

The Increasing Role of Dual Immunotherapy in mNSCLC Patients

Biagio Ricciuti, MD, PhD

Lowe Center for Thoracic Oncology

Dana-Farber Cancer Institute

Department of Medicine

Harvard Medical School



Dana-Farber
Cancer Institute

Disclosures



- Advisory board/Consultant: Amgen, Regeneron, AstraZeneca, AbbVie, Bristol-Myers Squibb, Bayer, CarisLife, Capvision, Guidepoint, ThirdBridge, Lilly, Johnson and Johnson, Takeda, Sanofi, Pfizer, Summit Therapeutics
- Honoraria: AstraZeneca, Society for ImmunoTherapy of Cancer, Targeted Oncology
- Speakers fee: AstraZeneca, Johnson and Johnson, Regeneron, Pfizer
- Travel support: Regeneron, AstraZeneca, Bristol-Myers Squibb, Genentech
- Research funds to Institutions: AstraZeneca

Program objectives: dual IO in first-line mNSCLC

Review the dual PD-(L)1 + CTLA-4 evidence in first-line metastatic NSCLC, with a focus on *STK11/KEAP1*-mutant disease, and gather insights on four practical questions

1

Patient selection

In which patients do we consider dual IO?

2

Actionability

Are we testing for *KEAP1* and *STK11*, and do the results change the treatment we choose?

3

Evidence gaps

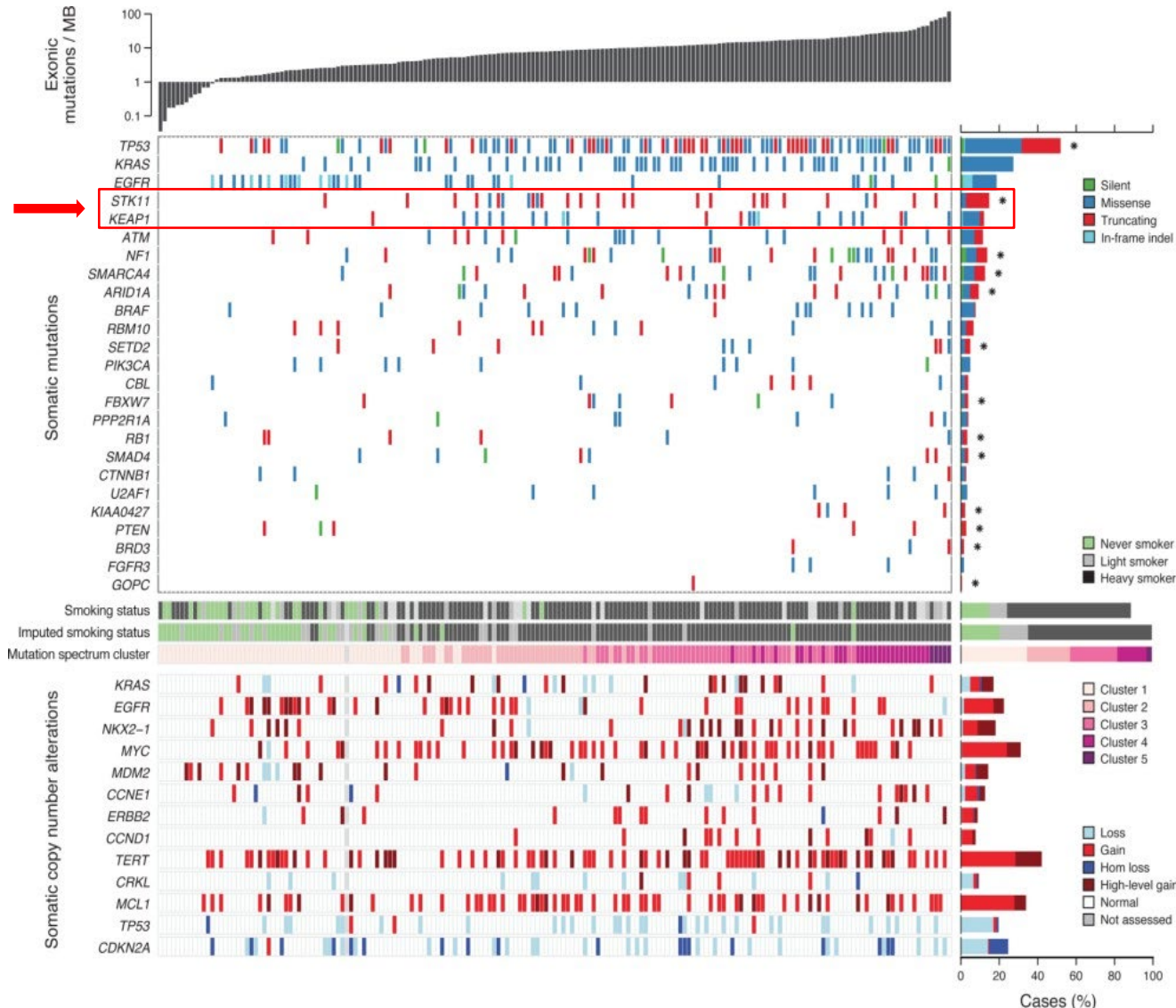
What additional evidence would we need before giving dual IO?

4

Regimen choice

How do we choose between POSEIDON and CheckMate 9LA?

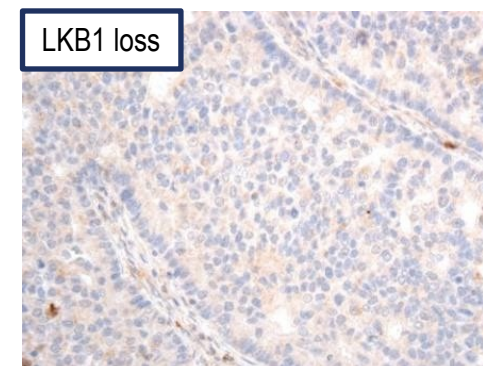
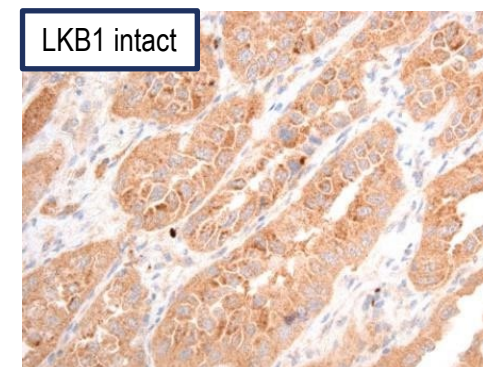
Lung cancer is genomically heterogeneous



- **STK11 and KEAP1 are the 2nd and 3rd most common TSG mutations** in lung adenocarcinoma (30%), also found in adenosquamous and squamous (KEAP1) carcinoma
- More frequently coexist with **KRAS** and **TP53** mutations, and **high TMB** but is rarely found with **EGFR** mutations
- More frequently found in **smokers**
- More frequently in **Caucasians** compared to Asian lung cancer patients

STK11/LKB1 diagnostic test in the clinic is challenging

Method	Pros	Cons
NGS	Comprehensive, information on the type of mutation	Cost, no activity assessment, false positive or negative results (e.g., promoter hypermethylation)
IHC	Rapid, cost efficient, mutation agnostic	Equivocal or false negative results, no information on the type of mutation

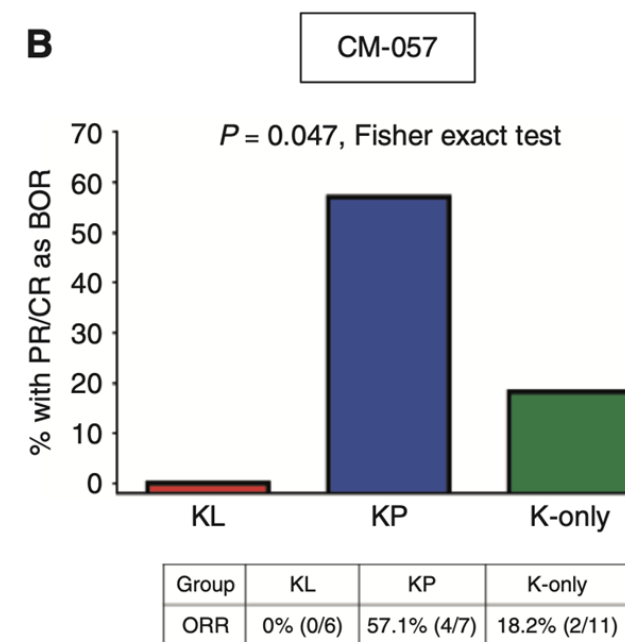
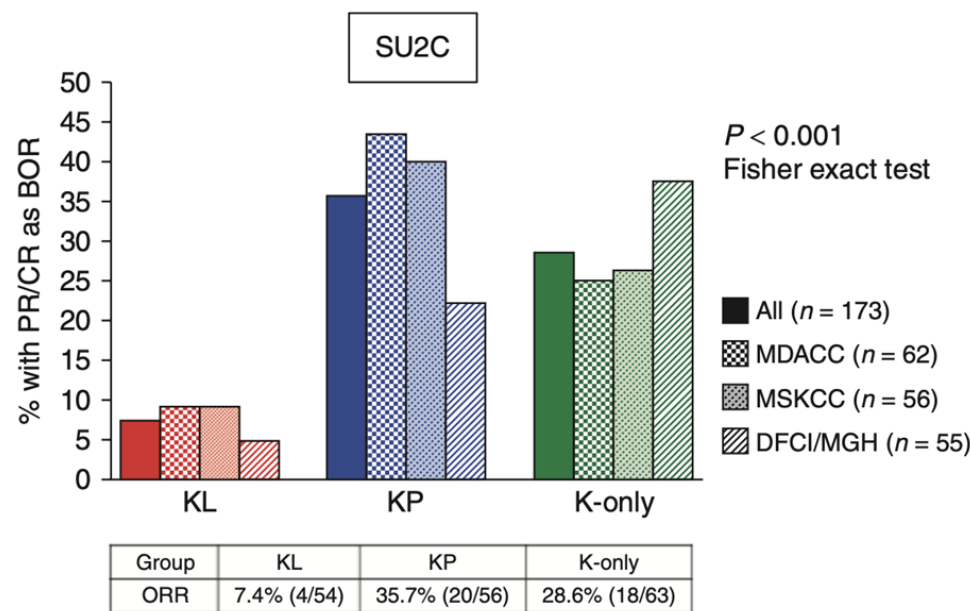
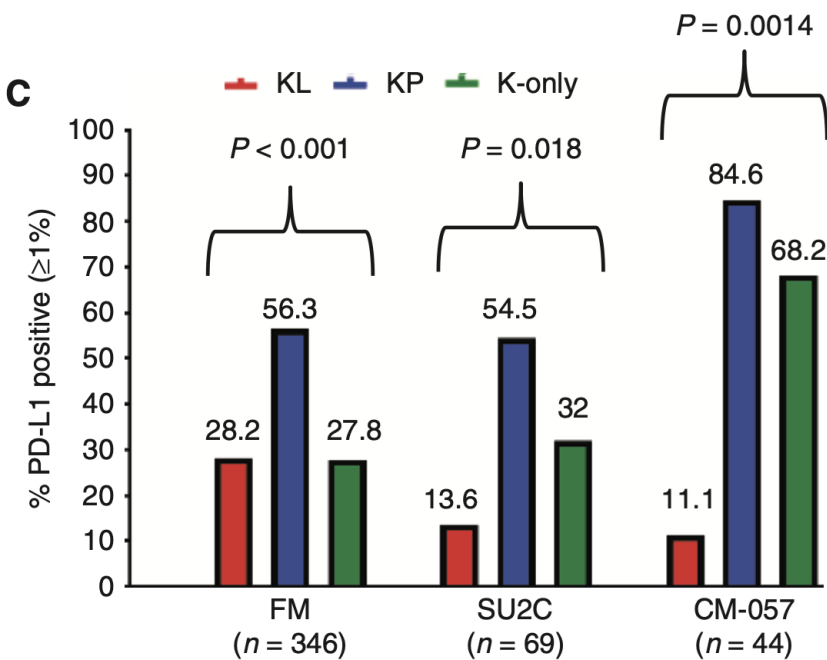


