Update on Squamous Cell Lung Cancer

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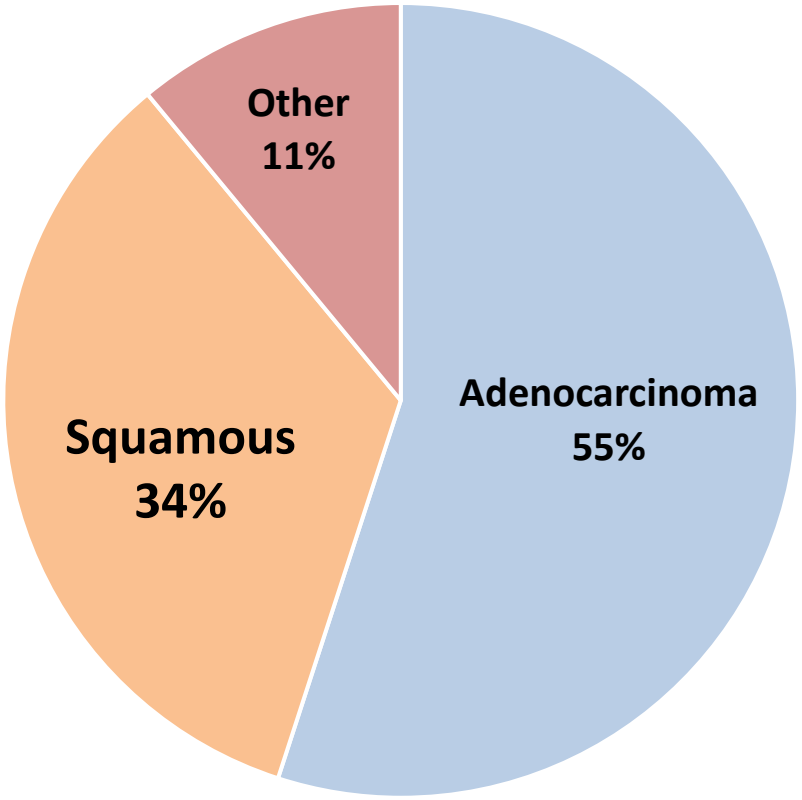
UCDAVIS COMPREHENSIVE CANCER CENTER

NCI Designated Comprehensive Cancer Center

NSCLC: Adenocarcinoma vs. Squamous Cell



	Adenocarcinoma	SqCC
Age	Bimodal with younger subset	Generally older
Sex	↑ female	↑ males
Smoking status	Never-smoker subset associated with oncogenic driver alterations	Current or former heavy smokers: no actionable alterations
Therapies contraindicated	None	Pemetrexed Bevacizumab

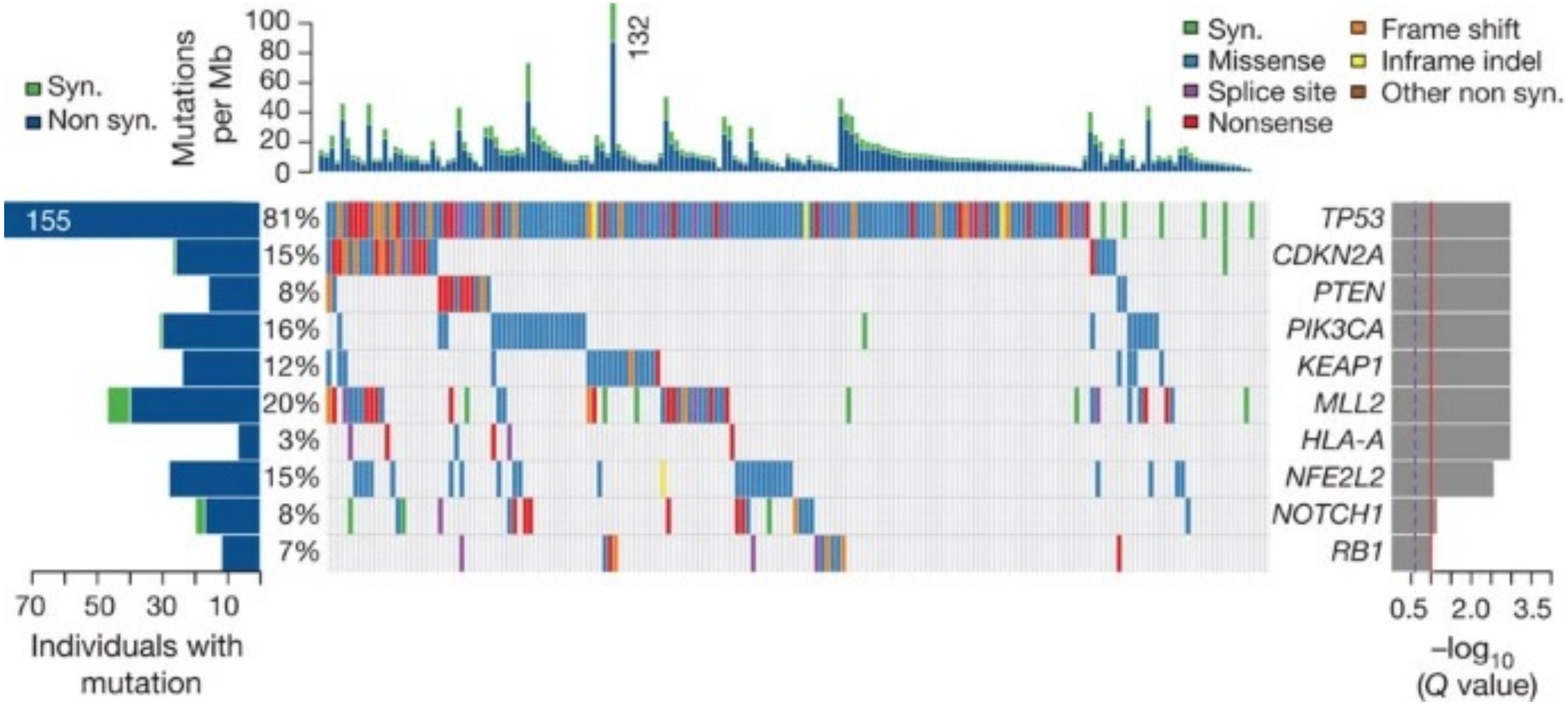
Gandara et al. *Clin Cancer Res.* 2016

The trouble with squamous lung cancer

- Advances in targeted therapy have largely bypassed squamous cell lung cancer
- Actionable oncogenic drivers are relegated to lung adenocarcinoma
  - Alterations in *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *NTRK,* or *RET*
  - No real progress in targeted therapy for squamous cancers despite many molecular targets and initiation of associated clinical trials
- Recent advances have resulted from immunotherapy

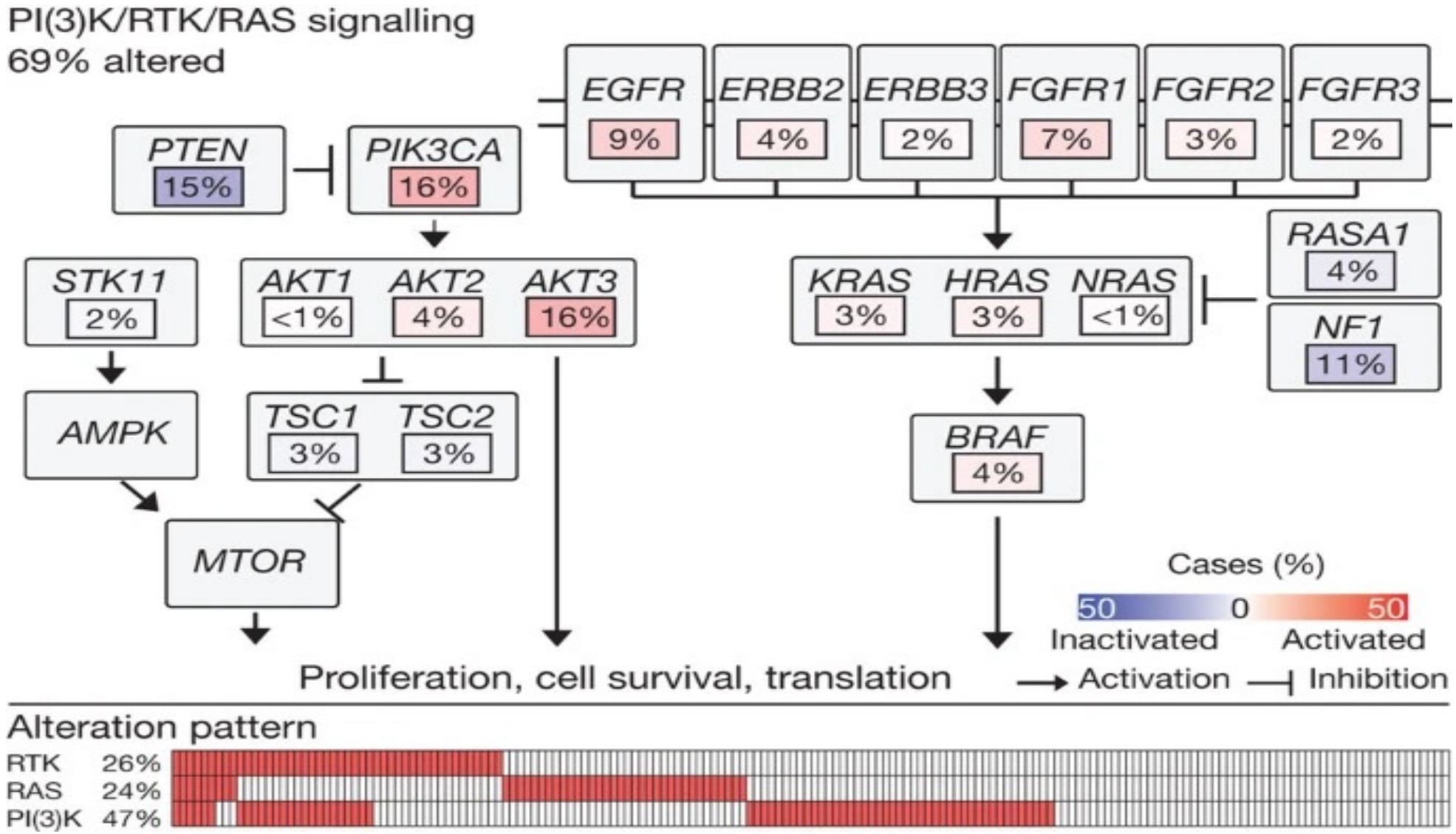
Gandara, Riess, & Lara, JAMA Oncology 2018

