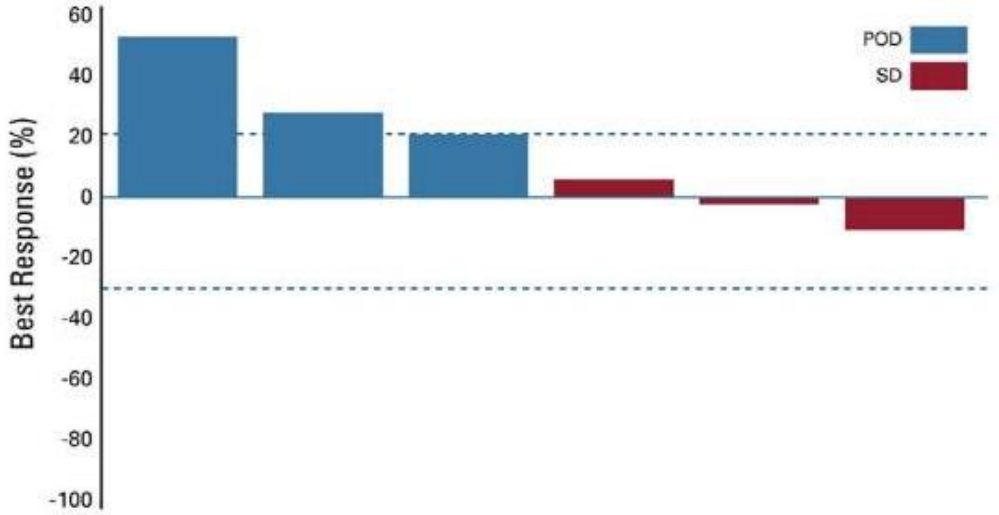
*Sabari JK, et al. J Clin Oncol. 2018;36(15_suppl):9034.
**Skoulidis F,, et al. Cancer Discov. 2015;5(8):860–77

Translocations much less studied: RET



Case	2	10	16	13	14	11
Immunotherapy	Pembrolizumab	Nivolumab	Ipilimumab plus Nivolumab	Atezolizumab	Atezolizumab	Nivolumab
PD-L1	0%	NA	50%	0%	NA	NA
TMB (mut/Mb)	NA	NA	3.51	2.95	NA	NA



Offin M, et al. *JCO Precis Oncol*. 2019;3:10

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In Immunotarget: N= 16**, 0% RR, PFS 2 mth**

Biomarkers: PD-L1 not a predictor in oncogene addicted NSCLC

- PD-L1 expression most reliable predictive biomarker in smokers*
  - → Both first** and second line NSCLC

- PD-L1
  - → can be induced by the oncogenic signaling, *but*
  - → **not necessarily associated with immune cell infiltration**

*Khunger M, et al JCO Precis Oncol. 2017;1(1):1–15
**Reck M, et al. N Engl J Med. 2016;375(19):1823–33..

Biomarkers: TMB

- Relevant predictor for in immune response in lung cancer*
- Correlates with smoking status

- LowTMB > lack of immunogenic neo-antigens, non-inflamed (“excluded”) microenvironment**

- Higher in KRAS, BRAF non-V600E, and even MET exon14 patients, associated with smoking**

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*Hellmann MD et al.N Engl J Med. 2018;378(22):2093–104.
** Spigel DR, et al. JClinOncol. 2016;34(15_suppl):9017.
Sabari JK, et al. J Clin Oncol. 2018;36(15_suppl):9034.

Tumor-infiltrating lymphocytes (TILs)

- Strong prognostic factor in NSCLC
- Not related to PD-L1 expression*

- Maybe best predictive marker of response

- **Targeted therapy > release neoantigens > inflame tumors > enhance anti-tumor immune responses > synergy with immunotherapy ?****

- An immunotherapy with or after targeted therapy lead to **durable and long-lasting remissions?**
  - → Melanoma
  - → BRAF inhibition could have favorable effects in the tumor microenvironment which becomes more immunogenic***

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*Mignon S, et al Pathol Oncol Res. 2019 Jun 21
**Pilotto S, et al. Transl Lung Cancer Res. 2015;4(6):721–7
*** Wilmott JS, et al Clin Cancer Res. 2012;18(5):1386–94..