LKB1 (clone Ley37D/G6) IHC 400x

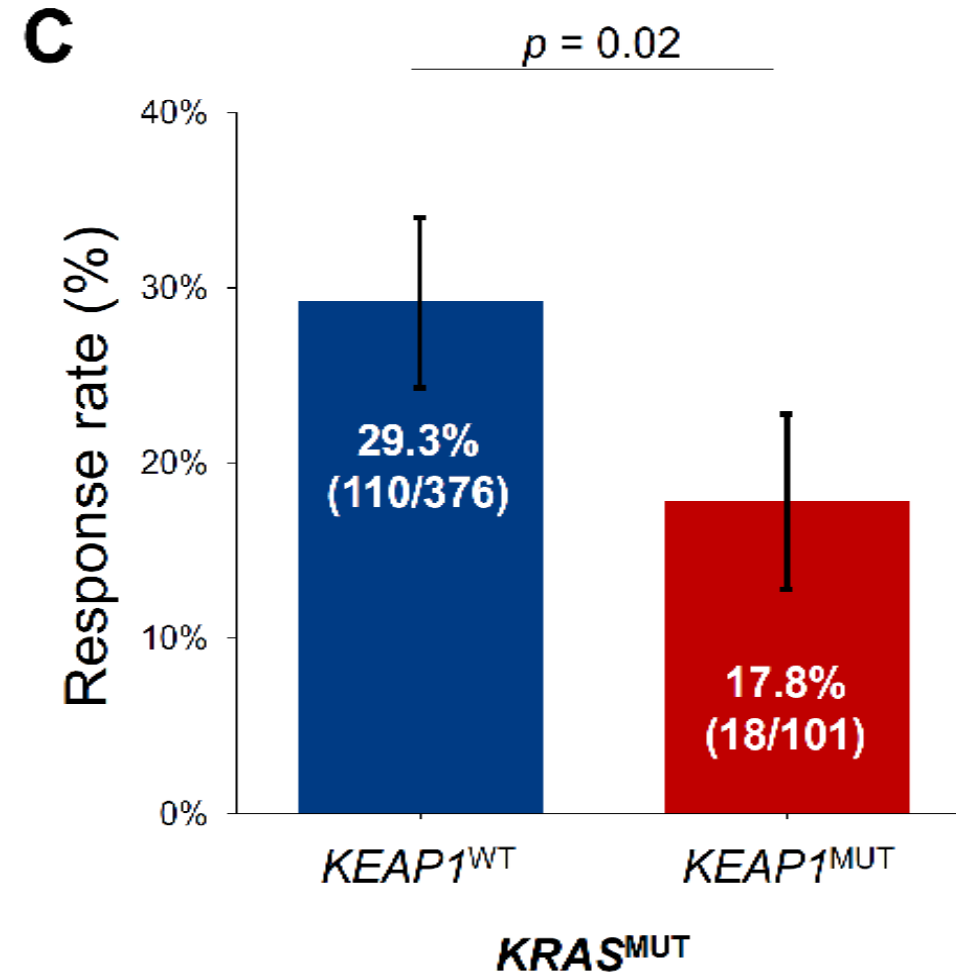
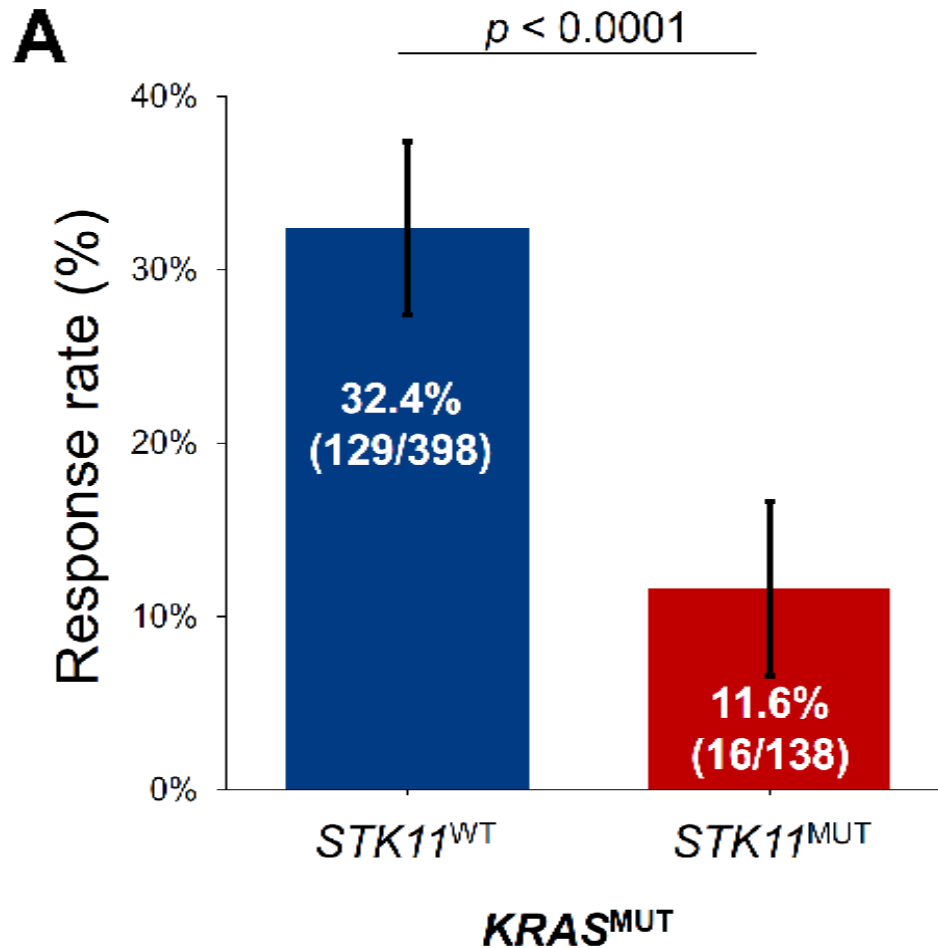
KEAP1/Nrf2 diagnostic test in the clinic is challenging

Method	Pros	Cons
NGS	Comprehensive, information on the type of mutation	Cost, no activity assessment, false positive or negative results (e.g., promoter hypermethylation)
IHC	Rapid, cost efficient, mutation agnostic	KEAP1 protein is often still expressed even when mutated, making IHC a poor surrogate.
RNA-seq, RT-qPCR (NQO1, GCLC etc.)	Rapid, mutation agnostic	Not clinically available and not validated