Significantly mutated genes in lung SQCC



TCGA, Nature 2014

Alterations in targetable oncogenic pathways in lung SQCCs



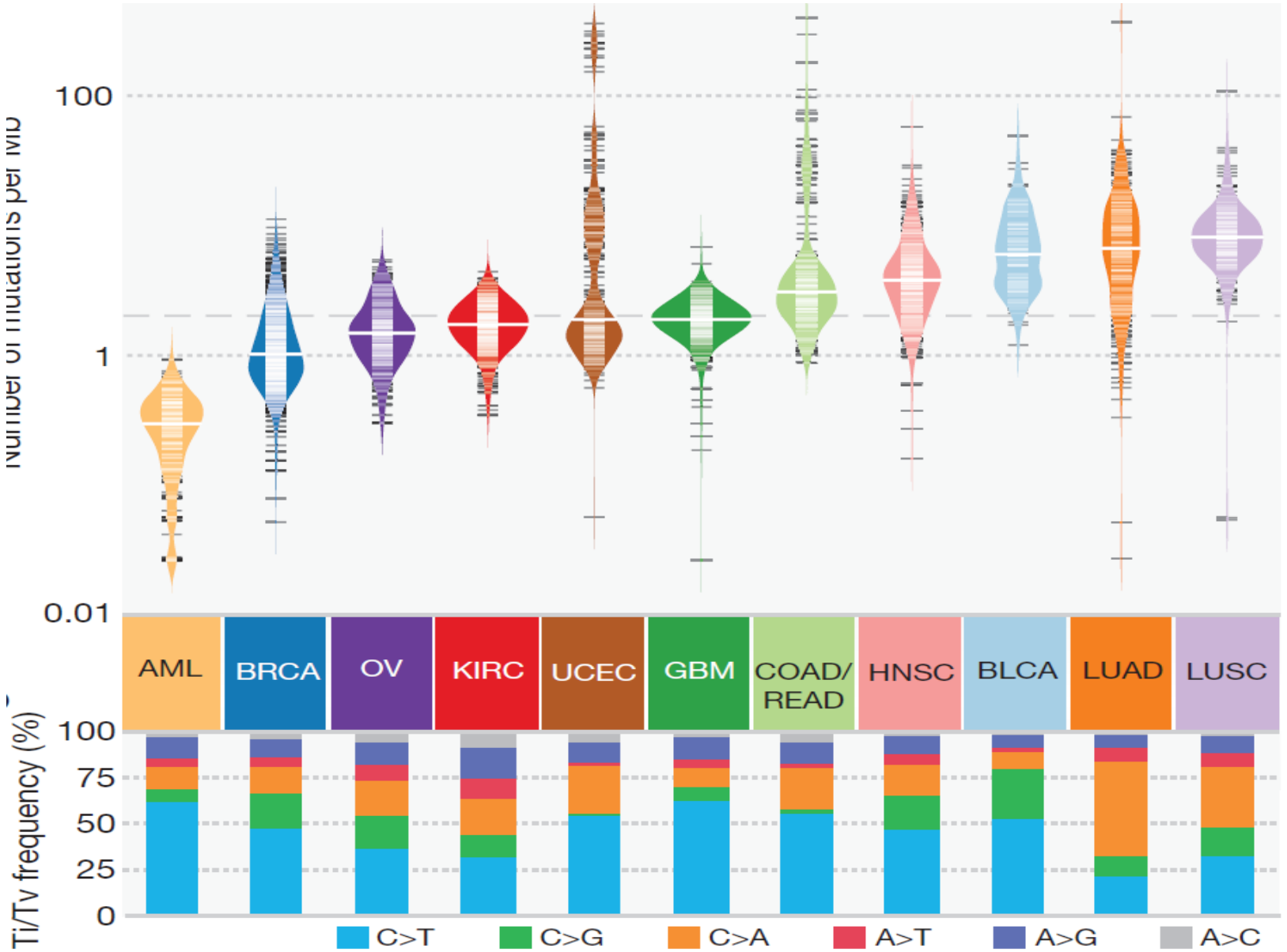
TCGA, Nature 2014

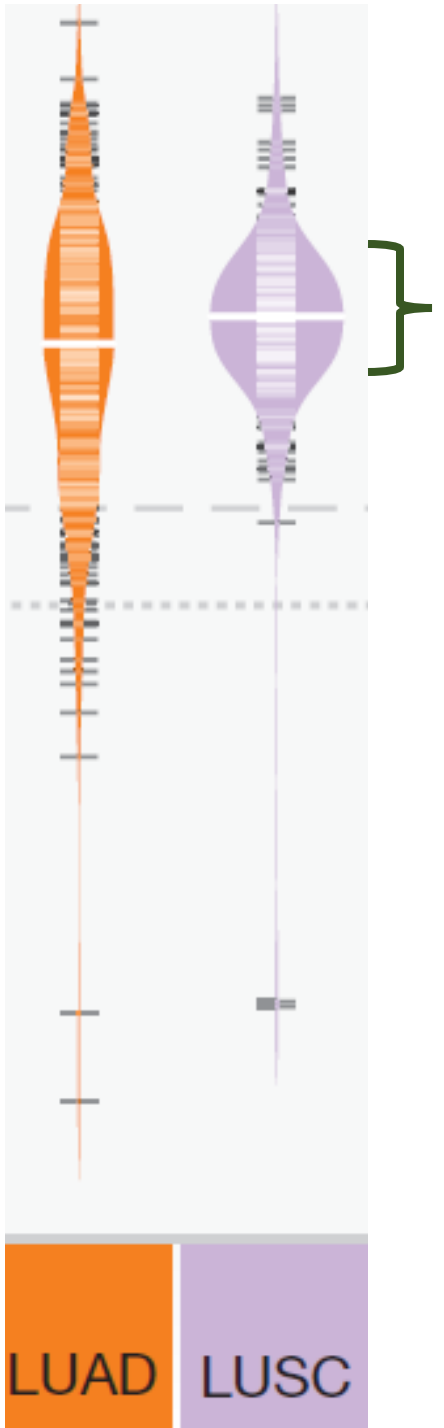
Selected precision medicine approaches in lung SQCC

Target	Drug	ORR (%)	Median PFS (95% CI)
PI3K	Taselisib	4	2.8 (1.7–4.0)
PI3K	Buparlisib	4.5	2.8 (1.4–3.7)
G1/S checkpoint	Palbociclib	6	1.8 (1.6–2.9)
FGFR1	AZD4547	7	2.7 (1.4–4.5)
FGFR1	Dovitinib	11.5	2.9 (1.5–4.3)
FGFR1	BGJ398	11	NA

Paik, ASCO 2019

Magnitude of Genomic Derangement in Various Cancers





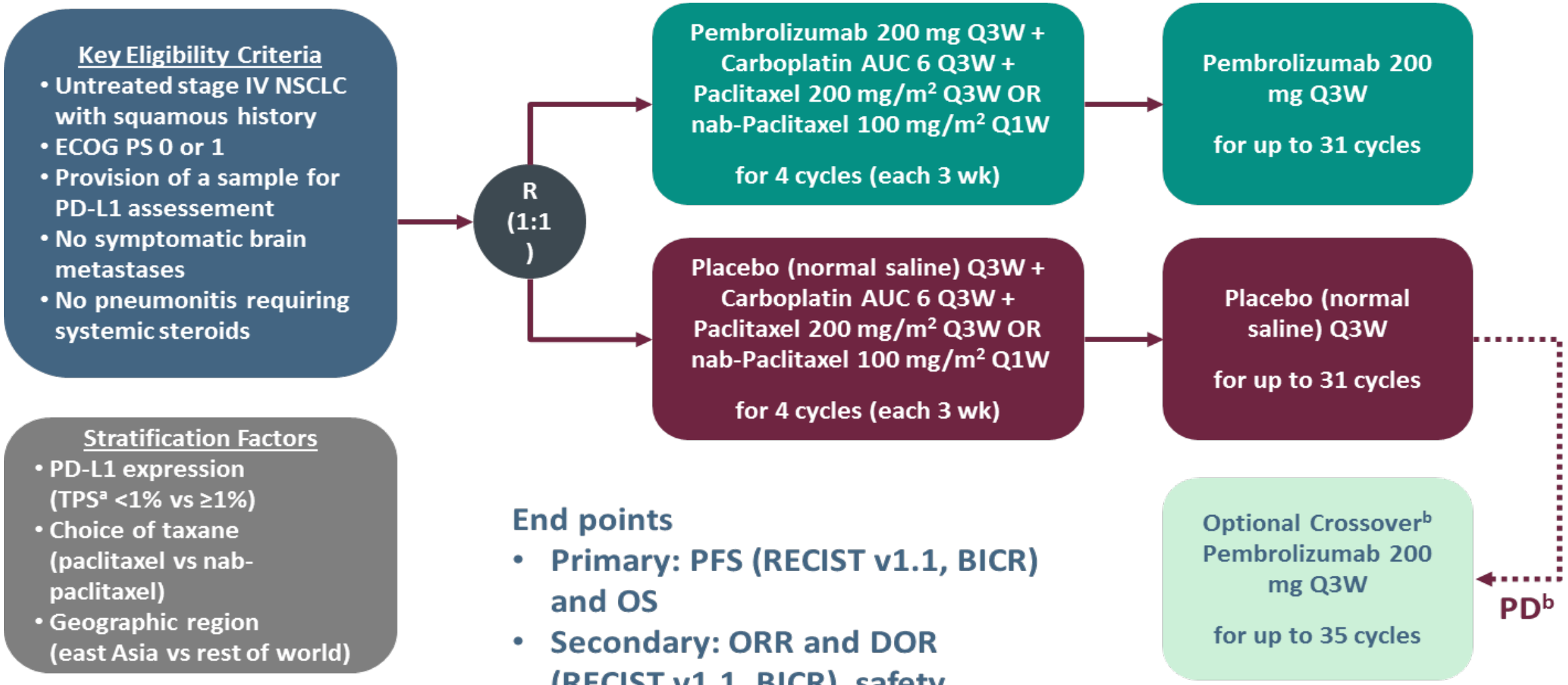
Adapted from The Cancer Genome Atlas Project: Kandoth et al *Nature* 2013.

Frontline immunotherapy approaches for lung SQCC

Study	Number of NSCLC Patients in Trial/Number with Lung SCC	Patient Population	Median PFS	Median OS	Survival HR vs Chemotherapy in Lung SCC Patients (95% CI)
First-line treatment					
Pembrolizumab vs platinum-based chemotherapy (KEYNOTE-024)[92,93]	305/56	PD-L1 TPS ≥50%	10.3 vs 6.0 months; *P*<0.001	30.0 vs 14.2 months; *P*=NR	PFS 0.35 (0.17–0.71)
Pembrolizumab vs platinum-based chemotherapy (KEYNOTE-042)[11]	1274/492	PD-L1 TPS ≥1%	TPS ≥1%: 5.4 vs 6.5 months; *P*=NR TPS 1–49%: NR	TPS ≥1%: 16.7 vs 12.1 months; HR=0.81; *P*=0.0018 TPS 1–49%: 13.4 vs 12.1 months; HR=0.92	NR (SCC patients were not analyzed separately)
Pembrolizumab + platinum-based chemotherapy vs platinum-based chemotherapy (KEYNOTE-407)[94]	559/559	Unselected (PD-L1 TPS <1% and ≥1%)	6.4 vs 4.8 months; *P*<0.001	15.9 vs 11.3 months; HR=0.64; *P*<0.001	PFS 0.56 (0.45–0.70)
Nivolumab + ipilimumab vs platinum-based chemotherapy (CheckMate 227)[13,15]	PD-L1 ≥1%: 1189/350	Unselected (PD-L1 <1% and ≥1%)	PD-L1 ≥1%: 5.1 vs 5.6 months; HR 0.82	PD-L1 ≥1%: 17.1 vs 14.9 months; *P*=0.007	PD-L1 ≥1%: OS 0.69 (0.52–0.92)
Atezolizumab vs platinum-based chemotherapy (IMpower110)[16]	554/167	PD-L1 ≥1% on TC or IC	TC3 or IC3 WT: 8.1 vs 5.0 months; *P*=0.0070	TC3 or IC3 WT: 20.2 vs 13.1 months; HR=0.59; *P*=0.0106	OS 0.56 (0.23–1.37) (for TC3 or IC3 WT)

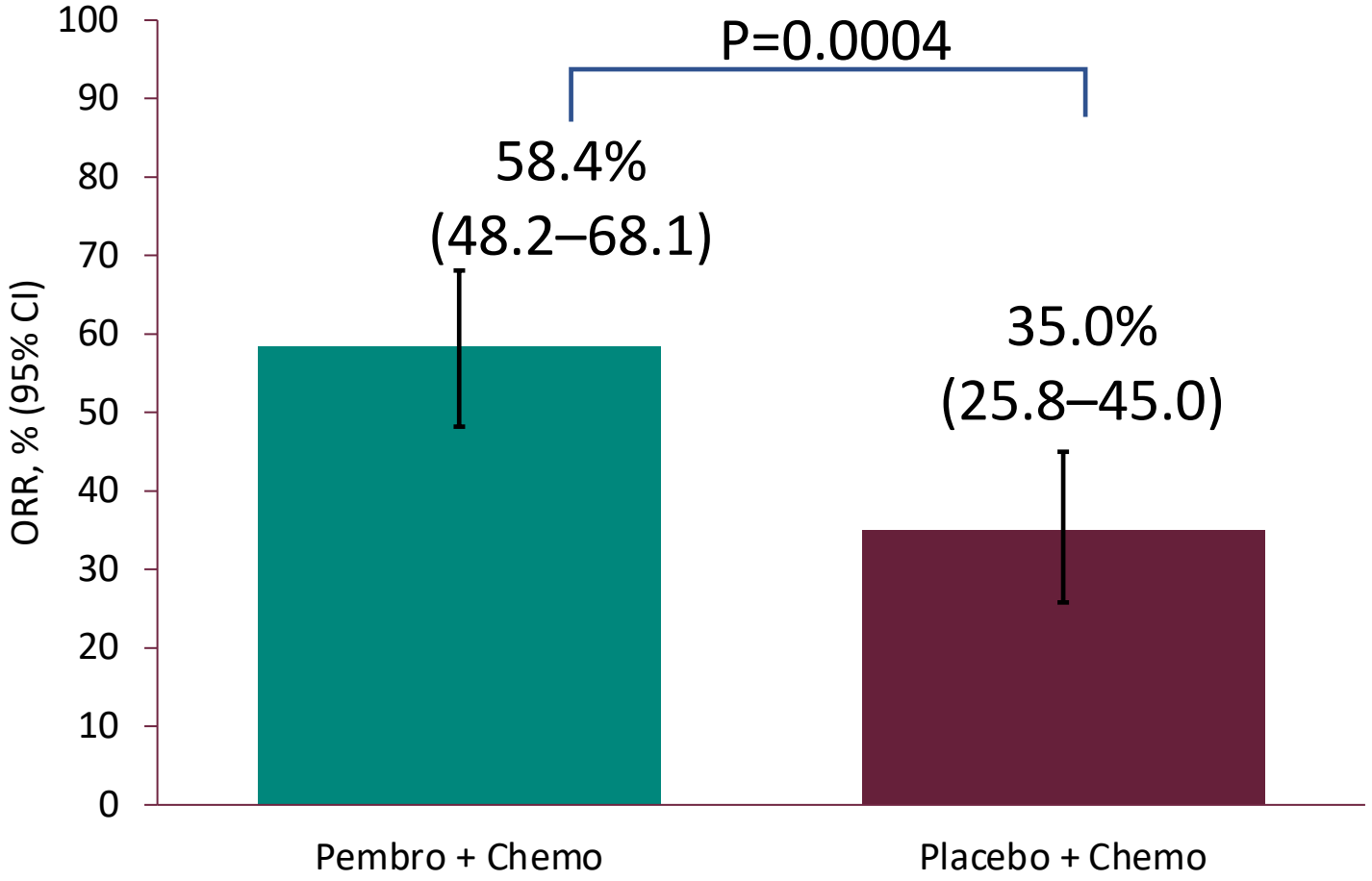
Santos & Hart, OncoTargets and Therapy, 2020

KEYNOTE-407: Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel ± pembrolizumab in patients with metastatic squamous NSCLC



Paz-Ares LG, et al. ASCO 2018. Abstract 105.