Combined targeted + immunotherapy

- First-line **nivolumab and erlotinib**
  → high response rates, even in EGFR–TKI pretreated
  → Increased toxicity
    - Grade 3–4 adverse-events 24%*

- Phase 1 ORR of 77.8% with **gefitinib + durvalumab**
  → (n = 10)*

- **Osimertinib and durvalumab**
  → Encouraging activity
  → Potentializes the risk of interstitial pneumonia.**
  → Stopped

* Rizvi NA, et al. J
Clin Oncol. 2014;32(15_suppl):8022.

Combi with anti-VEGF

- Cytotoxic chemotherapy > increased tumor antigen load > atezolizumab
- Normalization of tumor microvascularisation by bevacizumab > increase in TIL*
- ImPOWER 150 study

  → platine-based chemotherapy, bevacizumab, and atezolizumab

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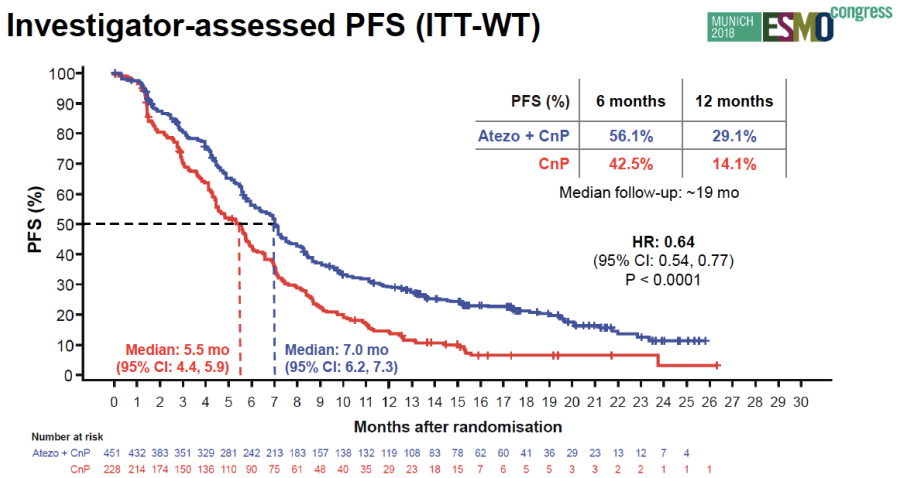
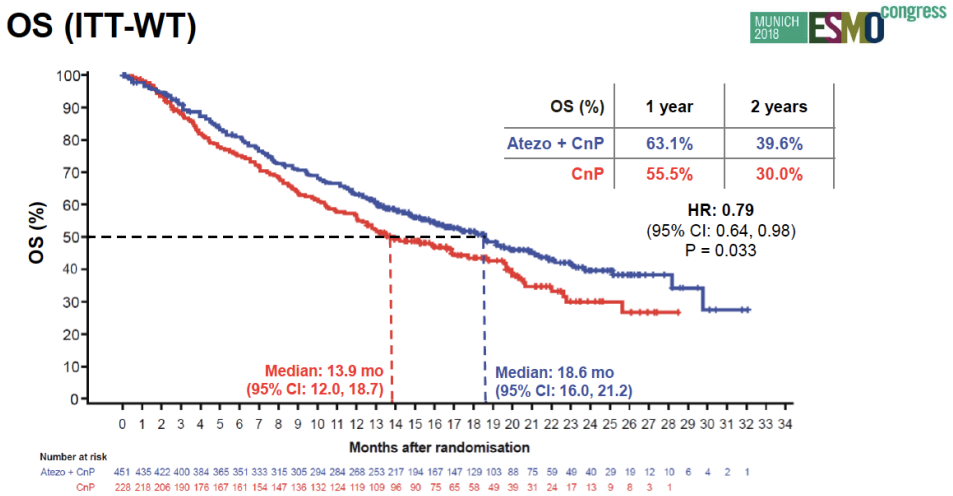
* Hegde PS, Semin Cancer Biol. 2018;52(Pt 2):117–24.