STK11 drives primary resistance to PD-(L)1 blockade

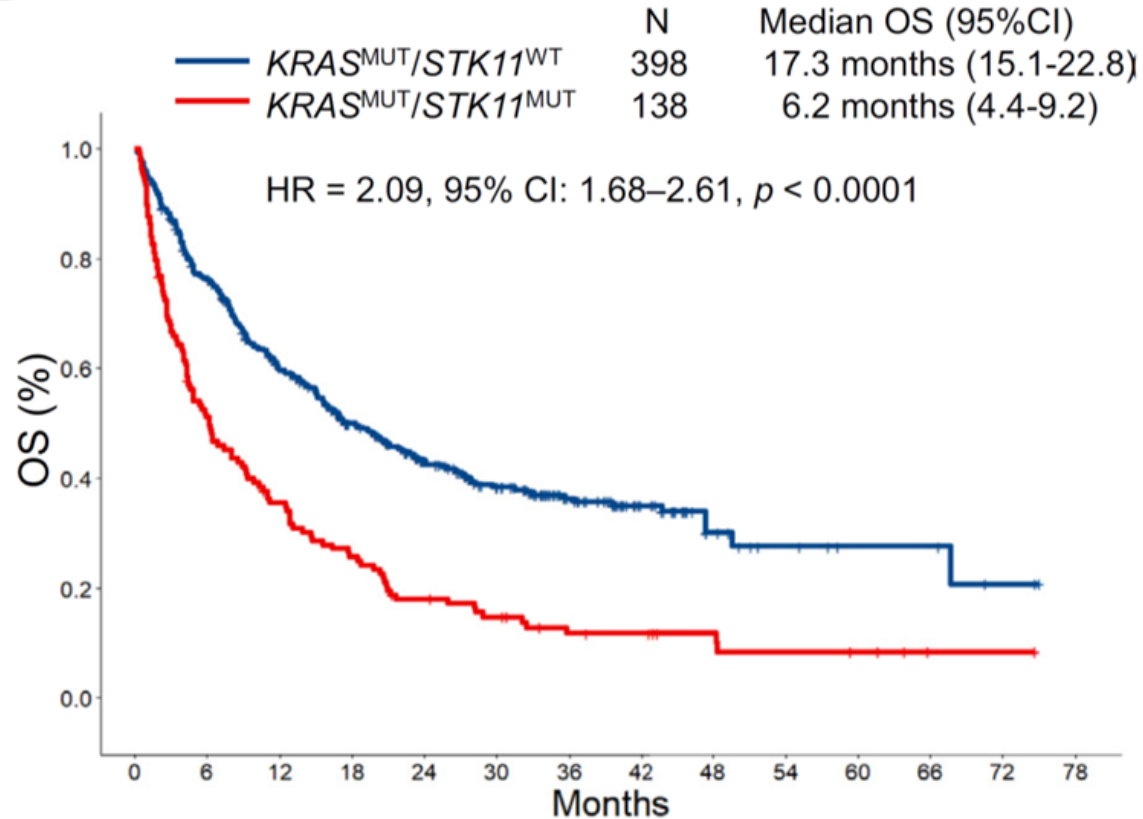


Impact of *KEAP1*/*STK11* mutations on PD-(L)1 monotherapy efficacy in NSCLC

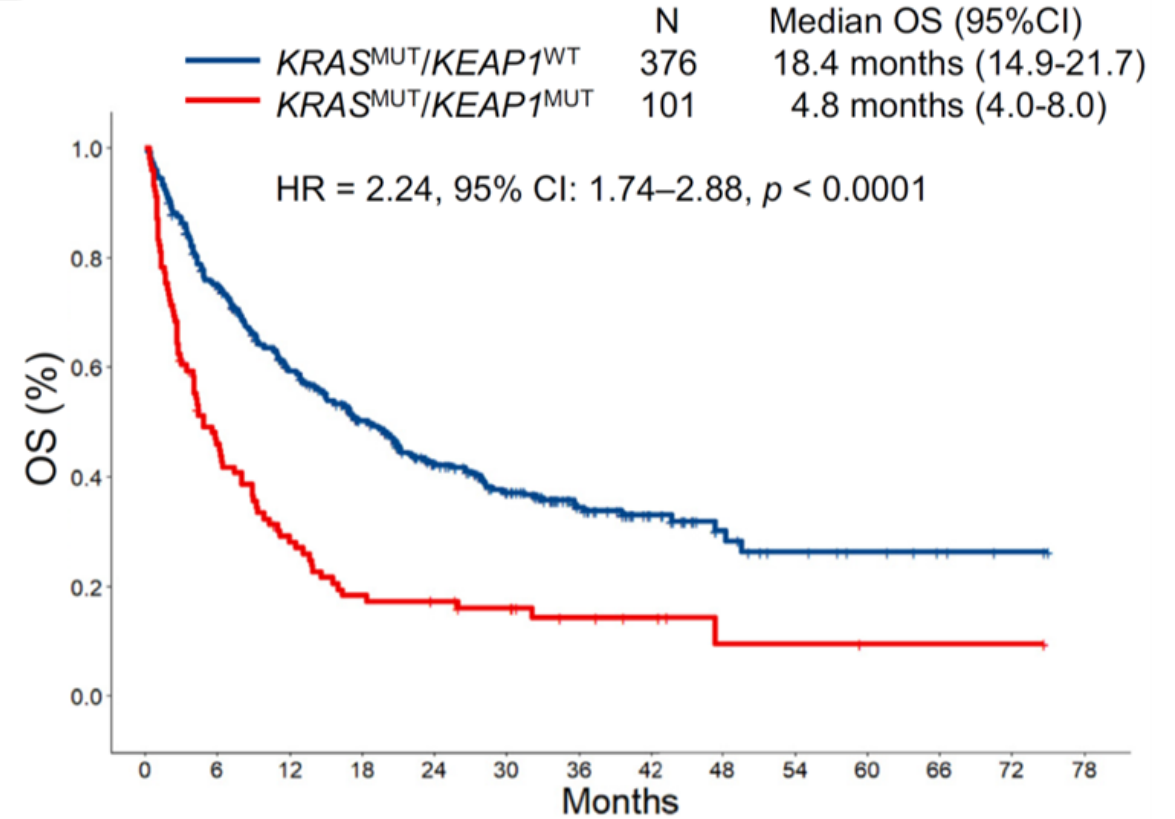


Impact of *KEAP1*/*STK11* mutations on PD-(L)1 monotherapy efficacy in NSCLC

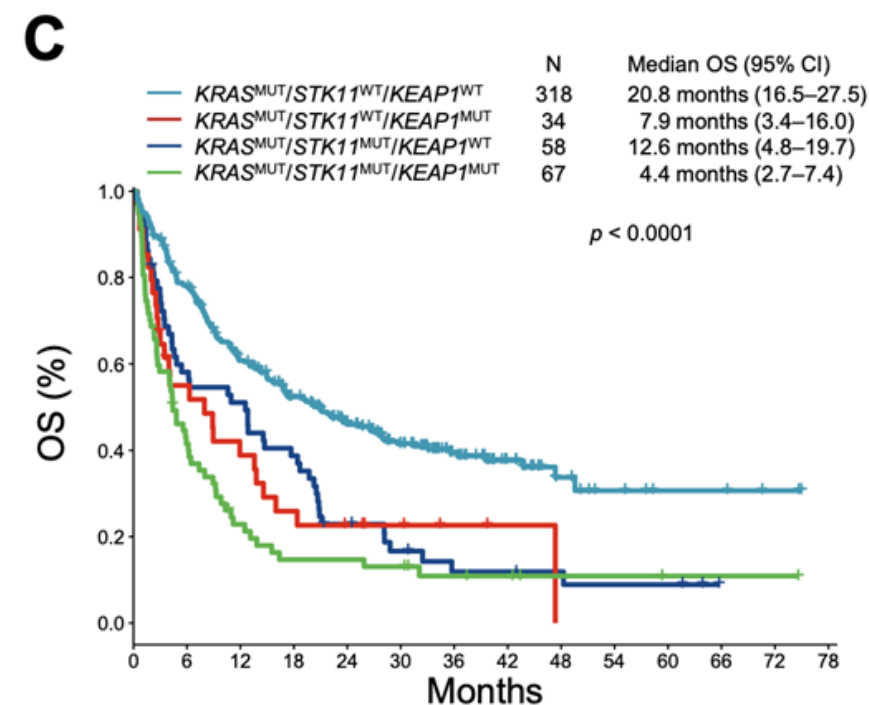
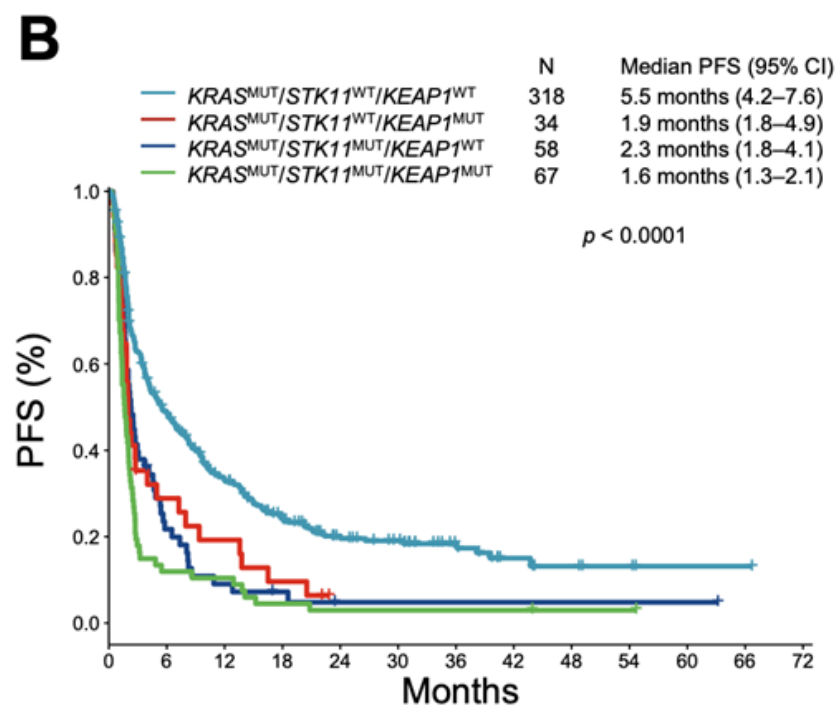
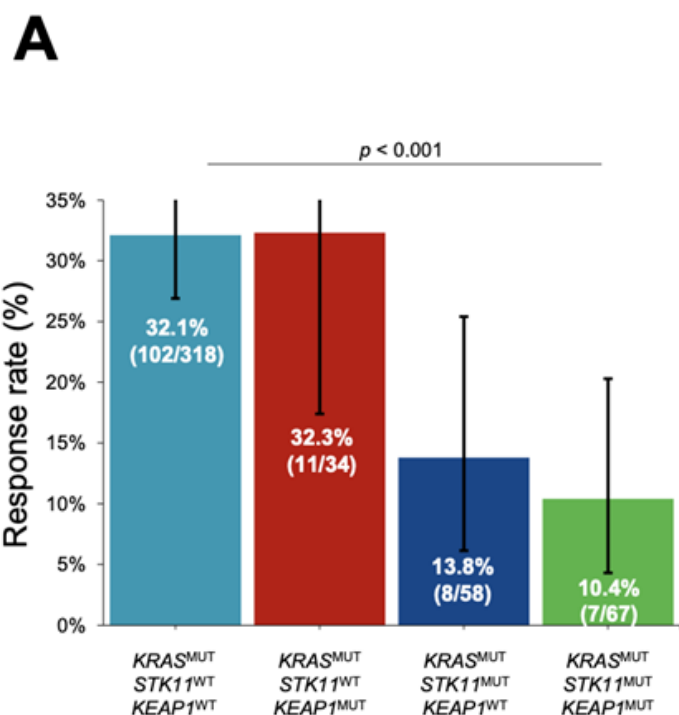
B



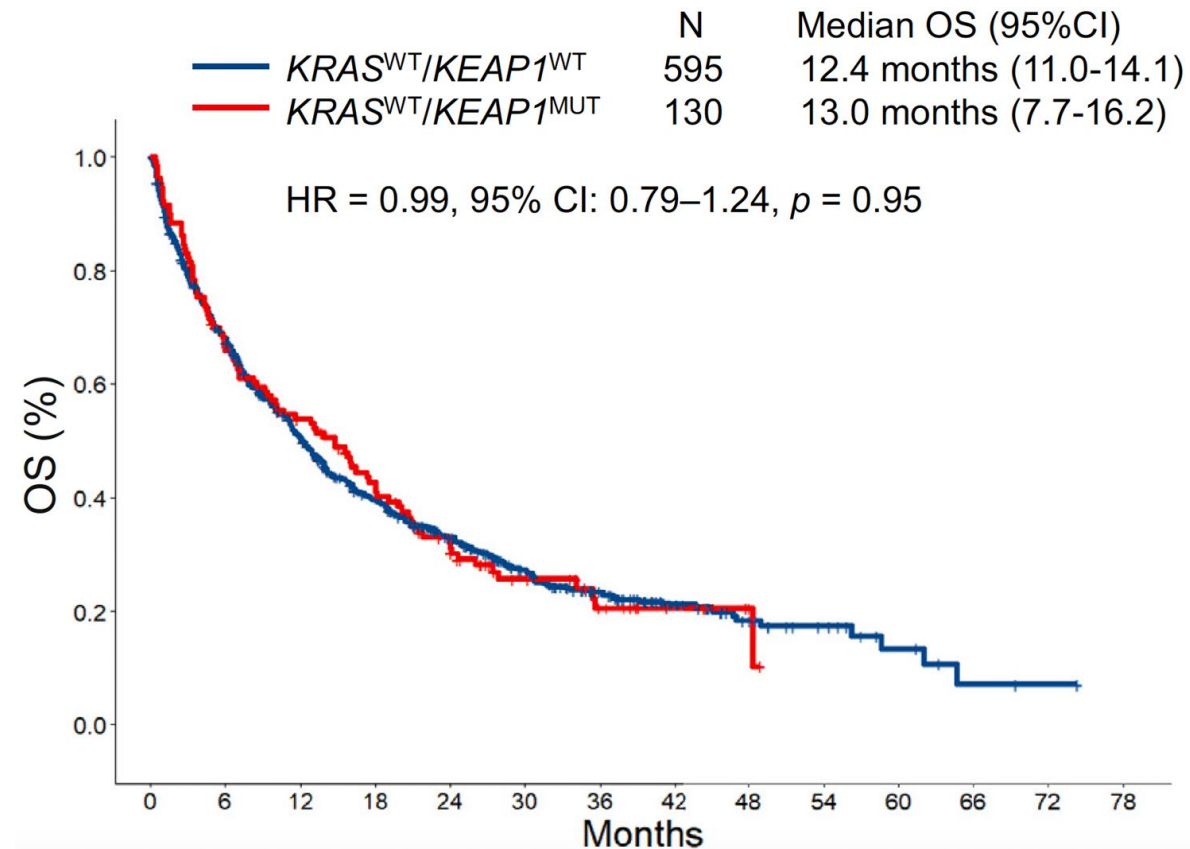
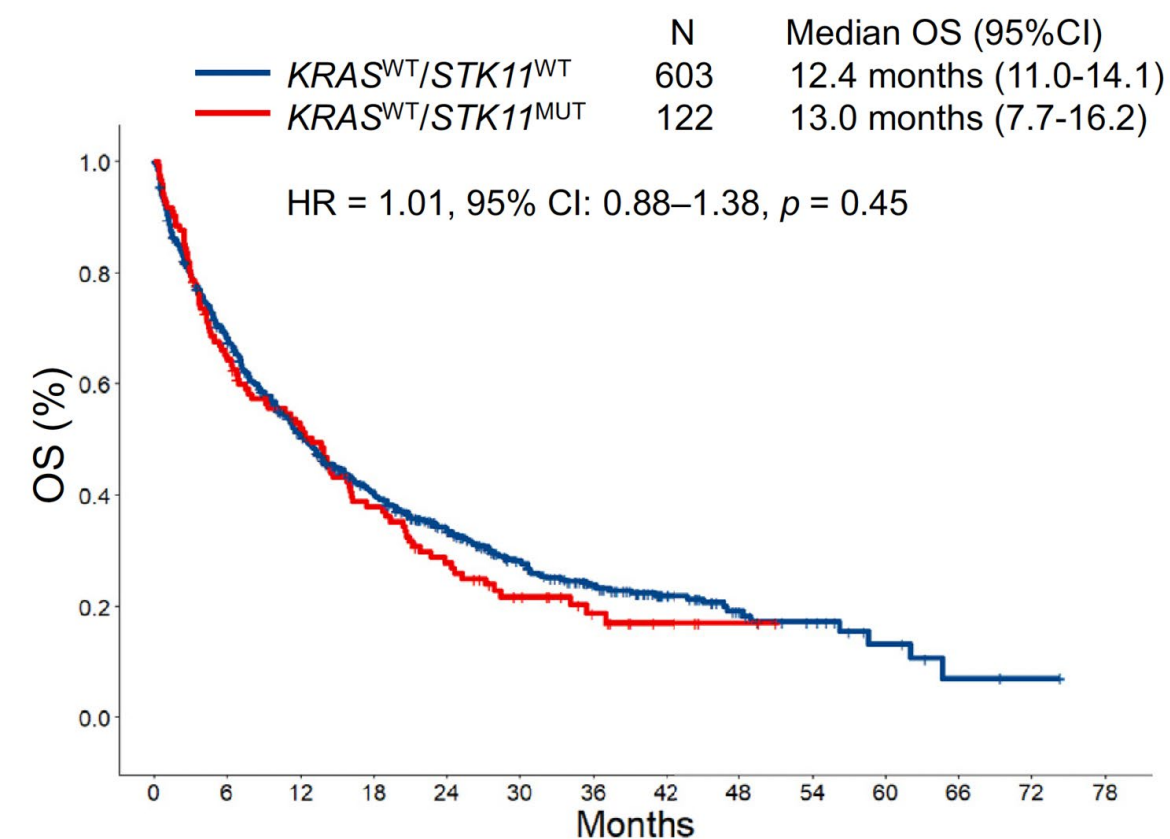
B