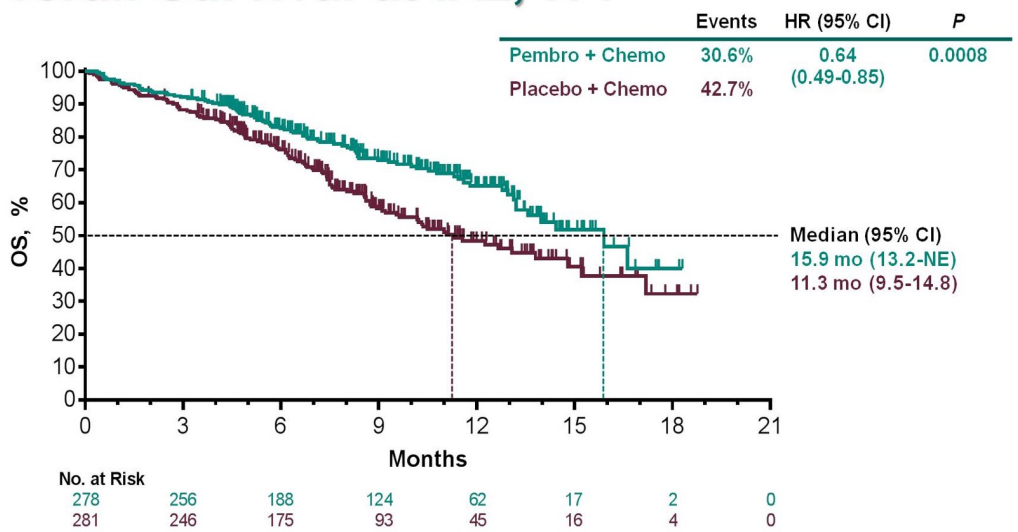
KEYNOTE-407: Objective Response Rate



Paz-Ares LG, et al. ASCO 2018

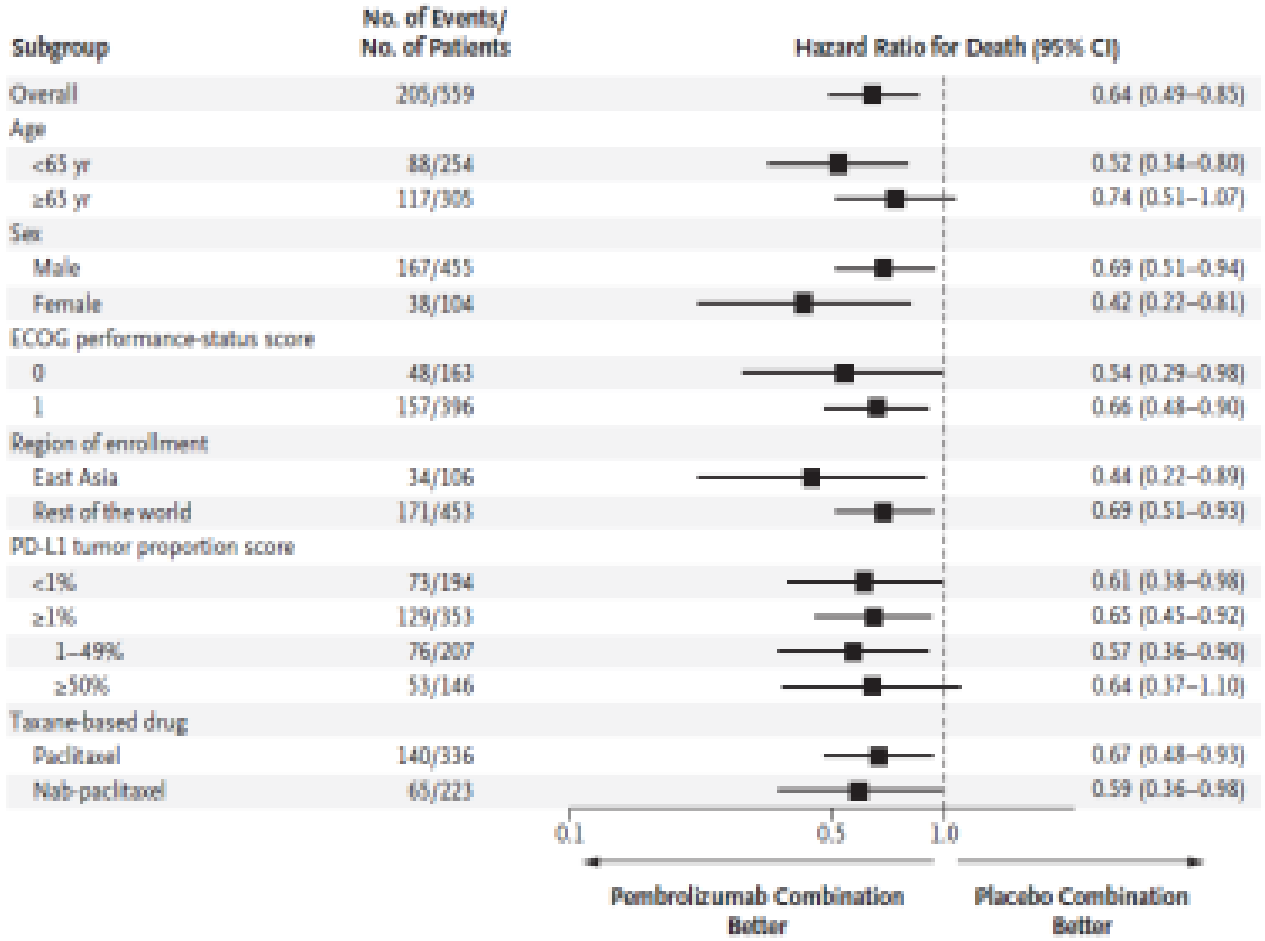
KEYNOTE-407: Overall Survival

Overall Survival at IA2, ITT



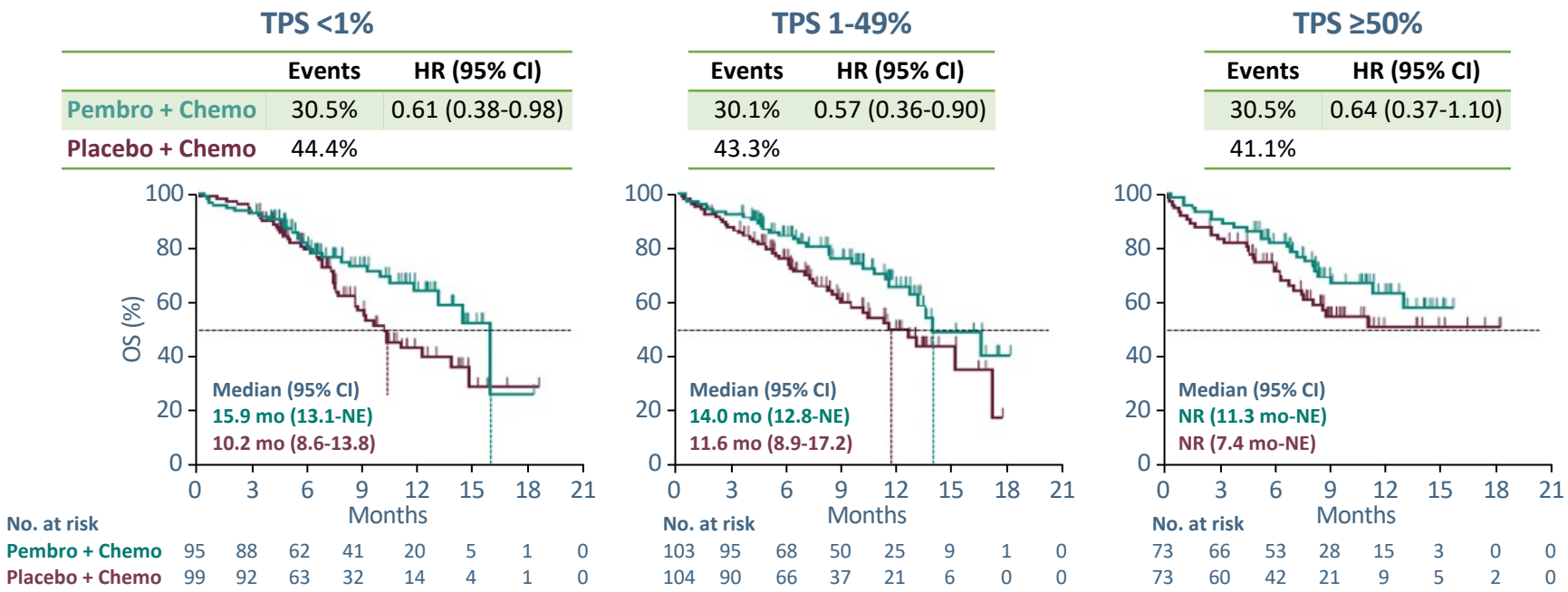
- **OS HR 0.64***; p=0.0008
- PFS HR 0.56; p<0.0001
- ORR 58% vs. 38%

*median f/u 7.8 months; 27% crossover



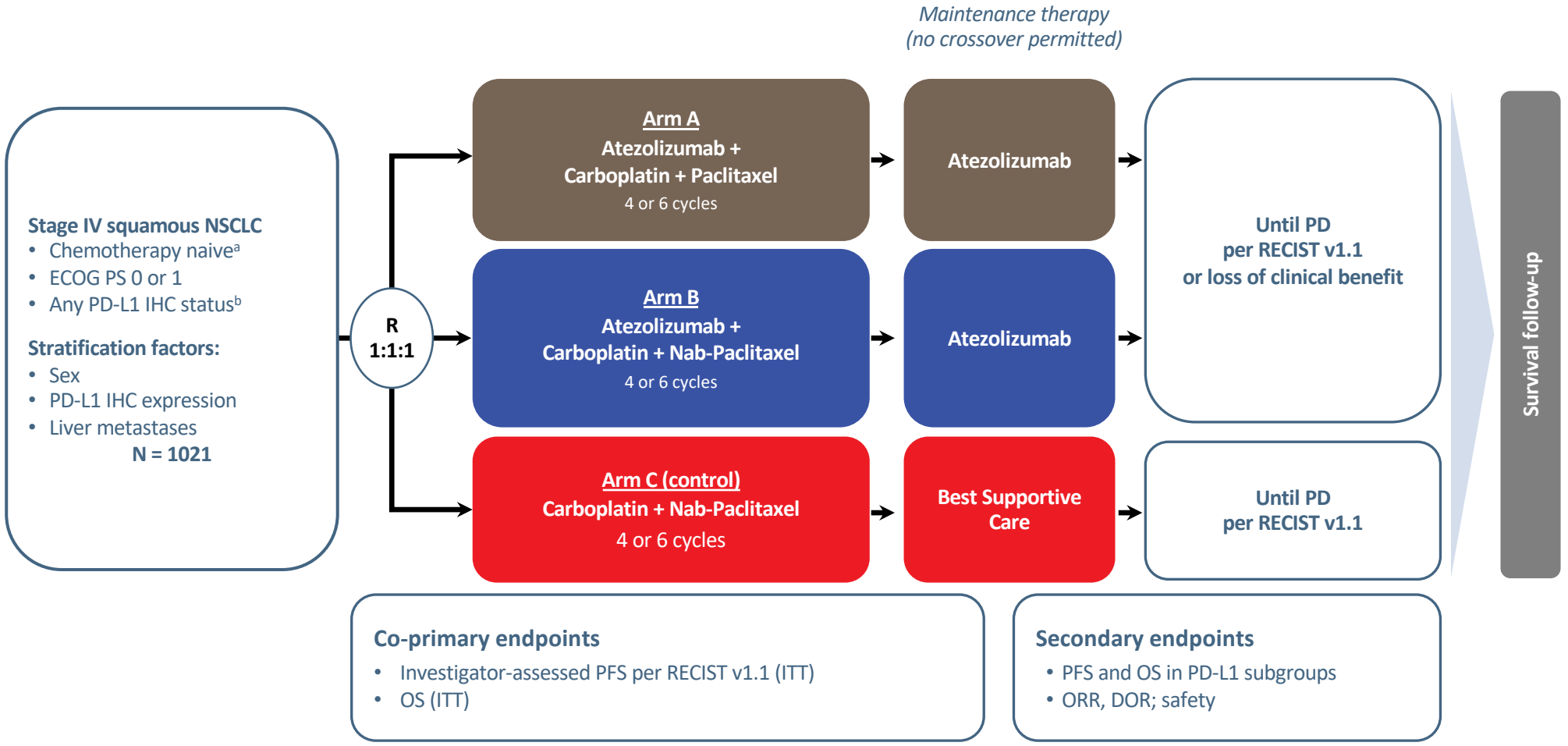
Paz-Ares et al. N Engl J Med. 2018 Nov 22;379(21):2040-2051.

KEYNOTE-407: Overall survival by PD-L1 tumor proportion score



Paz-Ares LG, et al. ASCO 2018. Abstract 105.