Impower130: non-Squamous

- RR 49 vs 32%
- mPFS 7 vs 5.5 mo; HR 0.64; p<0.0001
- mOS 18.6 vs 13.9 mo; HR 0.79; p=0.033





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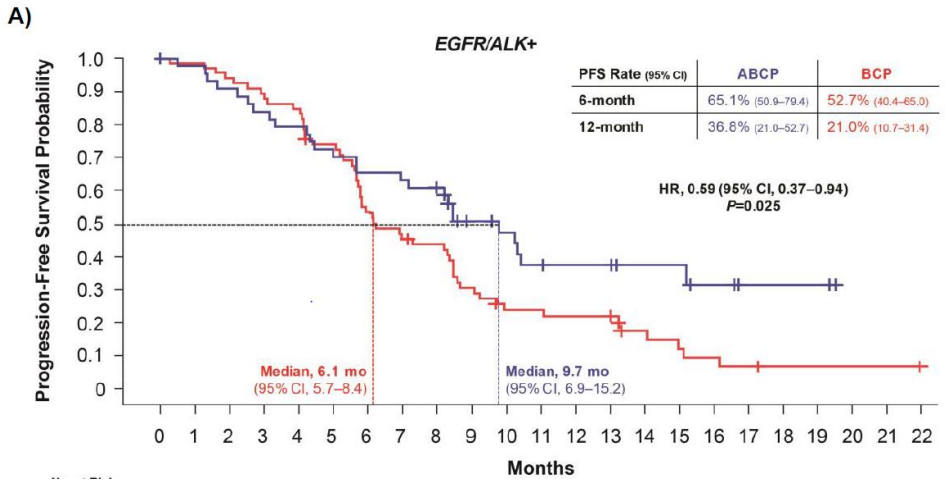
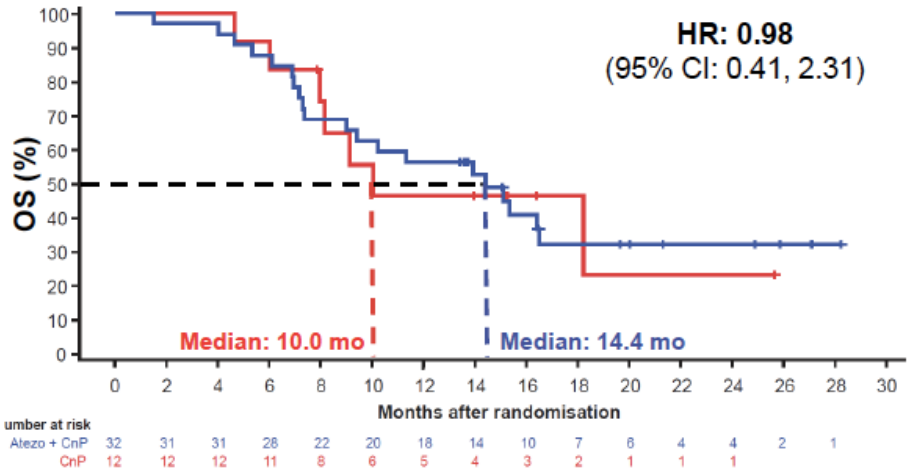
Cappuzzo et al. ESMO 2018