Triple-mutant tumors are very resistant to PD-(L)1 monotherapy

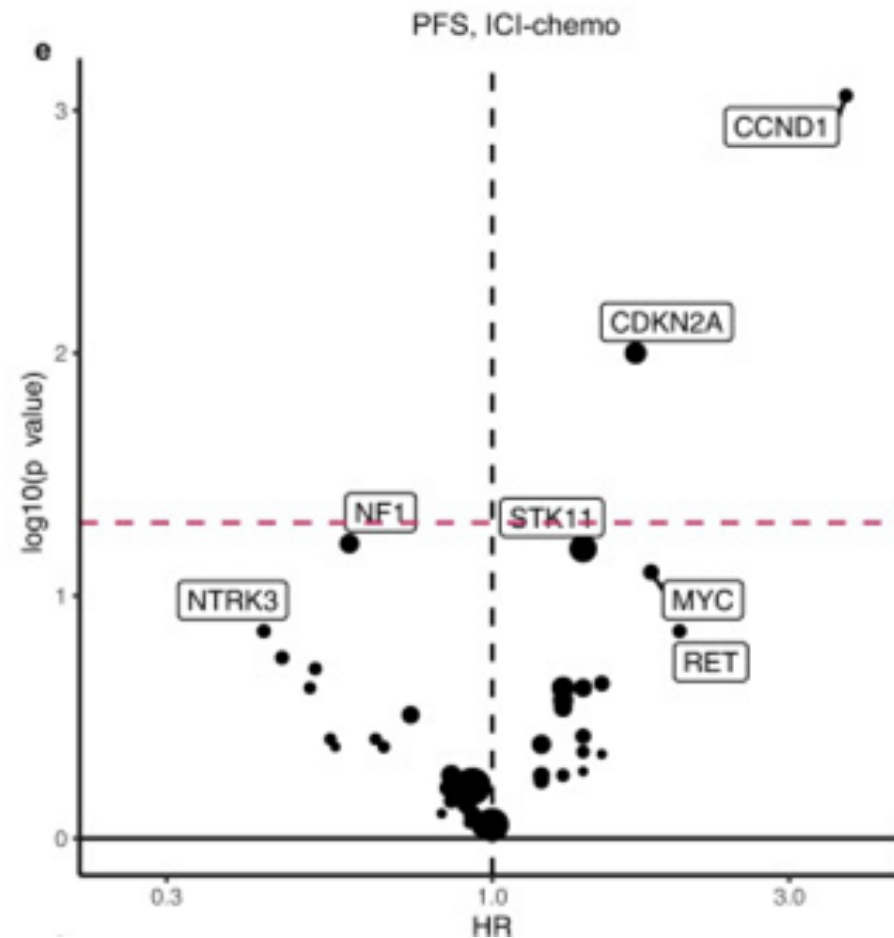
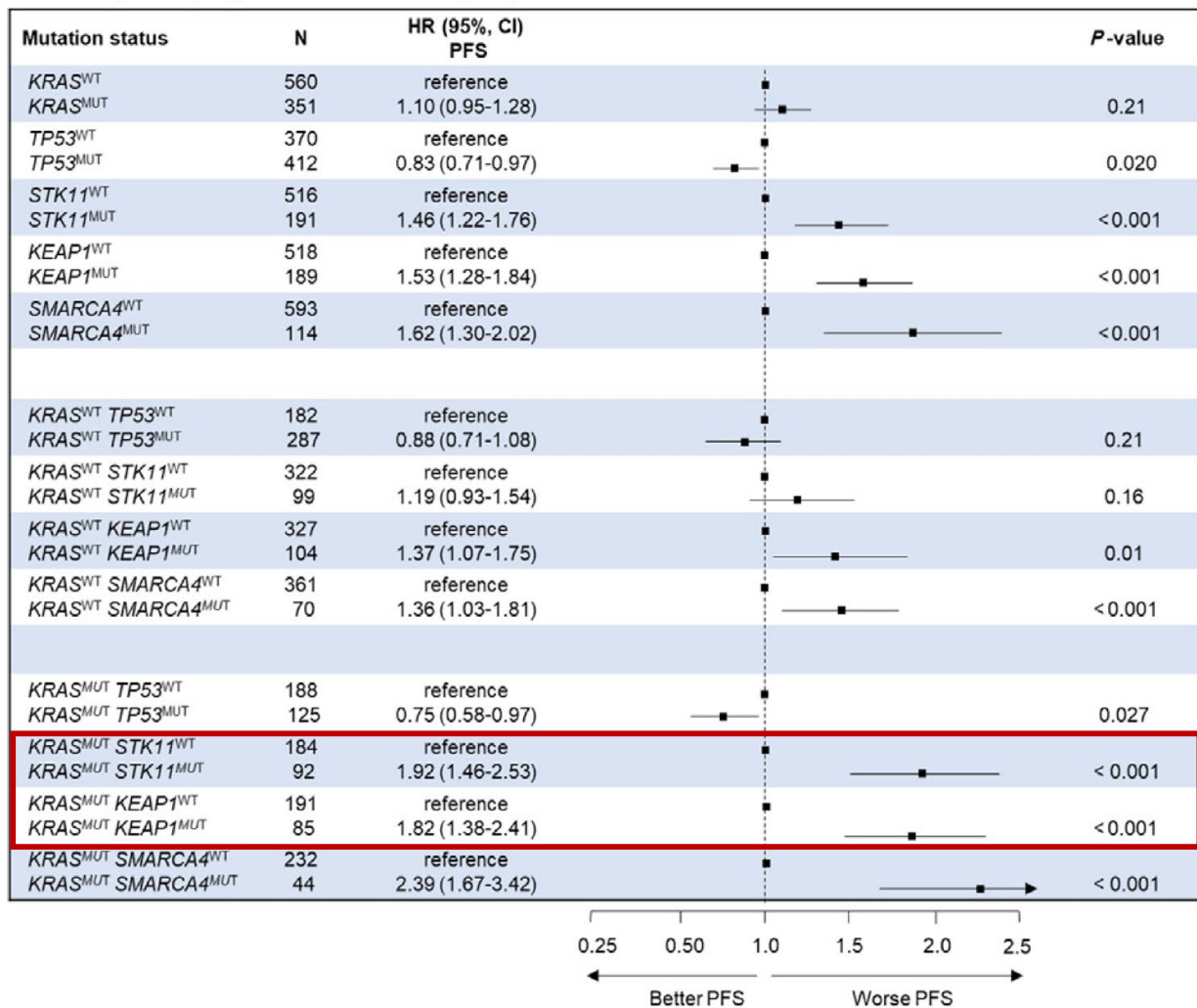


STK11/KEAP1 mutations are not associated with ICI efficacy in KRAS WT NSCLC



Impact of *KEAP1*/*STK11* mutations on chemo-immunotherapy efficacy in NSCLC

Forest-plot for progression-free survival (PFS)



CTLA4 blockade for STK11 and KEAP1 mutant NSCLC

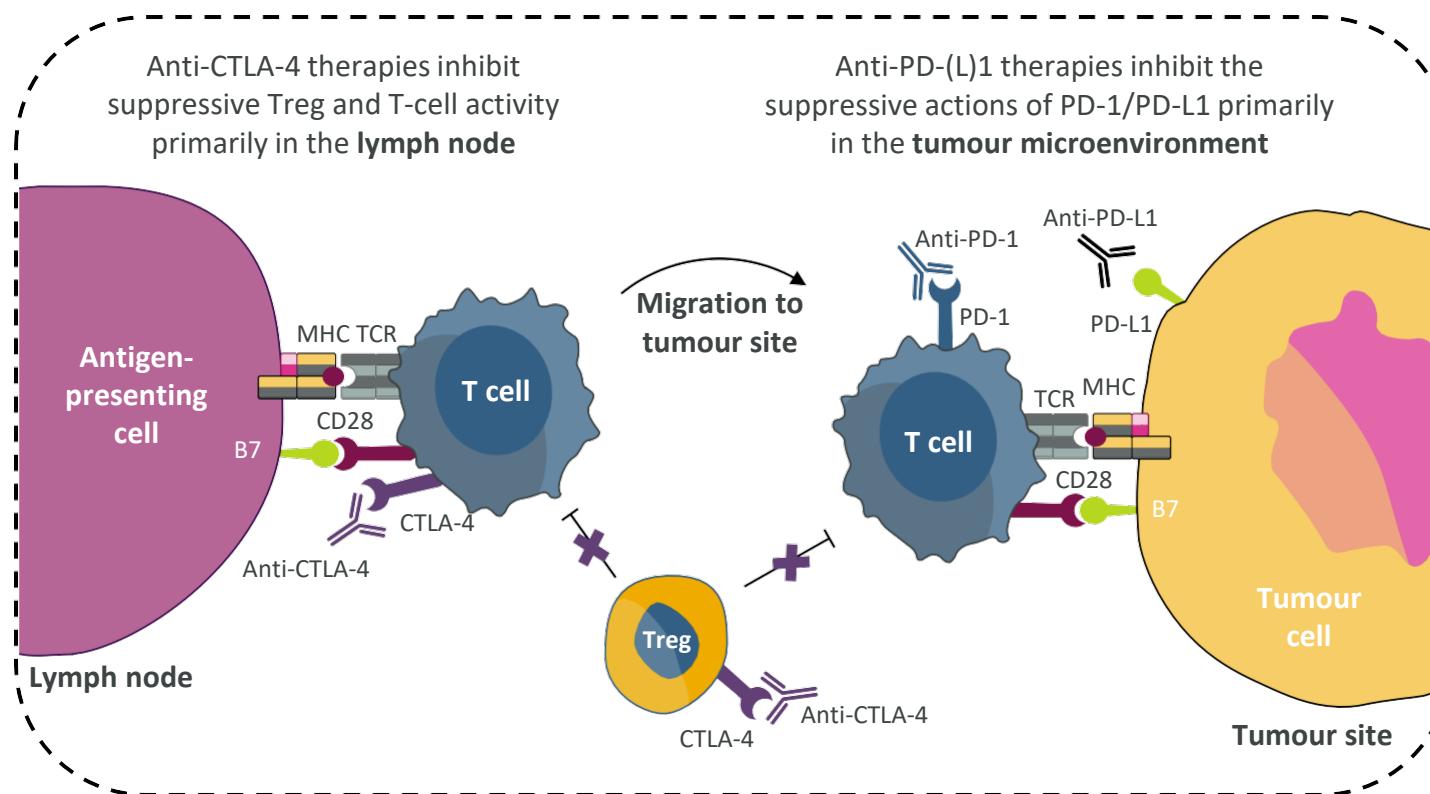


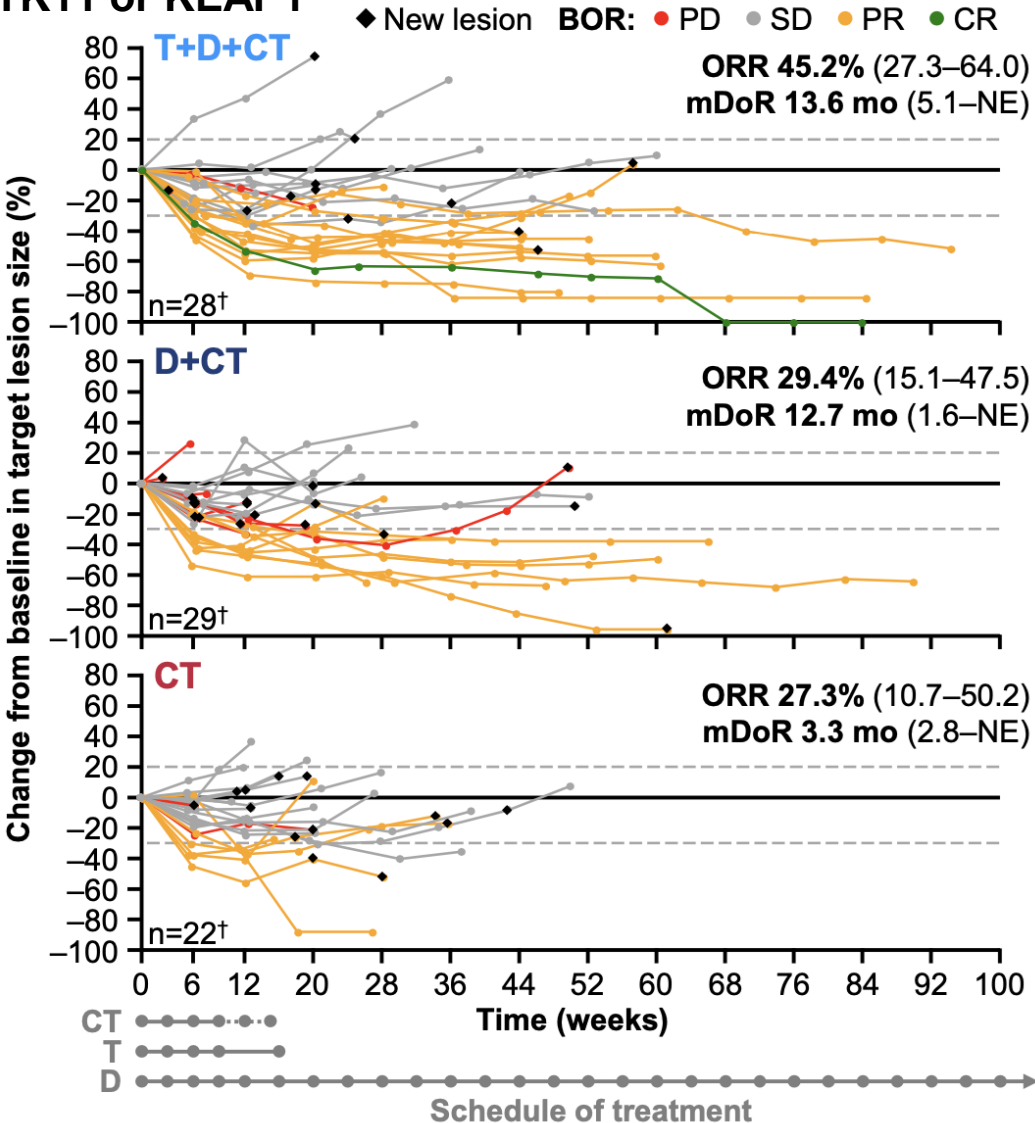
Image adapted from Buchbinder EI & Desai A. *Am J Clin Oncol* 2016;39:98–106¹

CD28, cluster of differentiation 28; CTLA-4, cytotoxic T-lymphocyte-associated antigen-4; MHC, major histocompatibility complex; PD-1, programmed cell death 1; PD-(L)1, programmed cell death-(ligand) 1; TCR, T-cell receptor; Treg, regulatory T cells