IMpower131: Phase III study of 1st-line Atezolizumab + Carboplatin/Paclitaxel/Nab-Paclitaxel vs Carboplatin/Nab-paclitaxel in advanced squamous NSCLC



Atezolizumab 1200 mg IV q3w; carboplatin AUC 6 IV q3w; nab-paclitaxel 100 mg/m^2 IV qw; paclitaxel 200 mg/m^2 IV q3w.

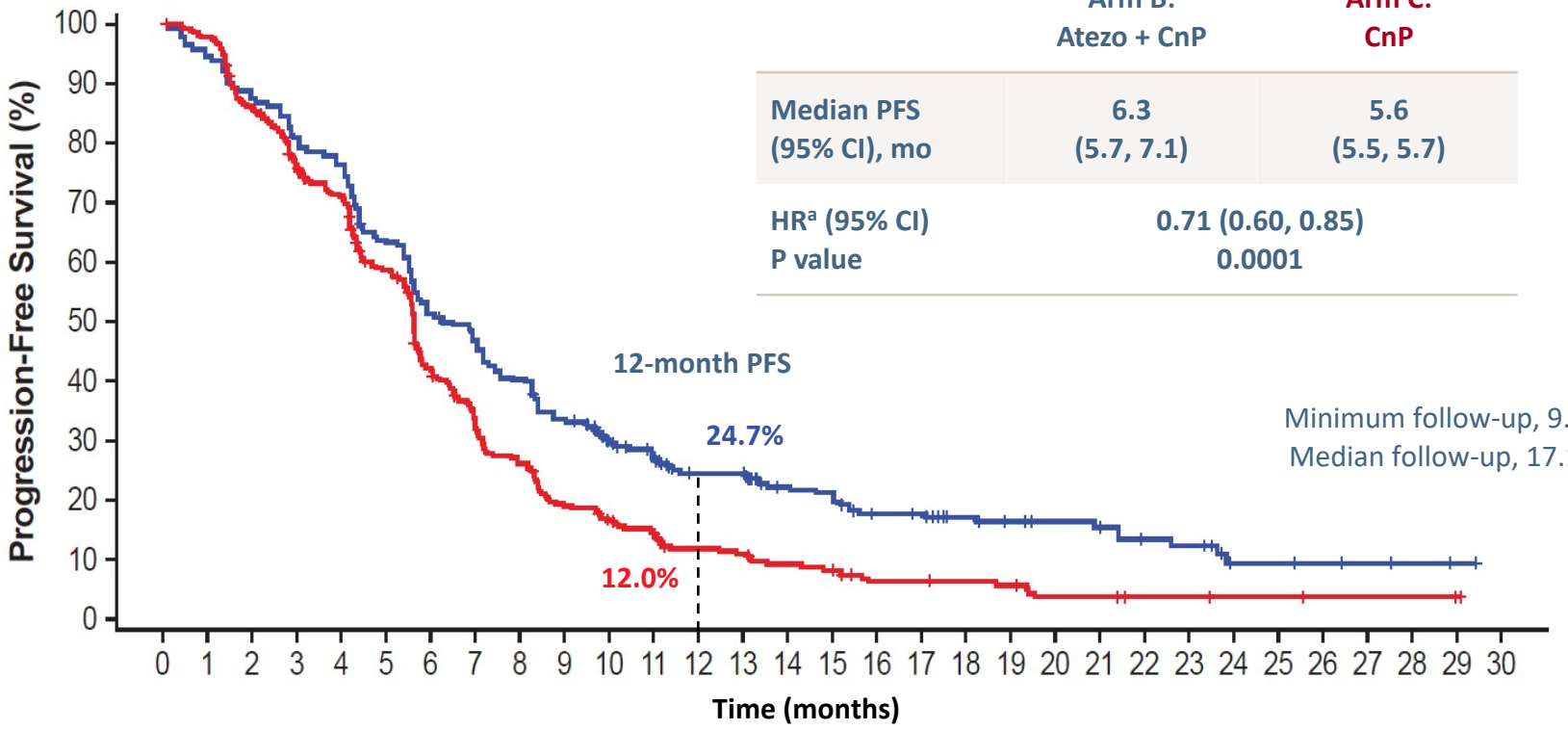
[a]Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with ≥ 1 approved targeted therapies. Testing for *EGFR* mutation or *ALK* translocation was not mandatory.

[b]PD-L1 expression was evaluated using the VENTANA SP142 IHC assay.

Jotte RM, et al. ASCO 2018. Abstract LBA9000.

IMpower131: PFS in ITT population (Arm B vs Arm C)

	Arm B: Atezo + CnP	Arm C: CnP
Median PFS (95% CI), mo	6.3 (5.7, 7.1)	5.6 (5.5, 5.7)
HR[a] (95% CI)	0.71 (0.60, 0.85)	
P value	0.0001	



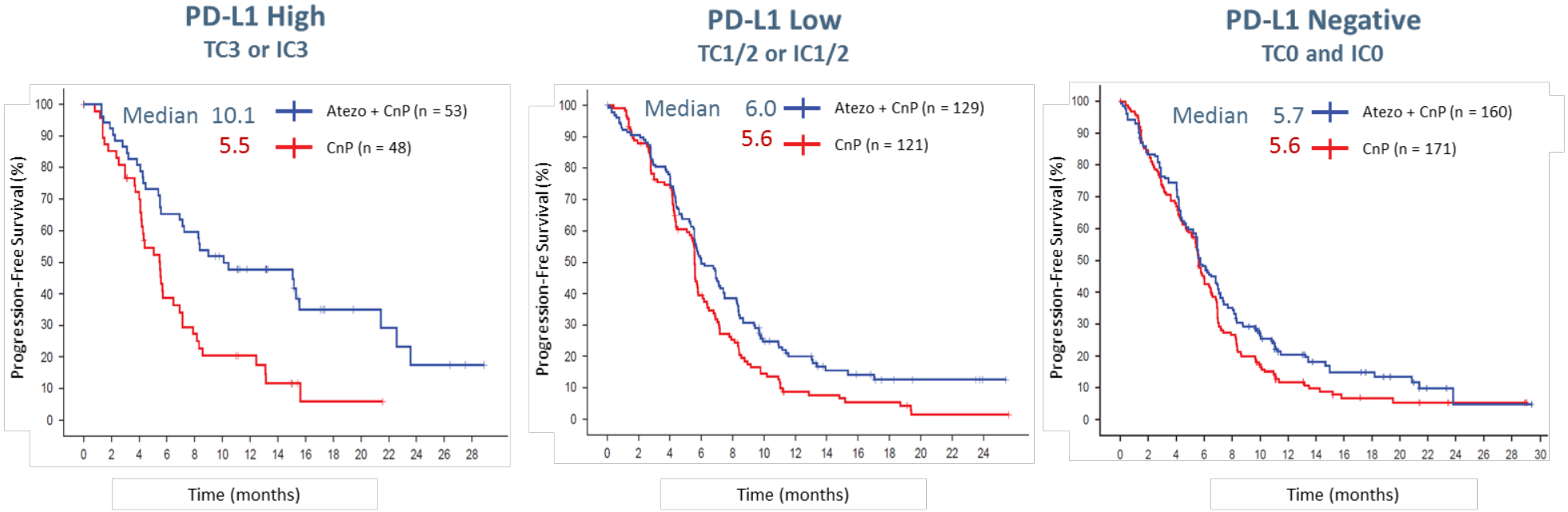
Minimum follow-up, 9.8 mo
Median follow-up, 17.1 mo

Atezo + CnP	343	318	294	268	257	212	172	151	134	111	88	76	61	61	44	42	33	32	24	21	18	16	12	11	5	5	4	3	2	1
CnP	340	322	279	244	227	183	128	95	79	57	48	40	28	26	21	19	12	12	11	10	6	6	4	4	3	3	2	2	2	1

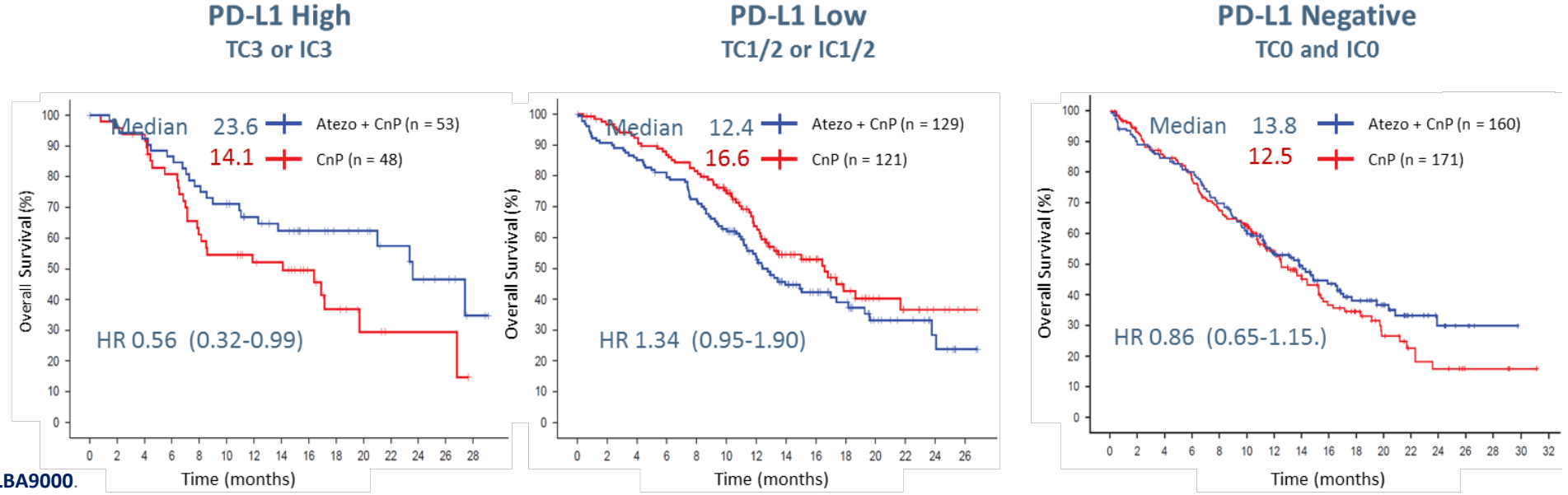
Jotte RM, et al. ASCO 2018. Abstract LBA9000.

IMpower131: Investigator-assessed PFS & OS in PD-L1 subgroups (Arm B vs Arm C)

PFS

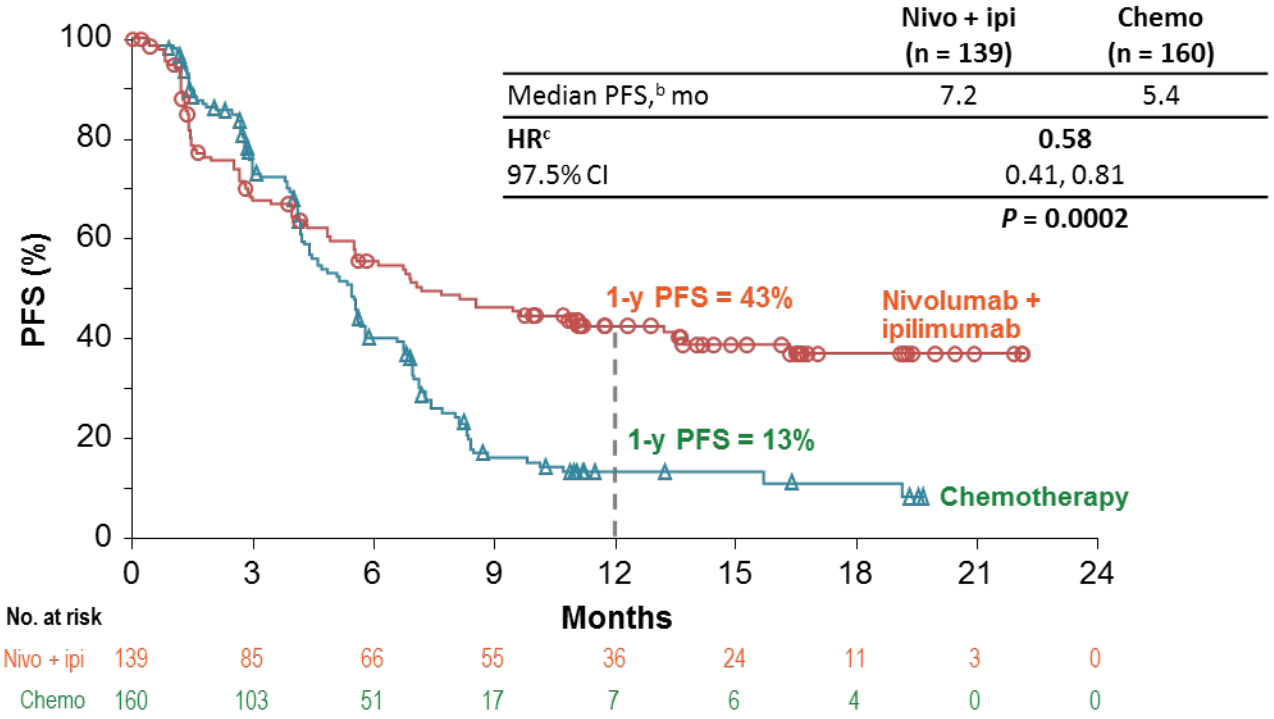


OS



Jotte RM, et al. ASCO 2018. Abstract LBA9000.