Impower150: EGFR/ALK



PFS in EGFR/ALK



OS in EGFR/ALK NSCLC in **Impower130**

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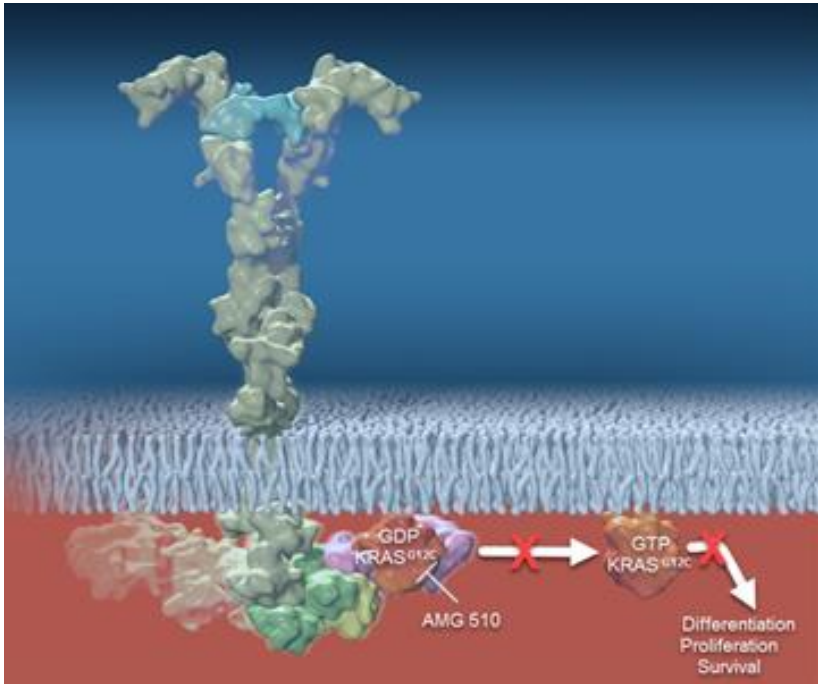
Cappuzzo et al. ESMO 2018

Promising target: KRAS G12C

- KRAS is a GTP-binding protein
  - → Mutation of KRAS favor the G-bound active state and constitutive activation of downstream effects (proliferation, survival)



- $KRAS^{G12C}$ in 13% of NSCLC

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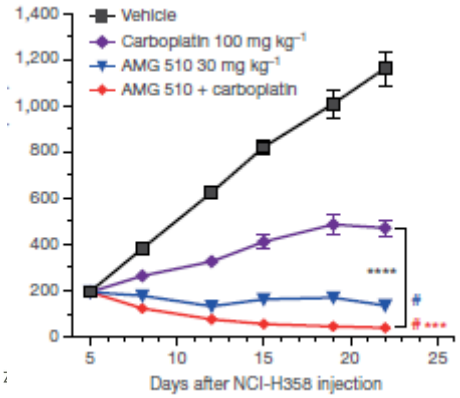
Shapiro et al. ASCO 2019; Govindan R et al WCLC 2019

Promising target: KRAS G12C

- AMG510*
  - → Specifically and irreversibly inhibits KRASG12C
    - locking it in an inactive GDP bound state
  - → Synergy MEK inhibition (preclinical)
  - → Synergy with carbo-pemetrexed (preclinical)
  - → Emerging clinical SA activity
  - → Inflames the tumor > combi with immunotherapy