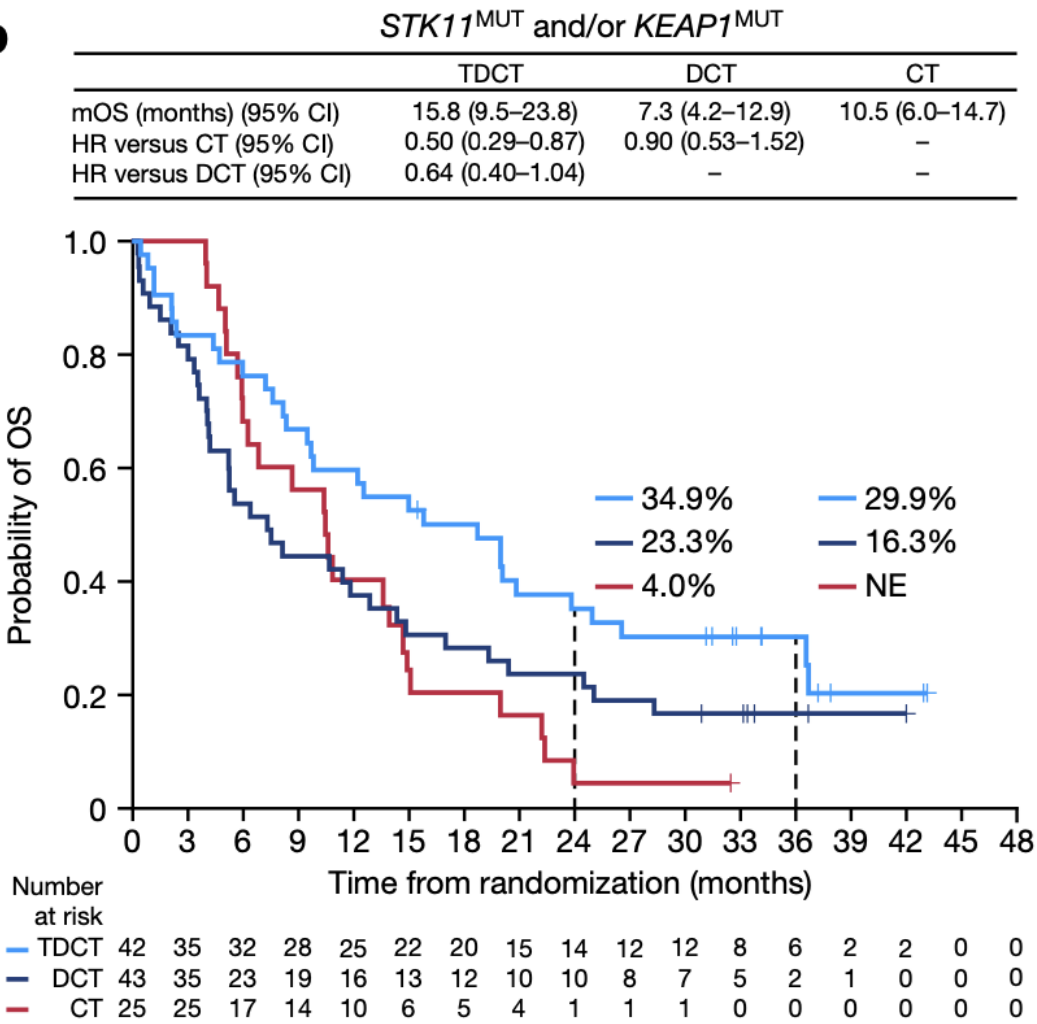
1. Buchbinder EI & Desai A. *Am J Clin Oncol* 2016;39:98–106; 2. Khan SK *et al. Clin Immunol* 2011;138:85–96; 3. Stewart R *et al. Cancer Immunol Res* 2015;3:1052–62

CTLA4 blockade may reduce KEAP1/STK11-related resistance to PD-(L)1 inhibitors

STK11 or KEAP1



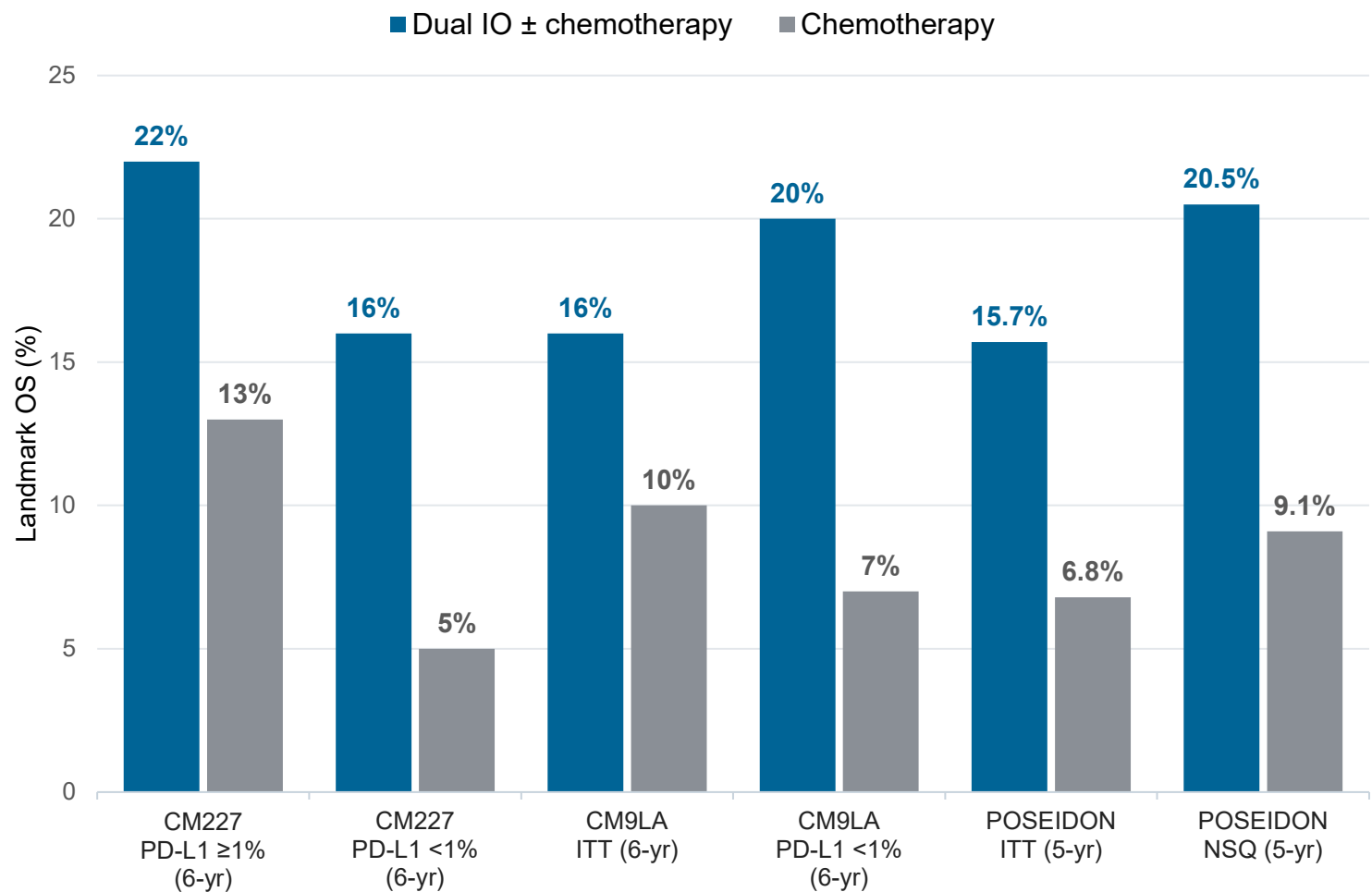
b



Dual IO in first-line mNSCLC: three phase 3 trials

	CheckMate 227 (Part 1)	CheckMate 9LA	POSEIDON
Experimental arm	Nivolumab 3 mg/kg q2w + ipilimumab 1 mg/kg q6w (chemo-free)	Nivolumab 360 mg q3w + ipilimumab 1 mg/kg q6w + 2 cycles platinum doublet	Durvalumab 1500 mg + tremelimumab 75 mg q3w + 4 cycles platinum doublet; 5th tremelimumab dose at wk 16
Control	Platinum doublet	Platinum doublet (4 cycles)	Platinum doublet (up to 6 cycles)
Population	Stage IV, <i>EGFR/ALK</i> WT; PD-L1 $\geq 1\%$ (primary) and $< 1\%$ cohorts	Stage IV, <i>EGFR/ALK</i> WT; any PD-L1, any histology	Stage IV, <i>EGFR/ALK</i> WT; any PD-L1, any histology
OS HR (ITT)	0.78 (PD-L1 $\geq 1\%$) 0.65 (PD-L1 $< 1\%$)	0.74	0.76
Long-term OS	6-yr: 22% vs 13% ($\geq 1\%$) 16% vs 5% ($< 1\%$)	6-yr: 16% vs 10%	5-yr: 15.7% vs 6.8%
Grade 3–4 TRAEs	33% vs 36%	47% vs 38%	52% vs 44%

Dual IO delivers a durable long-term survival tail



PD-L1 <1%

Largest relative benefit: CM9LA HR 0.64; CM227 HR 0.65 — the population where PD-(L)1 alone underperforms

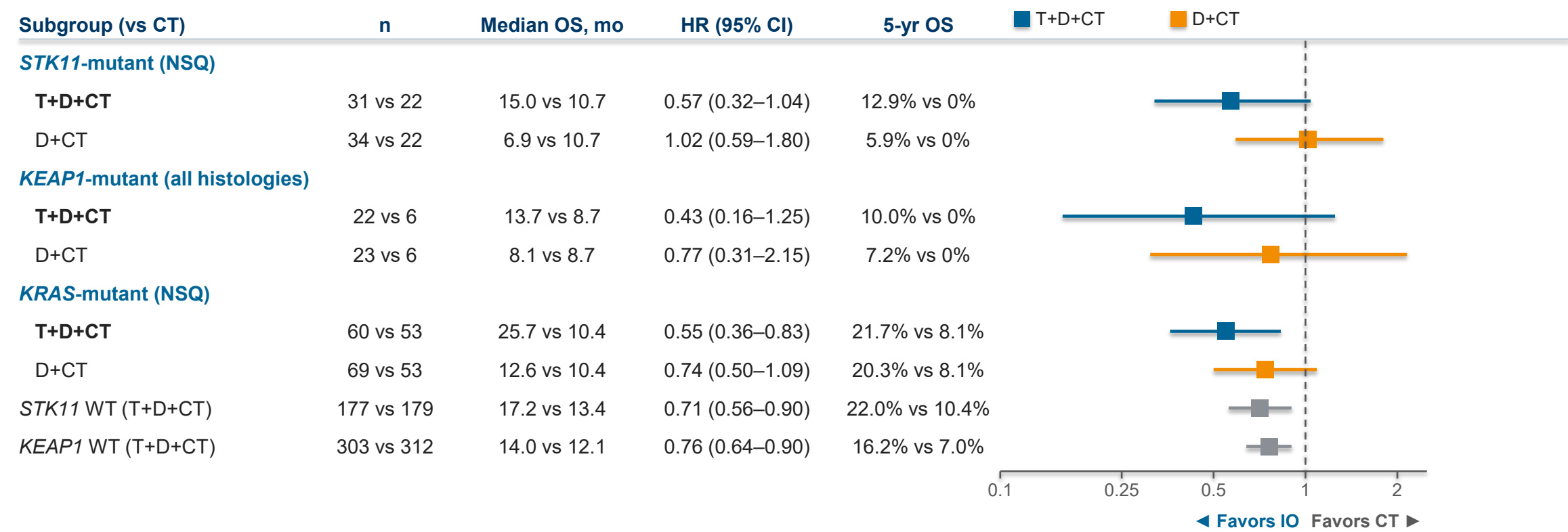
Squamous

CM9LA HR 0.65 (6-yr OS 14% vs 5%); POSEIDON HR 0.85 (5-yr 7.3% vs 2.9%)

Nonsquamous

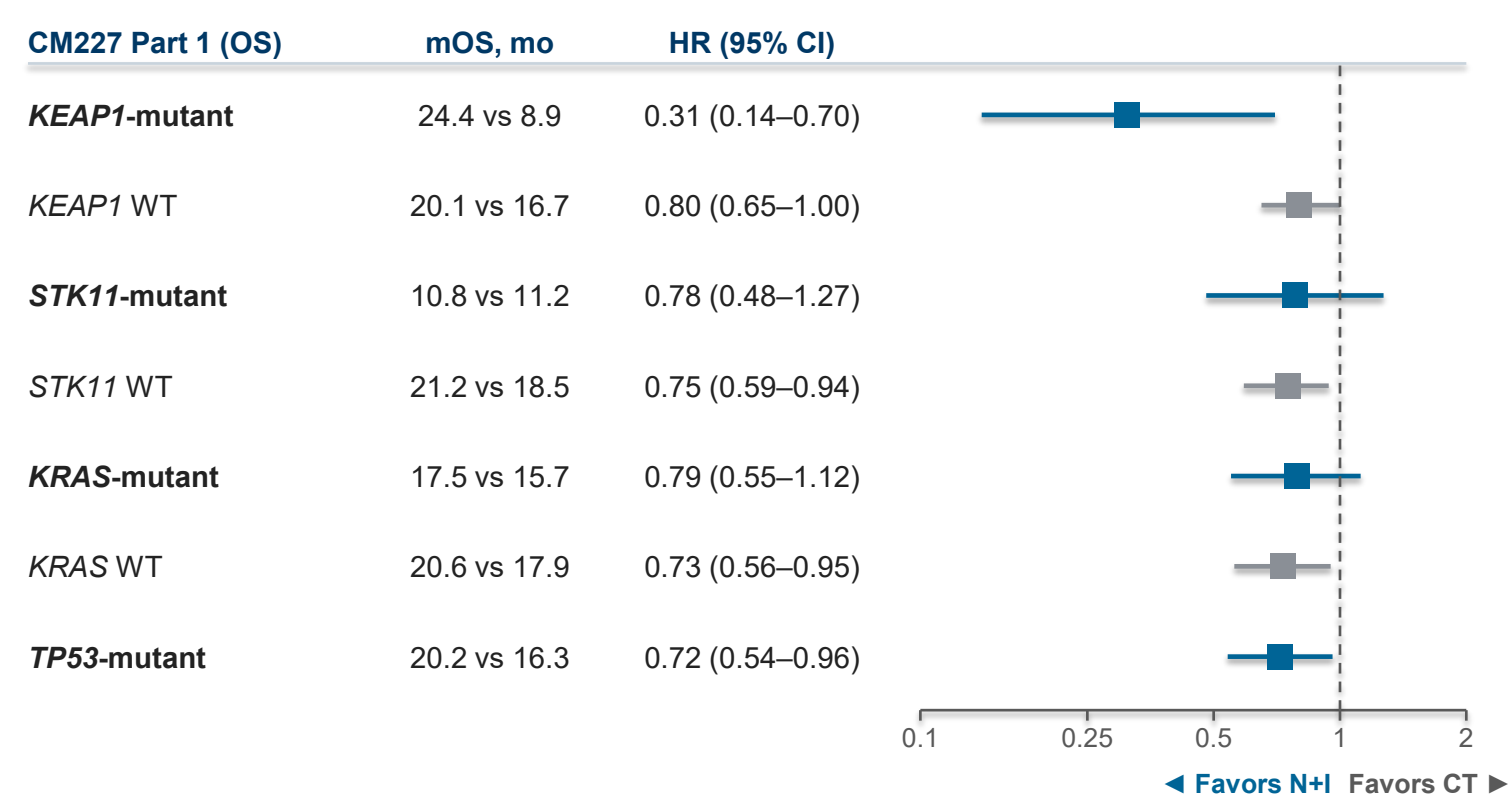
POSEIDON 5-yr OS 20.5% vs 9.1% (HR 0.81); CM9LA HR 0.79