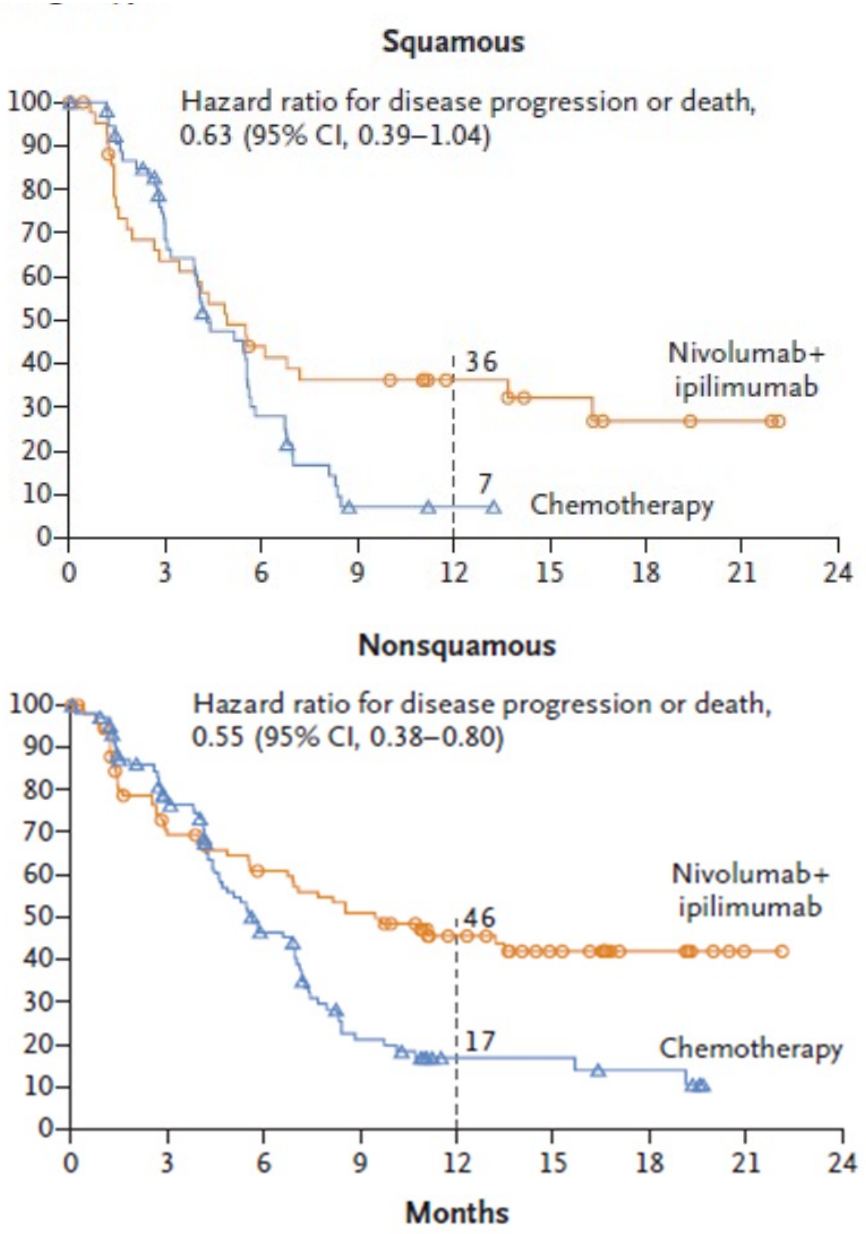
Checkmate 227: Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)[a]



	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	**0.58**	
97.5% CI	0.41, 0.81	
	***P* = 0.0002**	

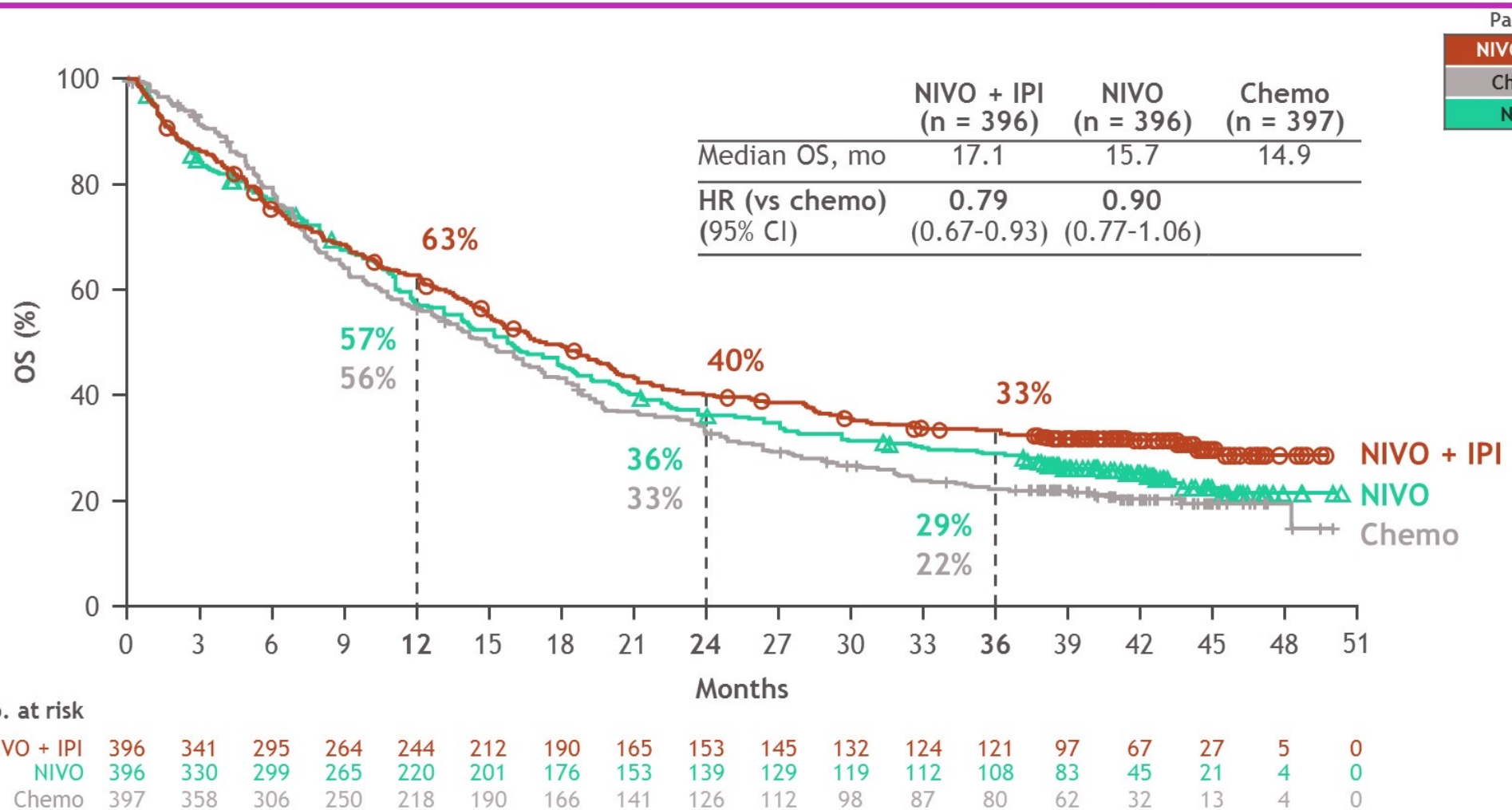
In patients with TMB <10 mut/Mb on nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)[d]

Results by Histology



Hellman et al, NEJM 2018

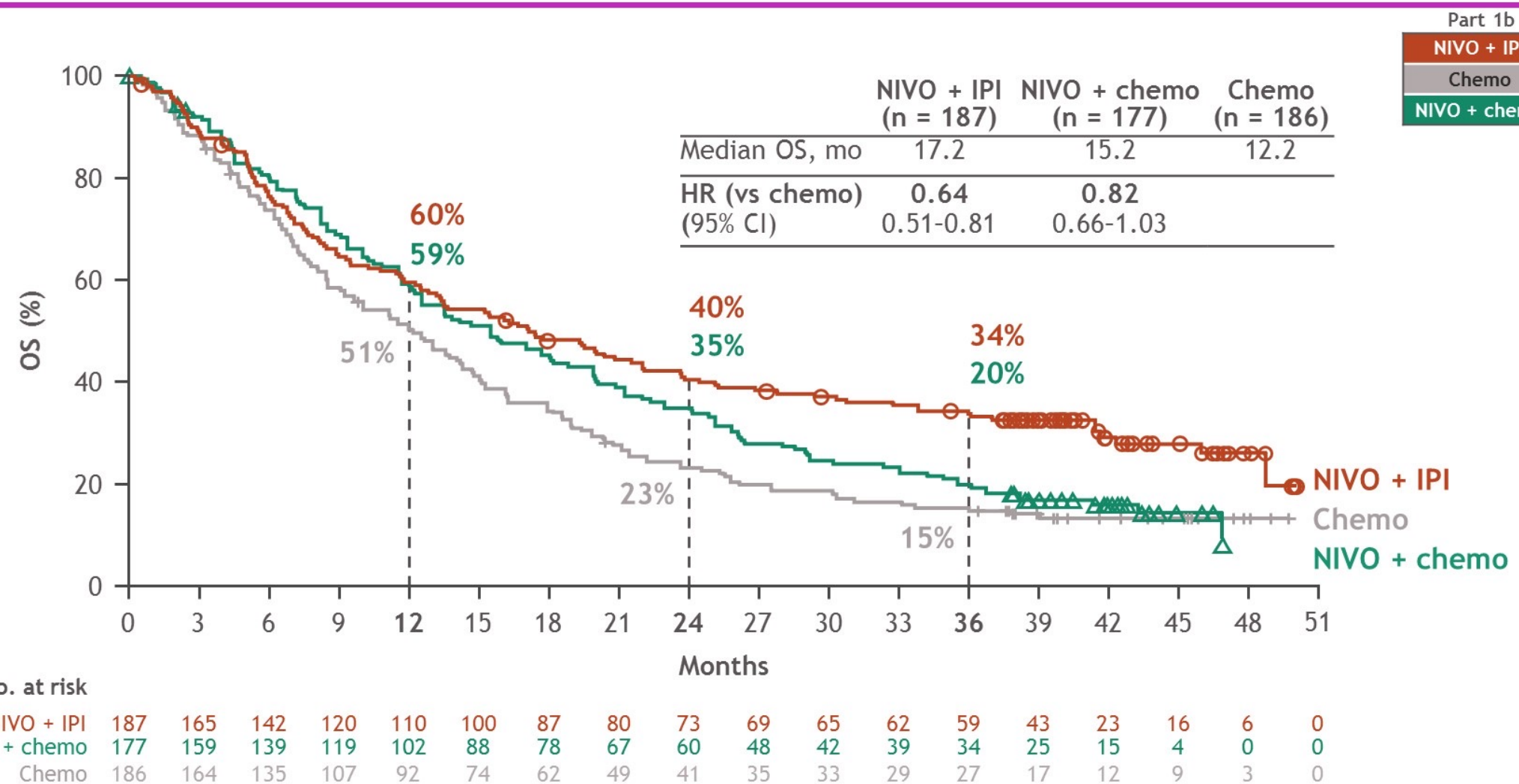
3-year update: OS with NIVO + IPI vs chemo vs NIVO (PD-L1 ≥ 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W) and NIVO (240 mg Q2W). Among patients who were alive at 3 years, subsequent systemic therapy was received by 35% in the NIVO + IPI arm, 45% in the NIVO arm, and 76% in the chemo arm; subsequent immunotherapies were received by 13%, 21%, and 71%; and subsequent chemotherapy was received by 28%, 33% and 30%, respectively.

3-year update: OS with NIVO + IPI vs Chemo vs NIVO + Chemo (PD-L1 < 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

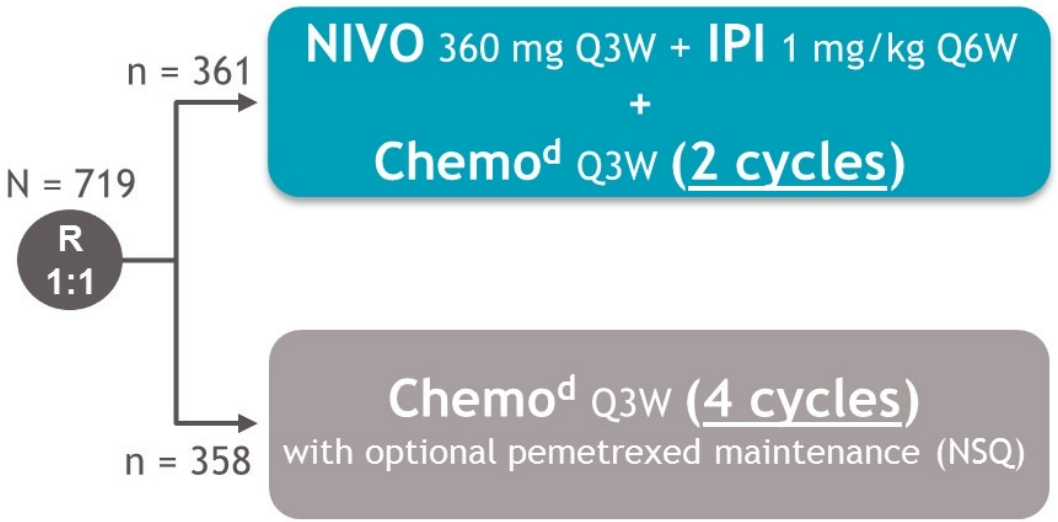
Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Among patients who were alive at 3 years, subsequent systemic therapy was received by 49% in the NIVO + IPI arm, 38% in the NIVO + chemo arm, and 78% in the chemo arm; subsequent immunotherapies were received by 12%, 12%, and 74%; and subsequent chemotherapy was received by 46%, 35% and 33%, respectively.