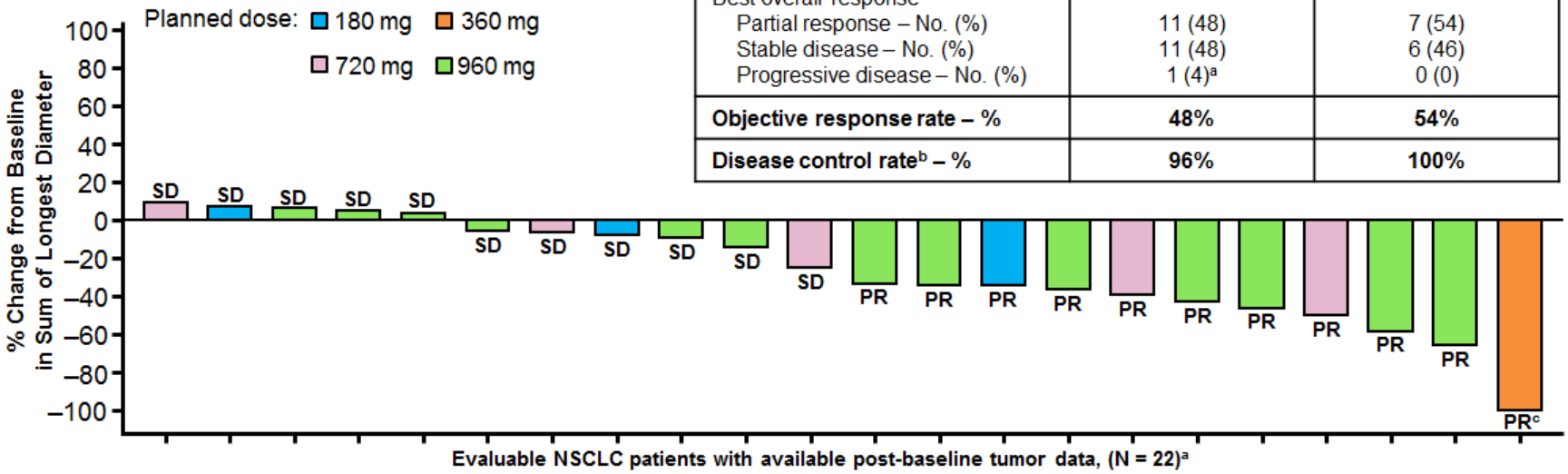
Combined with a PD-1 inhibitor
Definitive pCR in 9/10 mice

- Canon J, et al. Nature. 2019 Nov;575(7781):217-223.
- AMG 510 First to Inhibit "Undruggable" KRAS. Cancer Discov. 2019 ;9(8):988-989.

Promising target: KRAS G12C

- Phase I: ORR in 23 NSCLC 48%

Efficacy outcomes	All evaluable patients N = 23	Evaluable patients treated with 960mg N = 13
Best overall response		
Partial response – No. (%)	11 (48)	7 (54)
Stable disease – No. (%)	11 (48)	6 (46)
Progressive disease – No. (%)	1 (4)[a]	0 (0)
Objective response rate – %	**48%**	**54%**
Disease control rate[b] – %	**96%**	**100%**