POSEIDON: adding tremelimumab drives OS benefit in *STK11*, *KEAP1* and *KRAS*-mutant disease



ORR in *STK11*/*KEAP1*-mutant NSQ: 42.9% T+D+CT vs 30.2% D+CT vs 28.0% CT. Durvalumab + chemo alone did not overcome the resistance; the gain came with CTLA-4. Exploratory, small subgroups.

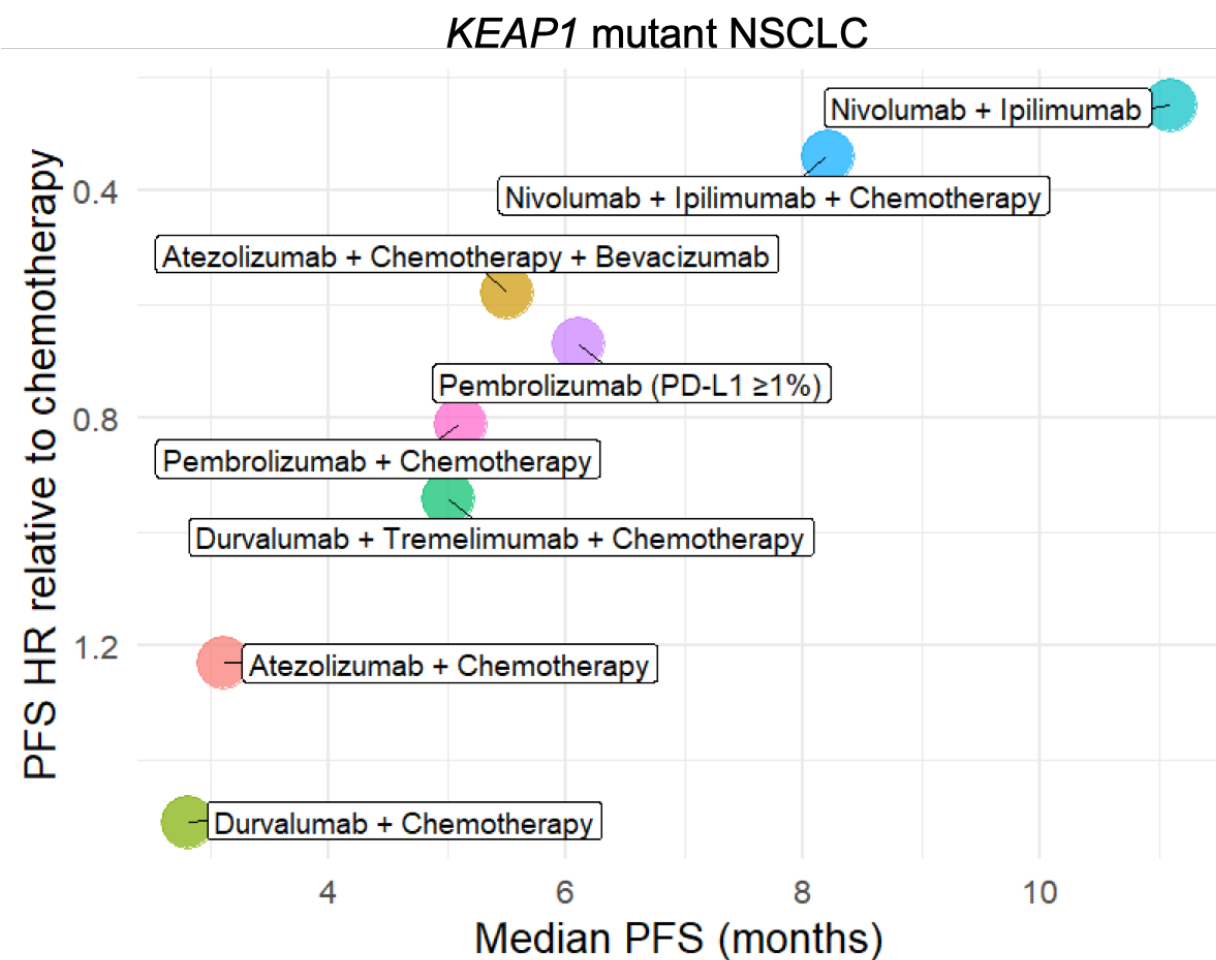
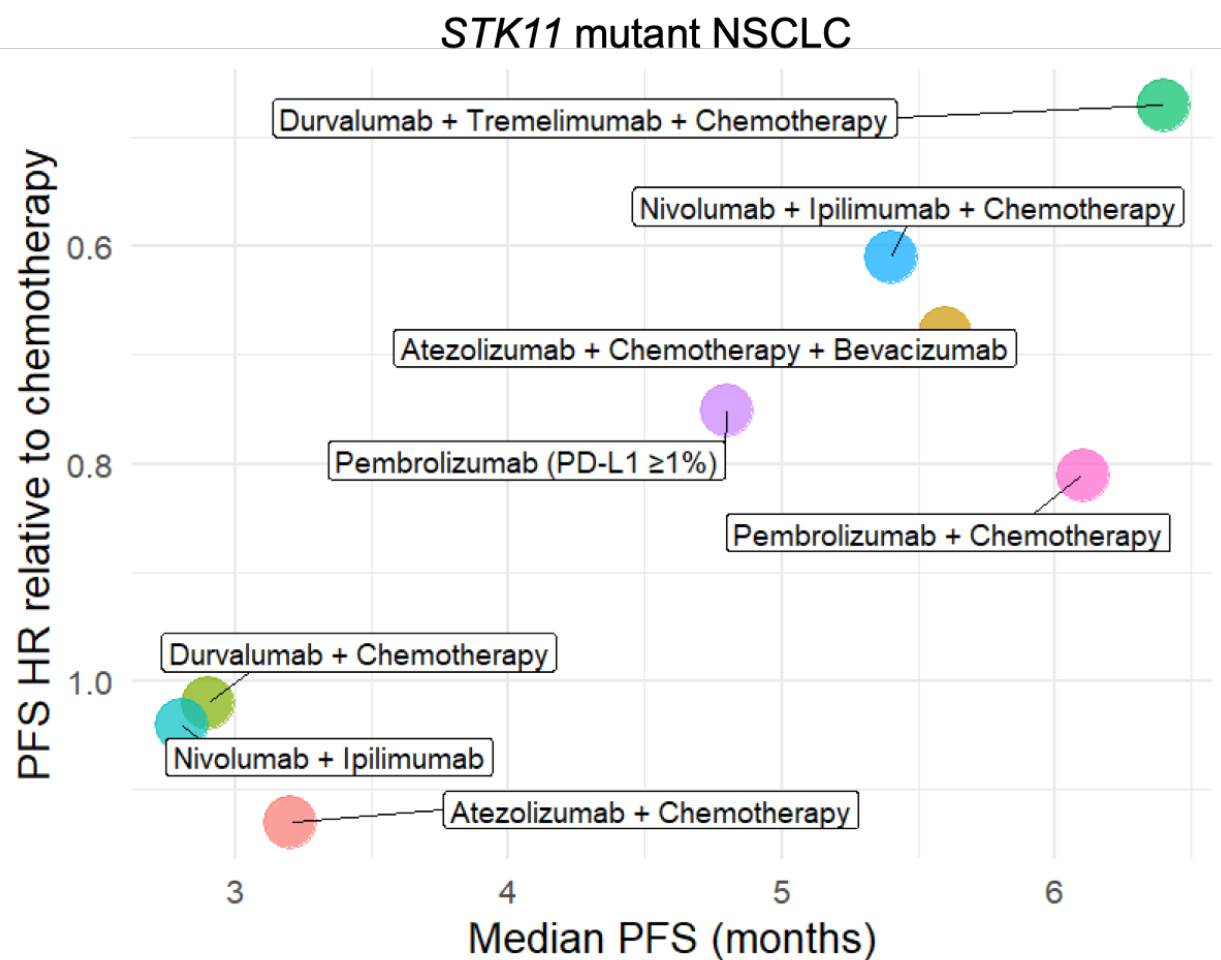
CheckMate 227 and 9LA: nivolumab + ipilimumab by co-mutation status



CheckMate 9LA

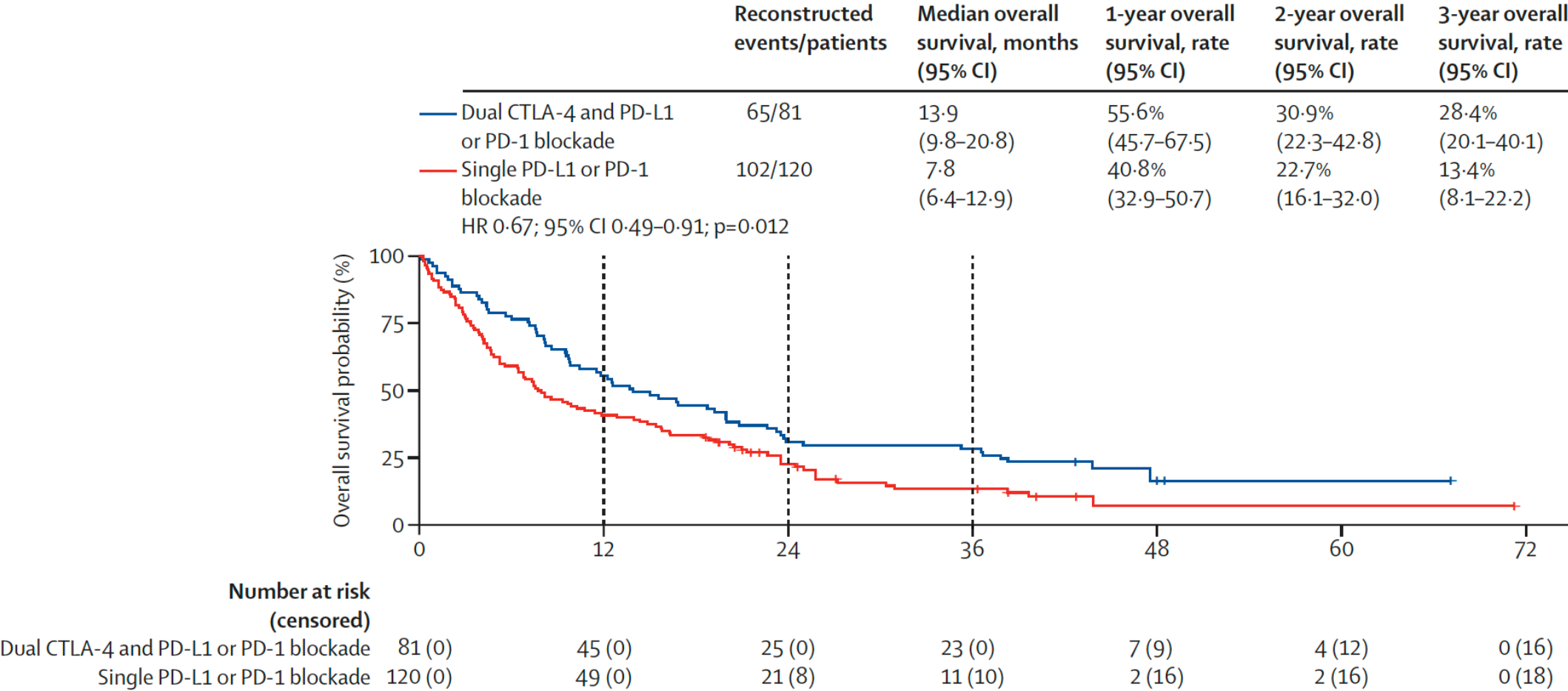
- OS benefit of N+I+CT vs CT consistent irrespective of *KRAS*, *TP53* or *STK11* status
- *KEAP1*-mutant subgroup small (~10% of evaluable NSQ), limiting interpretation
- Among 6-year survivors with evaluable tissue: 37% *STK11*-mutant, 32% *KRAS*-mutant
- Mutation analyses are exploratory; no head-to-head vs PD-1 + chemotherapy

Optimal treatment strategy for co-mutations?