CheckMate 9LA study design[a]

Key Eligibility Criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint

- OS

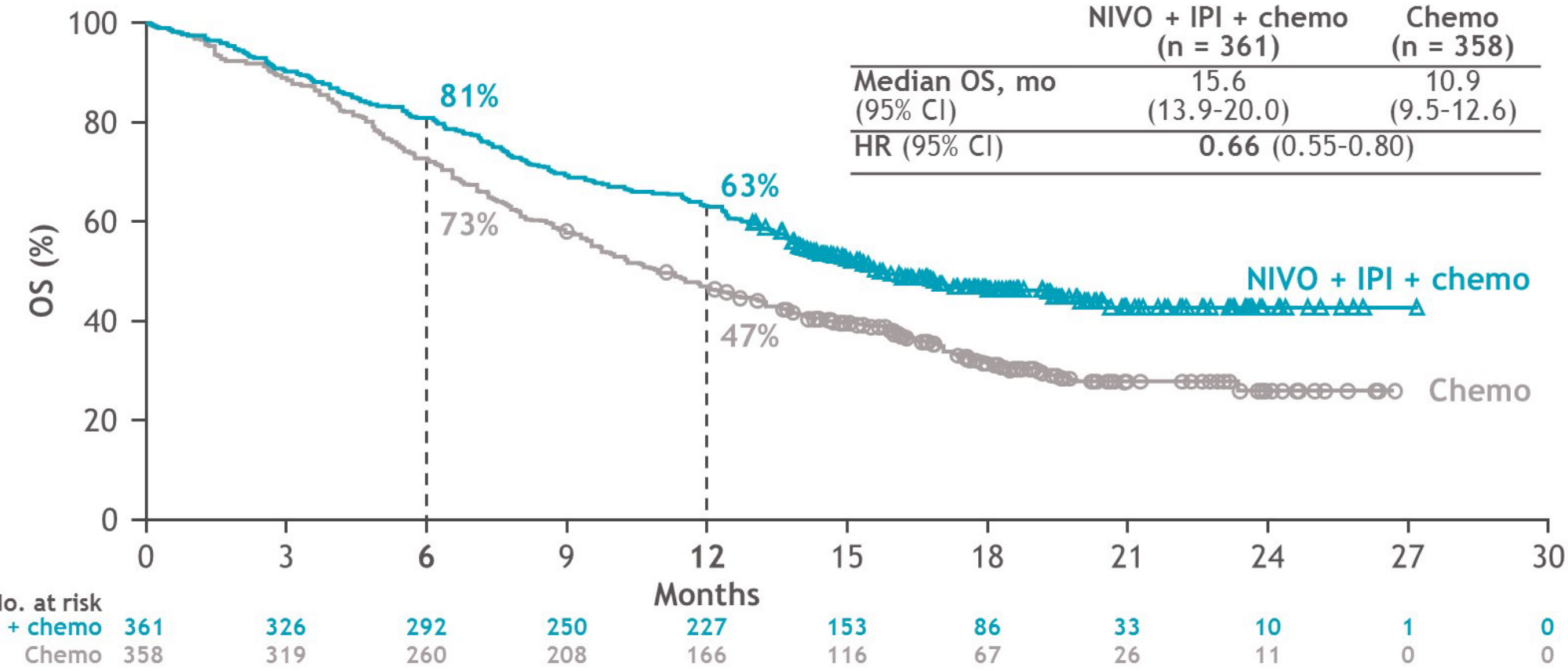
Secondary endpoints

- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]**NSQ**: pemetrexed + cisplatin or carboplatin; **SQ**: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Primary endpoint (updated): Overall survival[a]



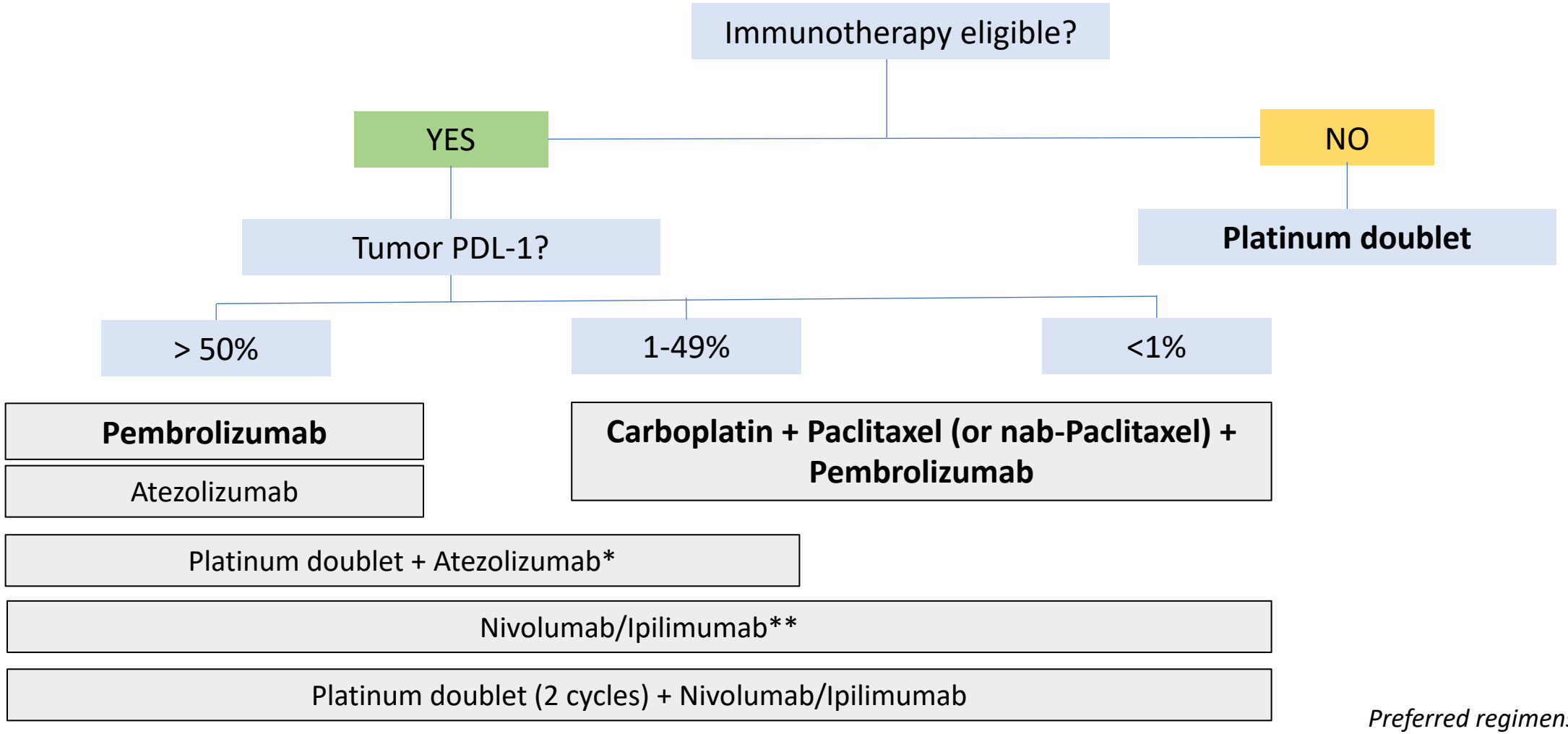
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	**0.66** (0.55-0.80)	

Minimum follow-up: 12.7 months.

Combination regimen resulted in longer mOS than chemotherapy alone for both squamous (14.5 vs 9.1 months, HR=0.62) and nonsquamous histology (17.0 vs 11.9 months, HR=0.69), and for both PD-L1-positive (≥1%, HR=0.64) and PD-L1-negative tumors (<1%, HR=0.62).

Treatment algorithm: Frontline SQCC

(no driver mutation, reasonable PS)



*Preferred regimens in **bold;***
**IMpower 110 – PFS benefit only*
***CM227 – also active in TMB>10*

Who is NOT eligible for immunotherapy?

- Active autoimmune disease
- History of solid organ transplantation
- Supraphysiologic corticosteroids
- Chronic immunosuppressive therapy
- Personal patient preference

Second-line and beyond: Squamous cell lung cancer

- **Cytotoxic chemotherapy** (if not already given in front line)
  - Platinum doublet or single agent
- **Nivolumab**
  - Checkmate 017 (n=272 SqCC): Nivolumab > Docetaxel
- **Atezolizumab**
  - OAK (n=850; 222 SqCC) : Atezolizumab > Docetaxel
- **Ramucirumab**
  - REVEL (n=1253; 328 SqCC): Ram/Doc > Docetaxel
- **Afatinib**
  - LUX-Lung 8 (n=795 SqCC): Afatinib > Erlotinib

Second-line Checkpoint Inhibitors in NSCLC

Trial	Primary Endpoint OS	mOS (months)	1-year OS rate	mPFS (months)	ORR	PD-L1+ matters?
Nivo: squam CM017	HR = 0.59 (95% CI: 0.44,0.79)	9.2 vs 6.0	42% vs 24%	3.5 vs. 2.8	20% vs. 9% P = 0.008	NO
Nivo: non-sq CM057	HR = 0.73 (95% CI: 0.59,0.89)	12.2 vs 9.4	51% vs 39%	2.3 vs. 4.2	19% vs.12% P = 0.025	YES
Pembro: KN010 TPS≥1%	P2:HR = 0.71 (95% CI: 0.58,0.88) P10:HR = 0.61 (95% CI 0.49,0.75)	10.4 (P2) vs 12.7 (P10) vs 8.5 mo (D)	43% vs 52% vs 35%	~4.0 all groups	18% (P2) vs 18% (P10) vs 9% D; P=.0005	YES
Atezo: OAK	HR = 0.73 (95% CI:0.62,0.87)	13.8 vs 9.6 mo	55% vs 41%	2.8 vs 4.0	14% vs. 13% NS	YES

Ramucirumab + Docetaxel modestly improves clinical outcomes in 2nd line NSCLC: REVEL trial

Non-squamous	465 (74%)	447 (72%)
Squamous	157 (25%)	171 (27%)
Unknown	6 (1%)	7 (1%)

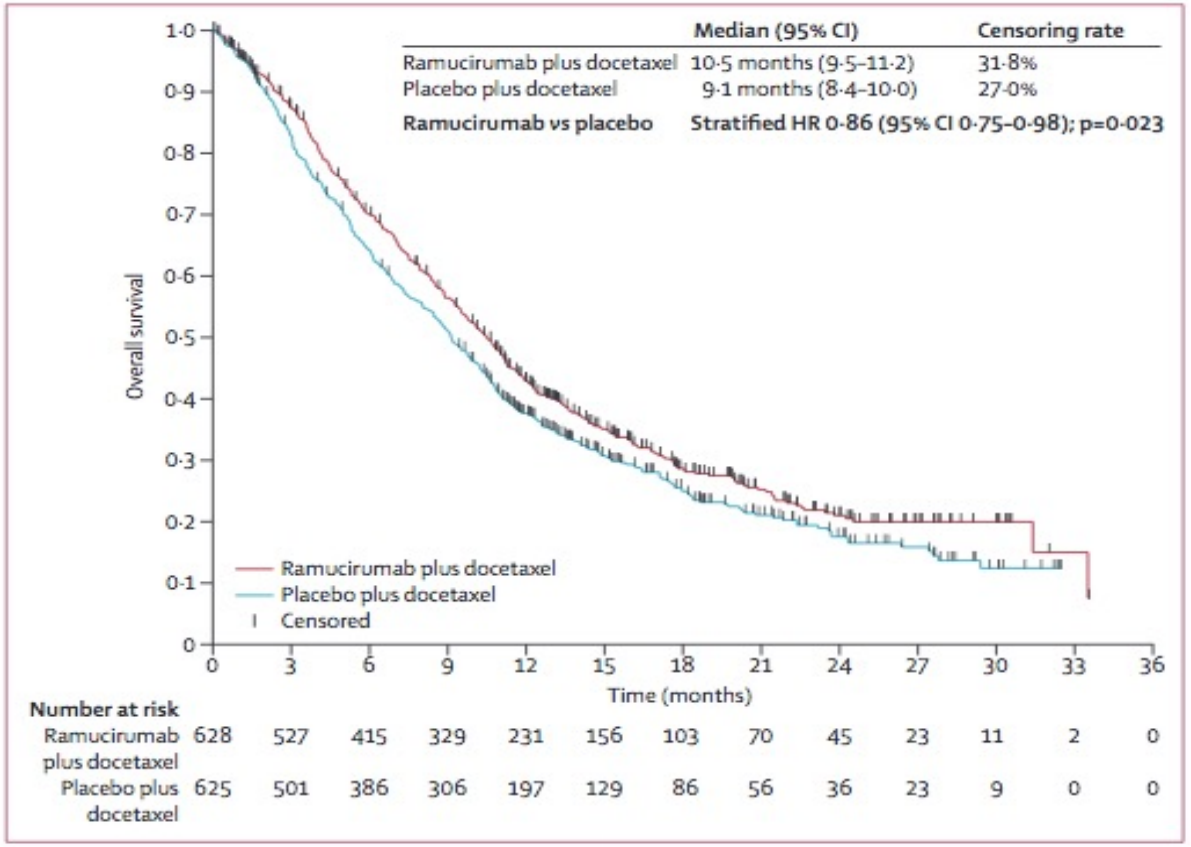


Figure 2: **Kaplan-Meier estimates of overall survival in the intention-to-treat population**
HR=hazard ratio.