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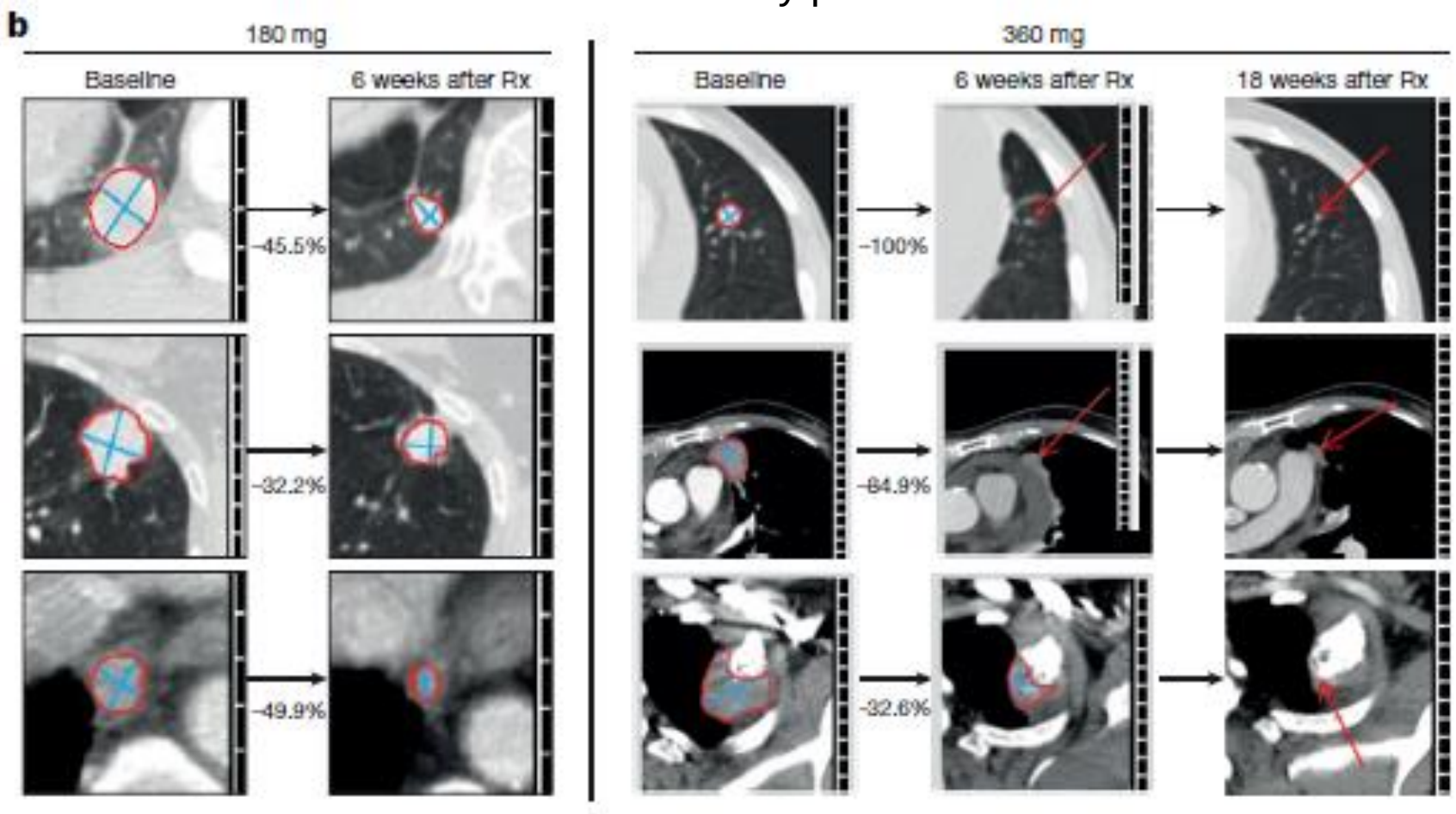
Govindan R et al WCLC 2019

KRAS inhibition AMG 510

6/13 RR in heavily pretreated



- Canon J, et al. Nature. 2019 Nov;575(7781):217-223.
- AMG 510 First to Inhibit "Undruggable" KRAS. Cancer Discov. 2019 ;9(8):988-989.

MRTX849 (Mirati)

- Potent, selective, and covalent KRASG12C inhibitor
- **RR in 17 of 26 (65%)** of KRASG12C cell line- and patient-derived **xenograft** models from multiple tumor types
- **Clinical responses in KRASG12C-positive lung and colon adenocarcinoma patients**
- Resistance mechanisms documented
  → KRAS nucleotide cycling and pathways that induce feedback reactivation and/or bypass KRAS dependence

James G. Christensen, Cancer Discovery, oct 2019 online

Conclusion immunotherapy in oncogene-addicted lung cancer

- **Immunotherapy no routine application in NSCLC with strong driver and no or minimal smoking history***
  - → Low response rates and short PFS with single-agent immune checkpoint inhibition in lung cancers with oncogenic drivers and no or little smoking history
  - → Sequential targeted and chemo are standard
    - Chemo quite active

- Immunotherapy should be driven by **PD-L1, mutational rate, TIL and smoking history**
  - → Can have KRAS, BRAF, METex14 mutations

- **Combined targeted-immunotherapy under investigation**, but toxicity issue

- **KRAS has become druggable** with clinical efficacy signal and potential for synergy with immunotherapy

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* Mazieres J, et al.: J Clin Oncol 36, 2018 (suppl; abstr 9010)