Pooled analysis of 6 randomized clinical trials reporting outcomes in STK11 mutant NSCLC

A STK11 mutated

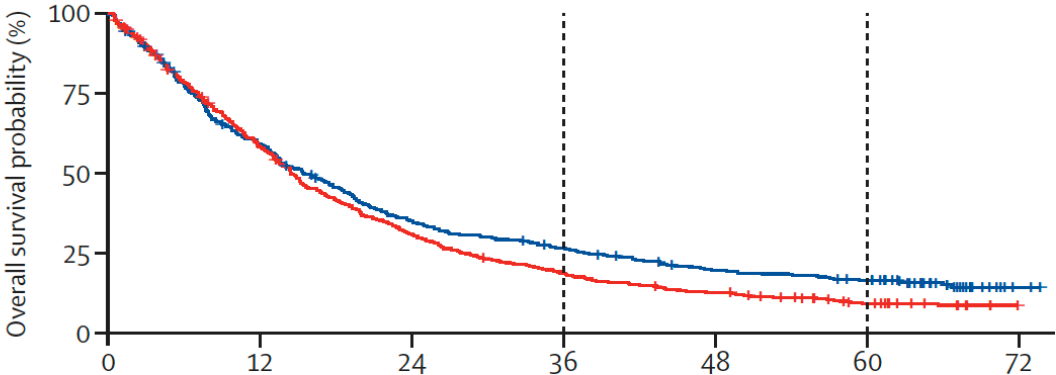


Pooled analysis of 6 randomized clinical trials reporting outcomes in PD-L1 negative vs positive NSCLC

A PD-L1 TPS <1%

	Reconstructed events/patients	Median overall survival, months (95% CI)	3-year overall survival, rate (95% CI)	5-year overall survival, rate (95% CI)
Dual CTLA-4 and PD-L1 or PD-1 blockade	367/447	15.5 (13.6–18.5)	26.8% (22.9–31.3)	16.6% (13.4–20.6)
Single PD-L1 or PD-1 blockade	452/512	14.5 (13.4–15.9)	18.7% (15.5–22.4)	9.3% (7.0–12.3)

HR 0.85; 95% CI 0.74–0.98; p=0.021

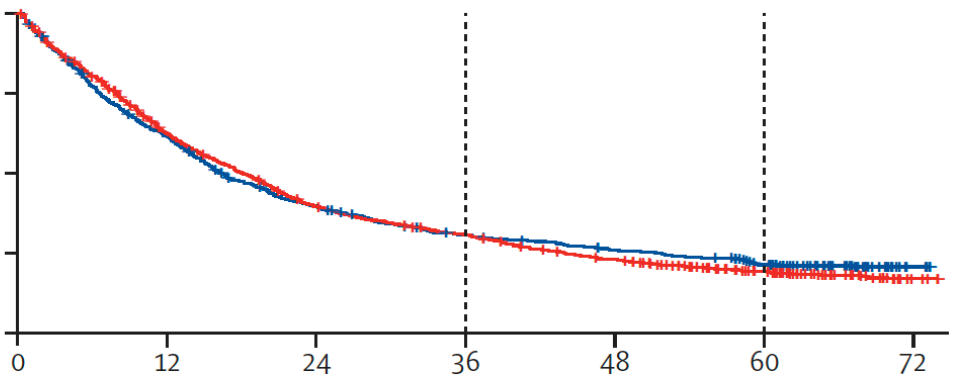


Number at risk (censored)							
Dual CTLA-4 and PD-L1 or PD-1 blockade	447	260	152	114	81	61	3
	(0)	(7)	(10)	(12)	(16)	(23)	(77)
Single PD-L1 or PD-1 blockade	512	292	155	92	62	36	1
	(0)	(11)	(12)	(13)	(14)	(25)	(59)

B PD-L1 TPS ≥1%

	Reconstructed events/patients	Median overall survival, months (95% CI)	3-year overall survival, rate (95% CI)	5-year overall survival, rate (95% CI)
Dual CTLA-4 and PD-L1 or PD-1 blockade	629/813	16.5 (15.0–18.9)	30.8% (27.8–34.2)	21.5% (18.8–24.6)
Single PD-L1 or PD-1 blockade	844/1056	18.1 (16.6–19.8)	30.9% (28.2–33.8)	19.3% (17.0–21.9)

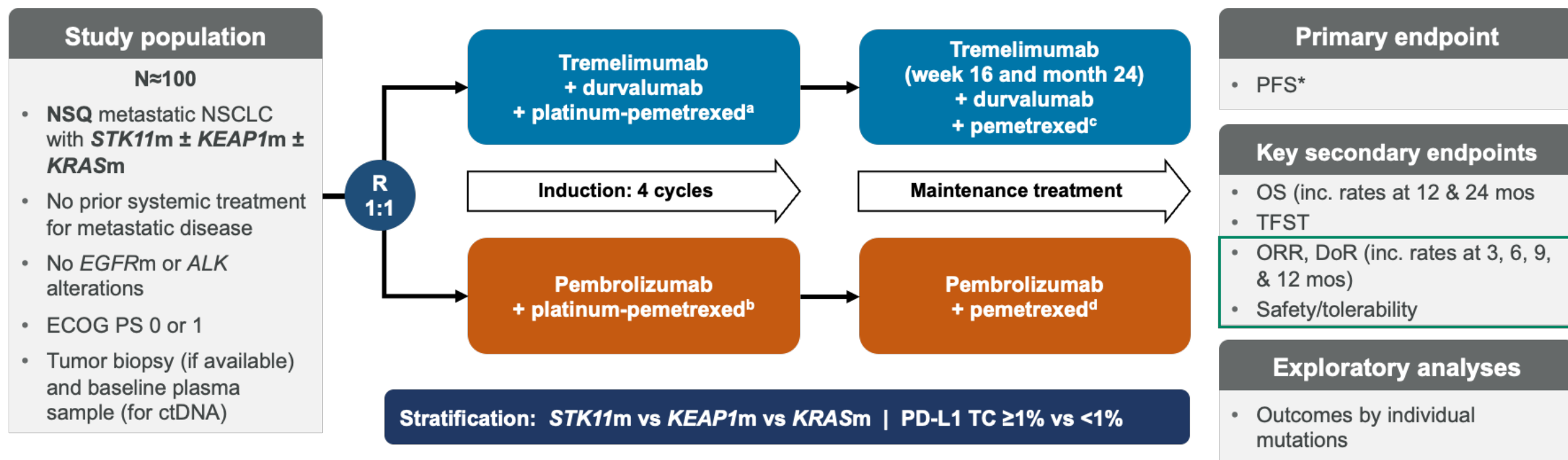
HR 0.97; 95% CI 0.88–1.08; p=0.60



Number at risk (censored)							
Dual CTLA-4 and PD-L1 or PD-1 blockade	813 (0)	496 (7)	317 (12)	239 (19)	199 (23)	155 (32)	6 (178)
Single PD-L1 or PD-1 blockade	1056 (0)	646 (17)	406 (21)	313 (25)	230 (31)	160 (66)	5 (207)

TRITON: Phase 2b randomized, open-label, US multicenter study

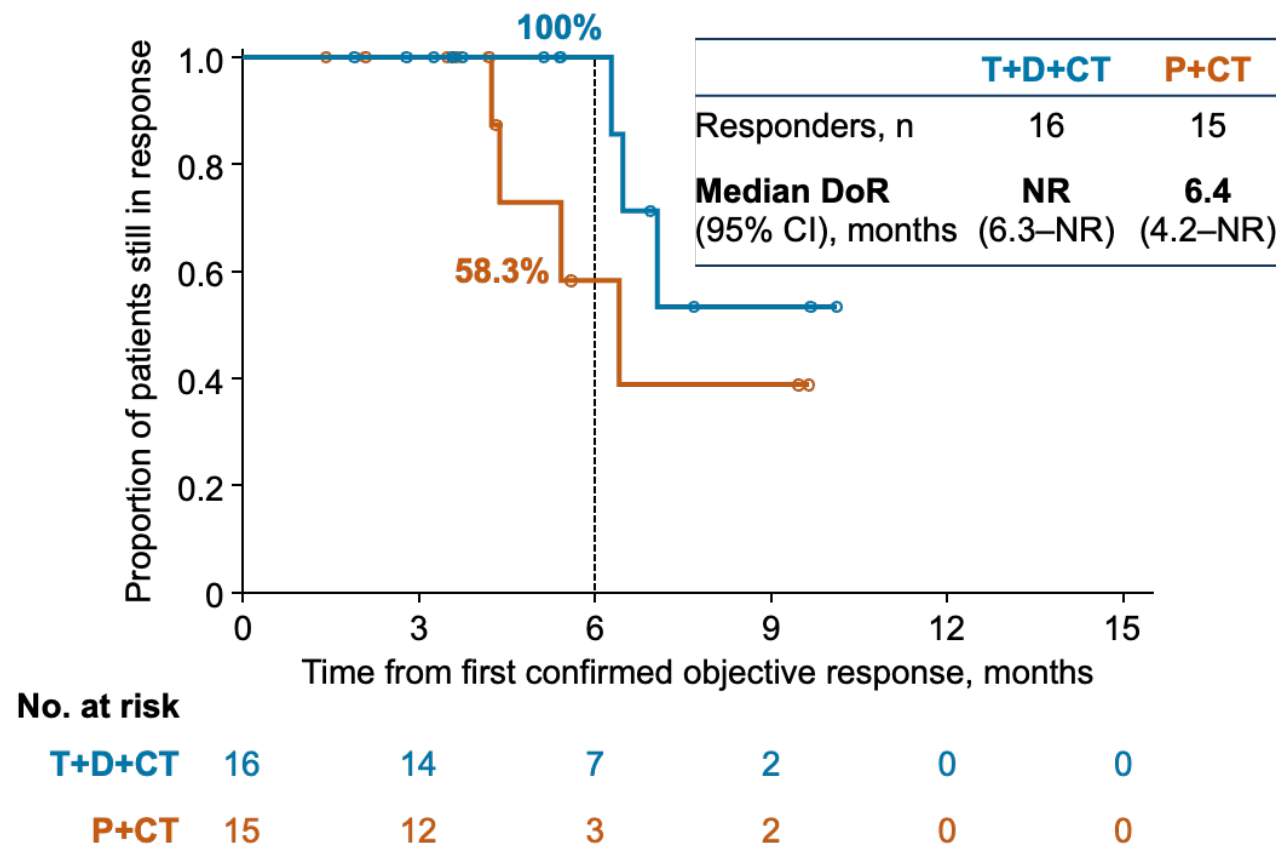
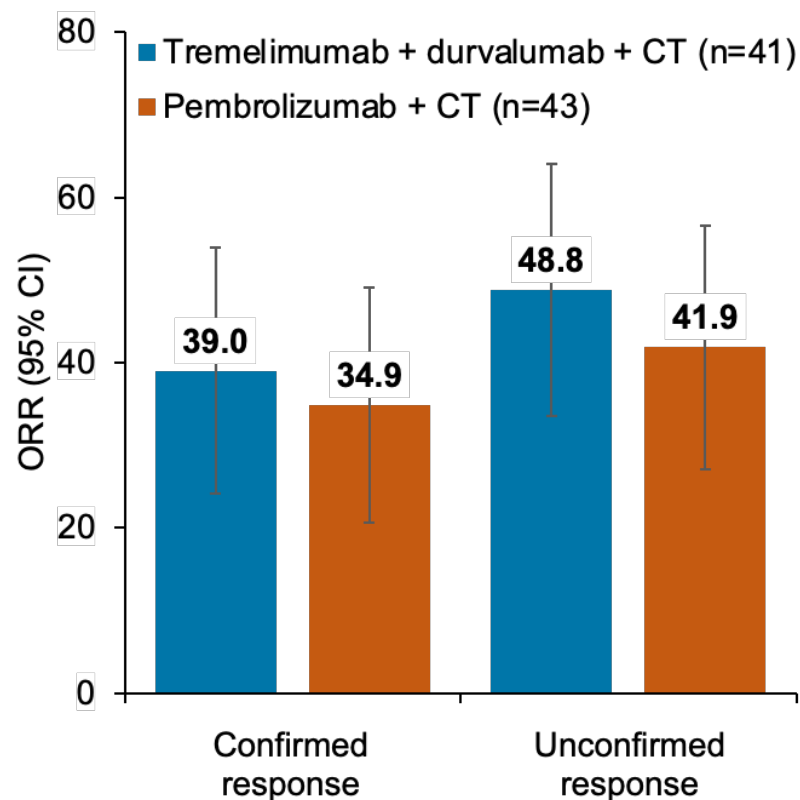
An interim analysis of ORR, DoR, and safety was planned when the first patient randomized had a minimum follow-up of 15 months; at this time, 84 patients had the opportunity for a minimum follow-up of 3 months