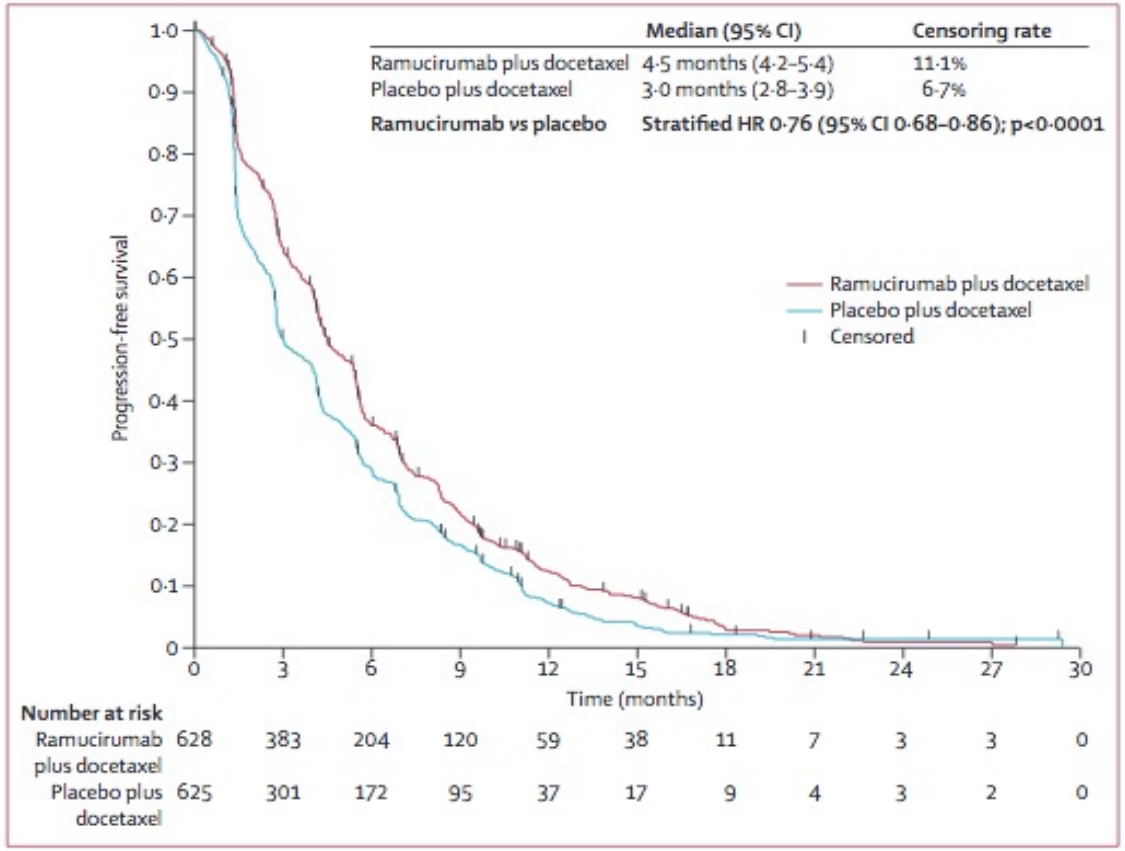
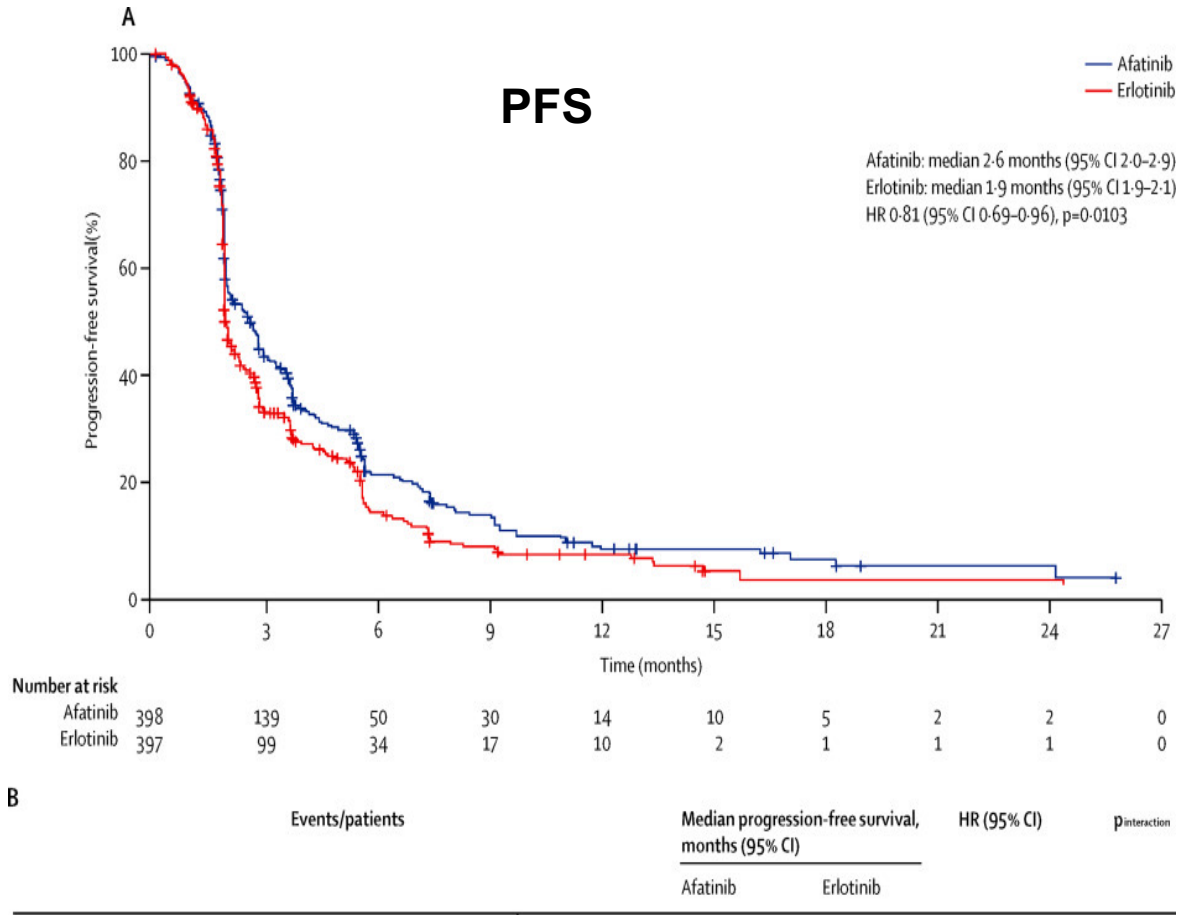
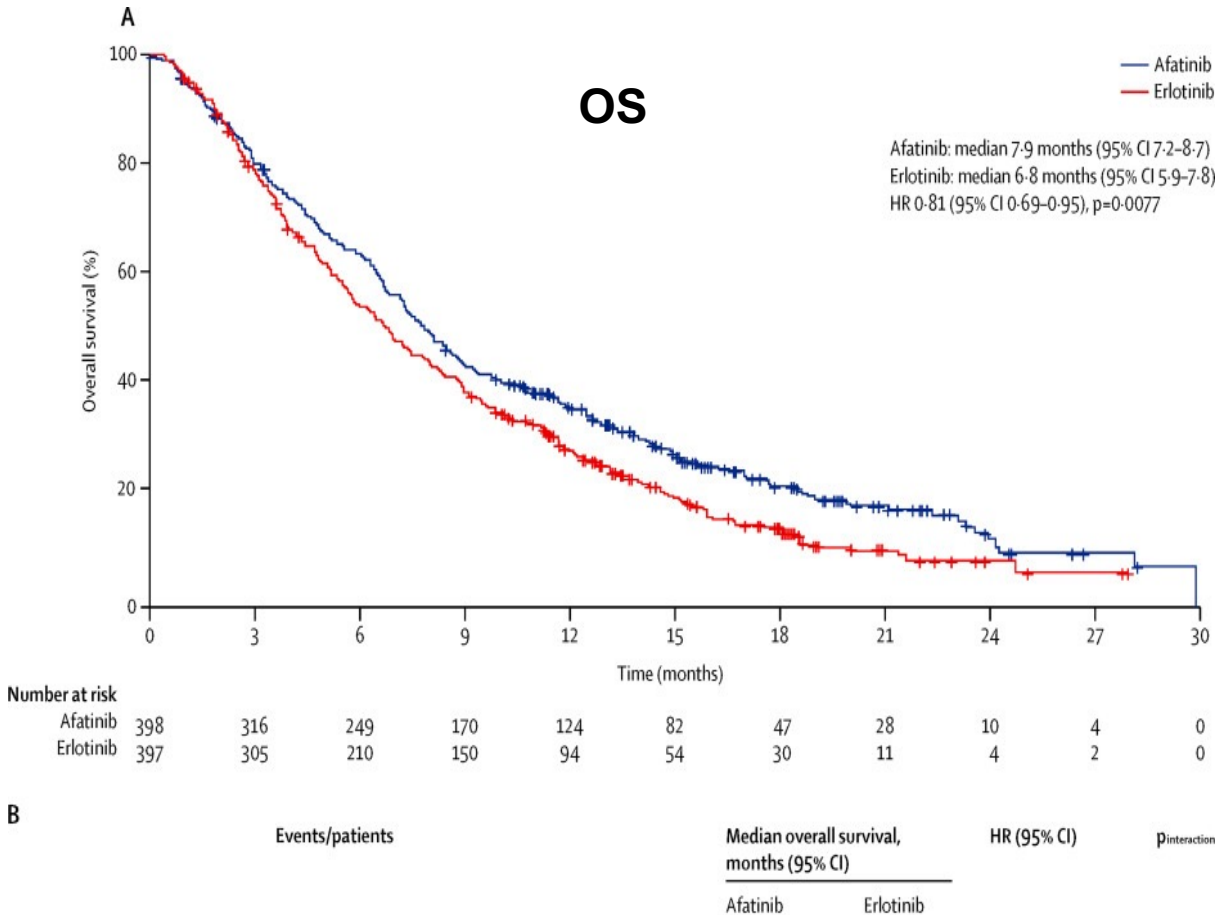


Figure 3: **Kaplan-Meier estimates of progression-free survival in the intention-to-treat population**
HR=hazard ratio.

Garon, Lancet 2014

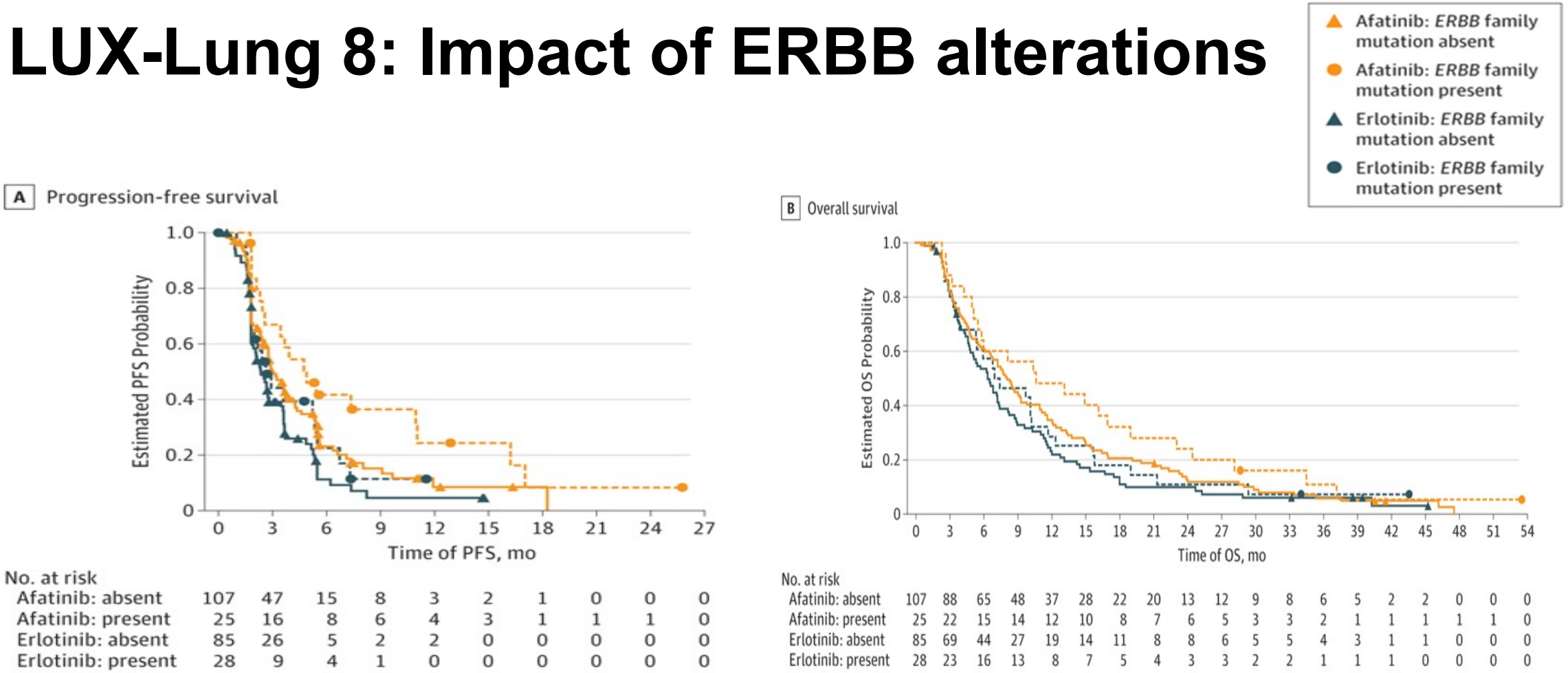
LUX-Lung 8: Afatinib vs Erlotinib in lung SQCC





Soria, Lancet 2015

LUX-Lung 8: Impact of ERBB alterations

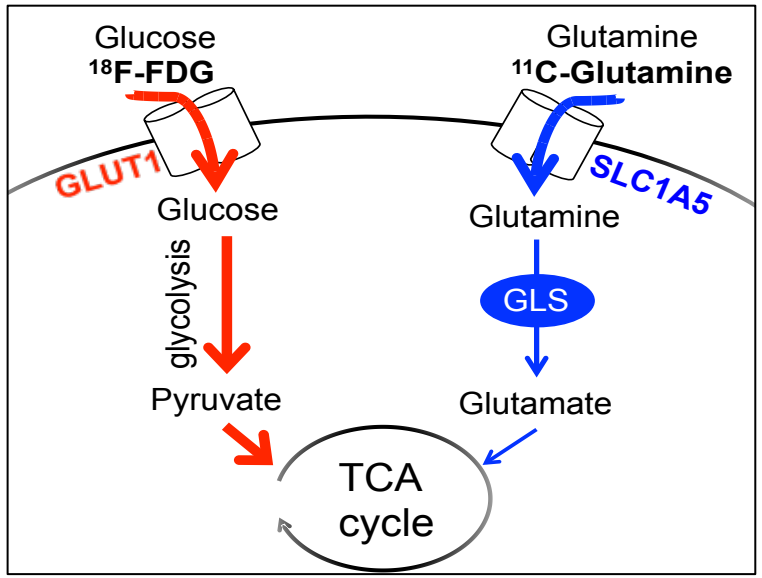


PFS and OS benefit with afatinib over erlotinib was more pronounced among patients with *ERBB* mutation–positive tumors than among those without, especially among patients with tumors having *HER2* or *HER4* mutations.

Goss, JAMA Onc 2018; Gandara JAMA Onc 2018

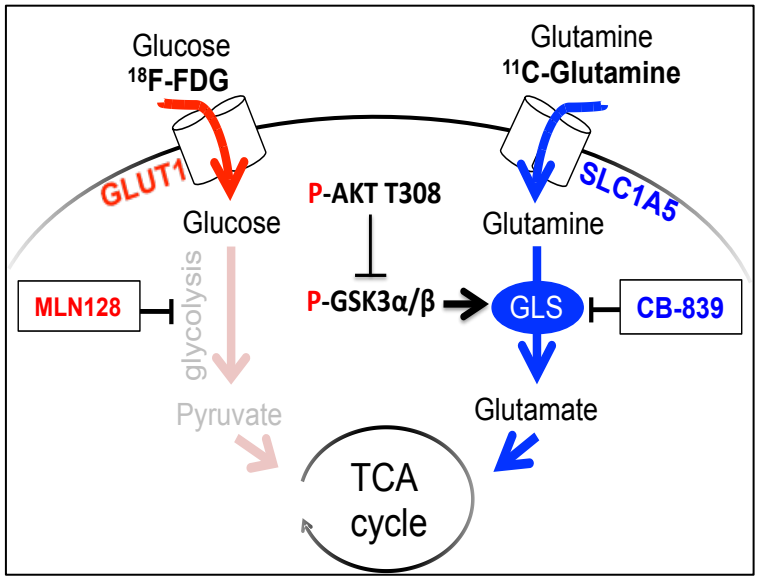
Adaptive Glutamine Metabolism by GSK3 Signaling Axis Circumvents TAK228 Inhibition of Glycolysis in Squamous NSCLC

Glucose and Glutamine Dependent Metabolism

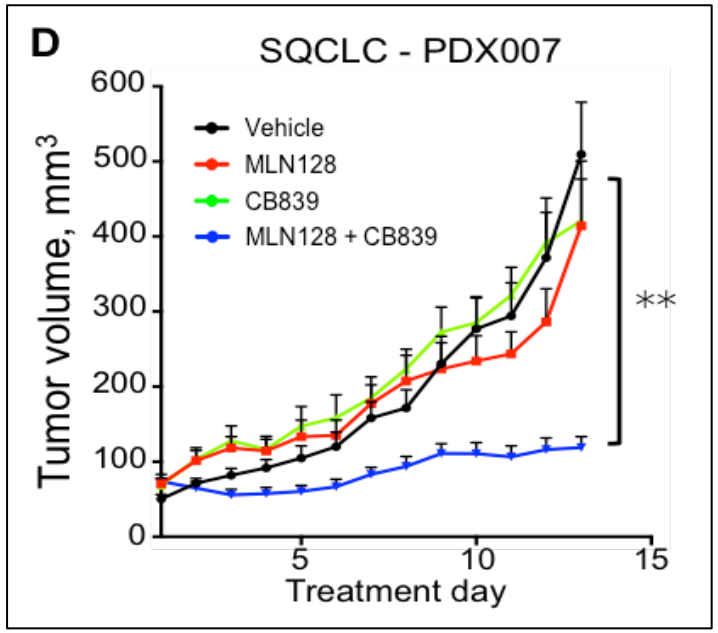


Basal metabolism – high uptake of glucose and glutamine to sustain SQCC growth

Adaptive Glutamine Metabolism



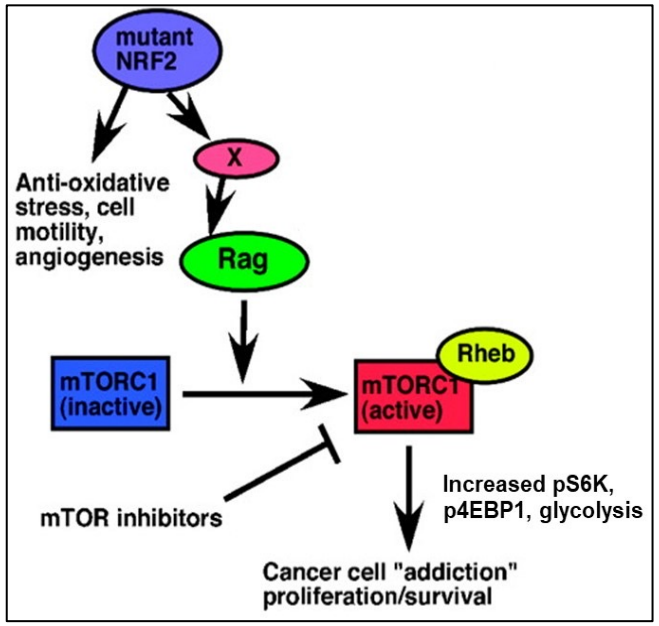
Overcoming resistance – GSK signaling axis with adaptive GLN metabolism



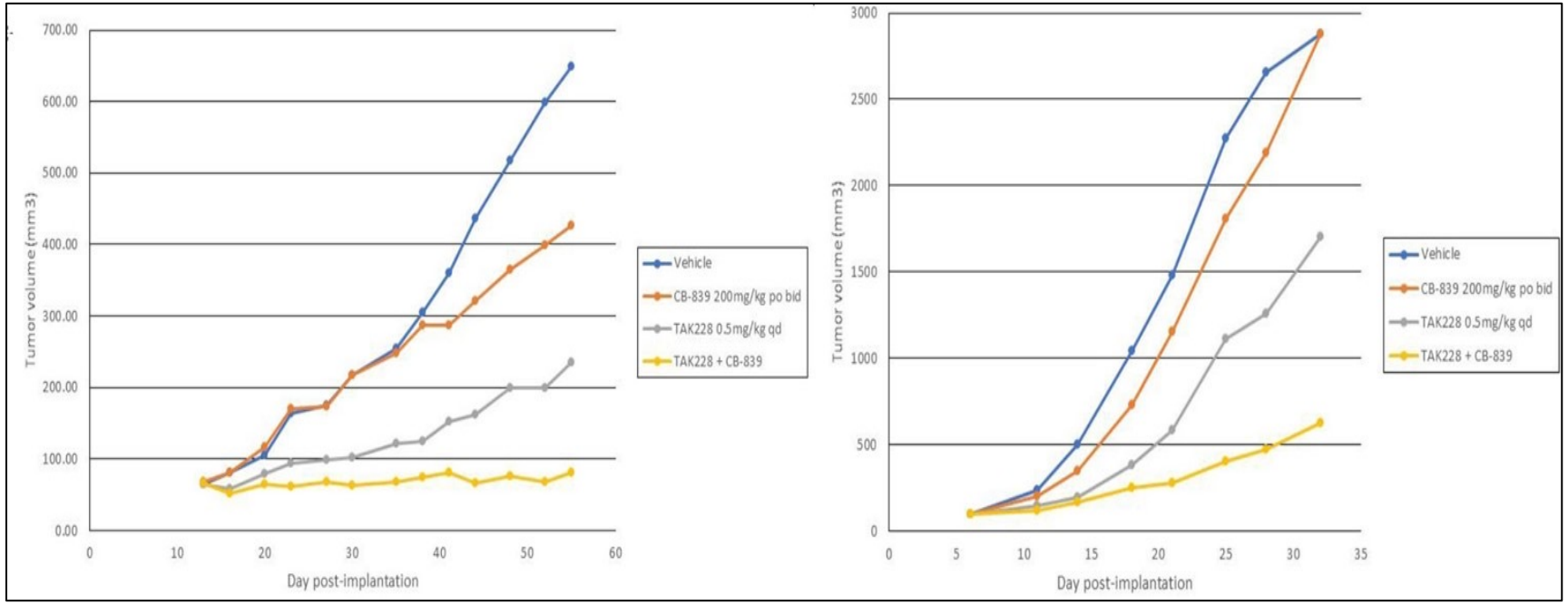
Actionable in vivo with dual mTOR and GLS inhibition

From the Shackelford lab. Momcilovic et al. Cancer Cell 2018.

NRF2 upregulation (~30% SQ-NSCLC) increases glycolysis and inhibition of glutaminolysis with CB-839 exhibits synergistic anti-tumor activity



NRF2 upregulation activated TORC1 with increase in pS6K, p4EBP1, glycolysis, and proliferation/survival (adapted from Shibata et al. CCR 2010)



TAK228 (MLN128, sapanisertib) and CB-839 exhibit synergistic anti-tumor activity in (A) LK-2 LUSC *NFE2L2* mutant xenograft and **(B)** A549 *KRAS/KEAP1* co-mutant xenograft. Mice were treated with vehicle, CB-839, TAK228, or the combination of TAK228 + CB-389. P. Paik et al. **Keap1 loss promotes dependence on glutaminolysis in KRAS mut NSCLC** (Romero et al Nat Med 2017)

A Phase 1 Trial of TAK-228 (Sapanisertib) and CB-839 in Advanced NSCLC (NCI 10327; ETCTN)

Stage IV NSCLC
PD on or after platinum and/or PD-(L)1
PS 0-2

Dose escalation to Recommended Expansion Dose

- **Genomic Profiling: Tissue and plasma NGS**
- **Plasma metabolite and PK profiling** (Joel Reid/Ian Lanza Mayo)
- **Intratumoral metabolic signaling profiling** (IHC Panel) (David Shackelford UCLA)
- **Paired ^{18}F-Glutamine-PET (^{18}F-Gln) and ^{18}FDG-PET analyses** (MSKCCC and UCD)

- Cohort A: LUSC harboring *NFE2L2* mutations (N=14)
- Cohort B: LUSC harboring *KEAP1* mutations (N=14)
- Cohort C: LUAD harboring KRAS mut with *KEAP1 or NFE2L2* mutations (N=14)
- Cohort D: LUSC "wild type" for NFE2L2/KEAP1 (N=14)

LUSC = Lung Squamous Cell Cancer

co-PIs: JW Riess, P. Paik

Summary

- Unmet needs persist in advanced squamous cell lung cancer
- Immunotherapy-based regimens represent the SOC for most patients
- Targeted therapies have thus far been disappointing
- Clinical trial participation remains the best option