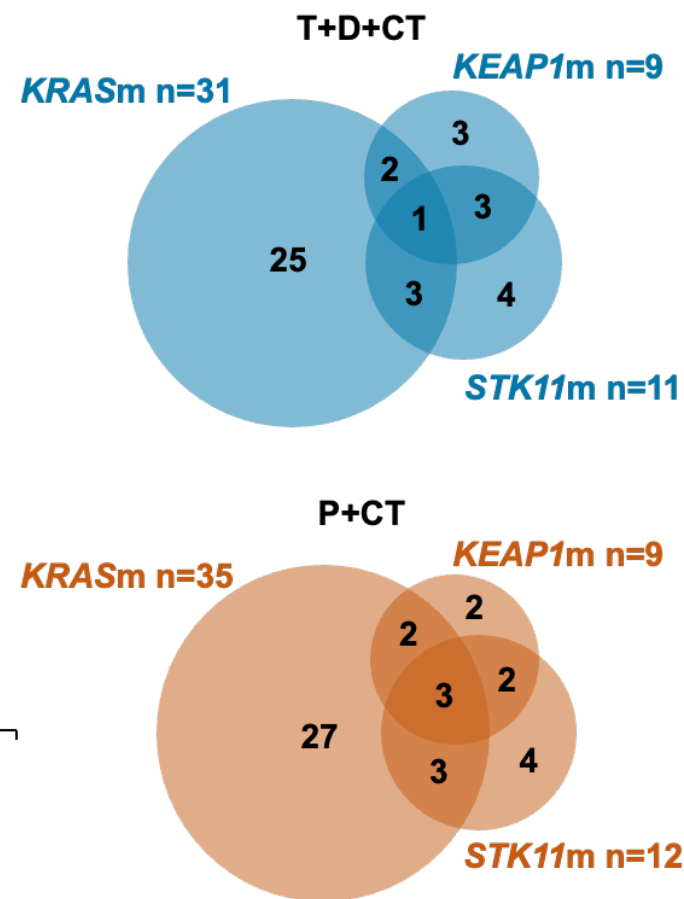
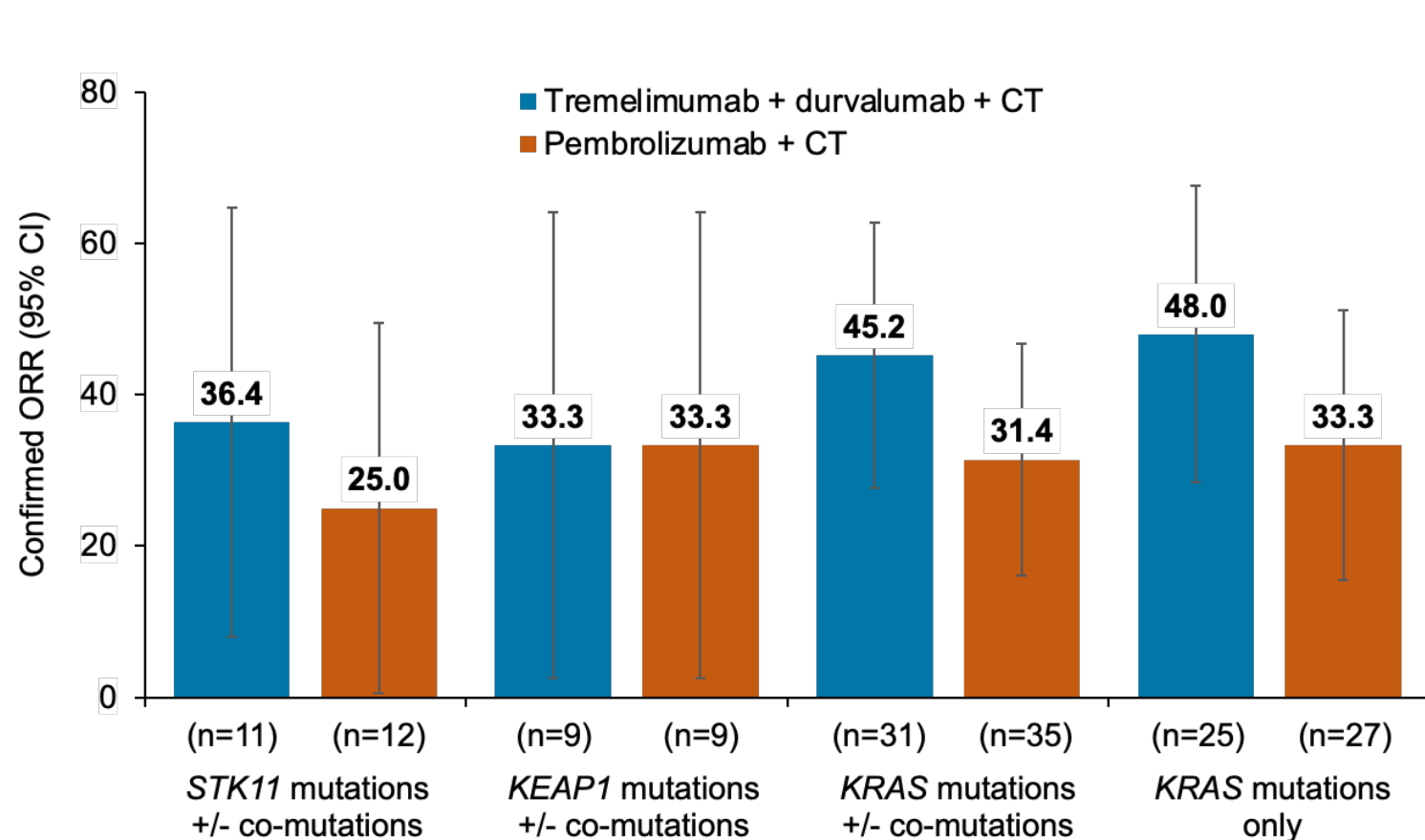
TRITON: Phase 2b randomized, open-label, US multicenter study

	T+D+CT n=41	P+CT n=43
Median age (range), years	69.0 (47–82)	69.0 (51–86)
Male, %	48.8	62.8
White / Black or African American / Asian,* %	70.7 / 14.6 / 7.3	72.1 / 20.9 / 4.7
ECOG PS 0 / 1, %	22.0 / 78.0	37.2 / 62.8
Adenocarcinoma typical / Other NSQ histology [†] , %	85.4 / 12.2	88.4 / 11.6
Current or former / Never smoker, %	90.2 / 9.8	93.0 / 7.0
<i>STK11</i> / <i>KEAP1</i> / <i>KRAS</i> mutation ^{‡§} , %	26.8 / 22.0 / 75.6	27.9 / 20.9 / 81.4
PD-L1 TC <1% / TC ≥1% [§] , %	39.0 / 61.0	39.5 / 60.5
CNS metastases, %	9.8	11.6
Liver metastases, %	17.1	11.6

TRITON IA: ORR and DoR were numerically greater with first-line T+D+CT vs P+CT in *STK11* and/or *KEAP1* and/or *KRAS*-mutated NSQ mNSCLC



ORR was numerically higher with T+D+CT vs P+CT in the *STK11*m, *KRAS*m, and *KRAS*m only subgroups



Incidence of AEs was similar between arms, with low discontinuation rates

	D+T+CT n=41	P+CT n=43
Median (range) safety follow-up for D/P, months	5.6 (0.0–14.0)	5.1 (0.0–17.5)
Any-grade all-cause AEs, n (%)	41 (100)	42 (97.7)
Grade 3/4 AEs*	31 (75.6)	27 (62.8)
Serious AEs	26 (63.4)	26 (60.5)
AEs leading to treatment discontinuation†	1 (2.4)	2 (4.7)
AEs leading to death	2 (4.9)	5 (11.6)
Any-grade treatment-related AEs‡, n (%)	36 (87.8)	38 (88.4)
Grade 3/4 AEs*	17 (41.5)	18 (41.9)
Serious AEs	11 (26.8)	11 (25.6)
AEs leading to treatment discontinuation†	1 (2.4)	2 (4.7)
AEs leading to death	0	1 (2.3)§
Any imAEs¶, n (%)	6 (14.6)	7 (16.3)
Grade 3/4 imAEs	0	3 (7.0)

TRITON interim analysis: summary

The TRITON interim analysis provides preliminary evidence in a prospective study setting that tremelimumab and durvalumab plus chemotherapy yields numerically greater ORR and DoR vs pembrolizumab plus chemotherapy in first-line NSQ mNSCLC with *STK11* and/or *KEAP1* and/or *KRAS* mutations, consistent with signals observed in POSEIDON and other published analyses¹⁻⁴

The incidence of adverse events was similar between arms and consistent with known profiles, with low discontinuation rates and no new safety signals, supporting the tolerability of tremelimumab and durvalumab plus chemotherapy

These results support a role for tremelimumab (anti-CTLA-4) and durvalumab (anti-PD-L1) plus chemotherapy in this *STK11* and/or *KEAP1* and/or *KRAS*-mutated mNSCLC population with high unmet need

In which patients do we consider dual IO?

Stronger rationale

- *STK11* and/or *KEAP1* loss-of-function mutation, especially with *KRAS* co-mutation
- PD-L1 <1%
- Squamous histology (CheckMate 9LA)
- ECOG PS 0–1, no contraindication to CTLA-4

Weaker rationale

- PD-L1 ≥50% without *STK11/KEAP1* alteration (PD-1 alone or PD-1 + CT)
- *STK11/KEAP1* VUS or subclonal mutation
- *KRAS* wild-type with isolated *STK11* mutation

Usually avoid

- ECOG PS ≥2 or frail
- Active autoimmune disease
- Actionable driver (*EGFR*, *ALK*, *ROS1*, etc.)

Discussion: Which features trigger dual IO in your practice — PD-L1, histology, co-mutations, fitness? How much weight do *STK11/KEAP1* carry?

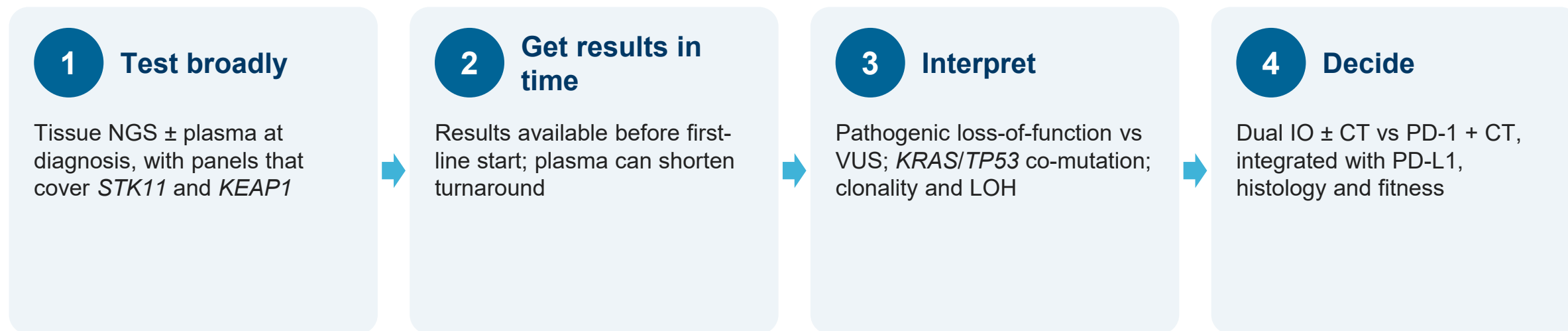
How do we choose between POSEIDON and CheckMate 9LA?

	POSEIDON (T+D+CT)	CheckMate 9LA (N+I+CT)
Chemotherapy	4 cycles	2 cycles
CTLA-4 exposure	Tremelimumab, 5 doses in total	Ipilimumab q6w, up to 2 years
Maintenance	Durvalumab q4w ± pemetrexed (NSQ)	Nivolumab + ipilimumab; no pemetrexed
Long-term OS	5-yr 15.7% vs 6.8% (HR 0.76)	6-yr 16% vs 10% (HR 0.74)
Strongest signals	Nonsquamous; <i>STK11/KEAP1/KRAS</i> -mutant	Squamous (HR 0.65); PD-L1 <1% (HR 0.64)
<i>STK11/KEAP1</i> data	Exploratory OS benefit; prospective TRITON ongoing	Consistent benefit; <i>KEAP1</i> subgroup small
Grade 3–4 TRAEs	52% vs 44%	47% vs 38%

Practical drivers

- Histology: NSQ → POSEIDON data, incl. pemetrexed maintenance; SQ → 9LA
- Molecular profile: *STK11/KEAP1/KRAS* → strongest data with POSEIDON
- Need for rapid response or high burden: more chemotherapy up front
- Fitness and chemo tolerance: fewer chemo cycles in 9LA
- Fixed, finite CTLA-4 course with tremelimumab

Is the data actionable? From NGS report to first-line decision



Real-world barriers

- Smaller hotspot panels omit *STK11* and/or *KEAP1*
- Pressure to start therapy before results return
- Neither NCCN pathways nor most guidelines include *STK11/KEAP1*

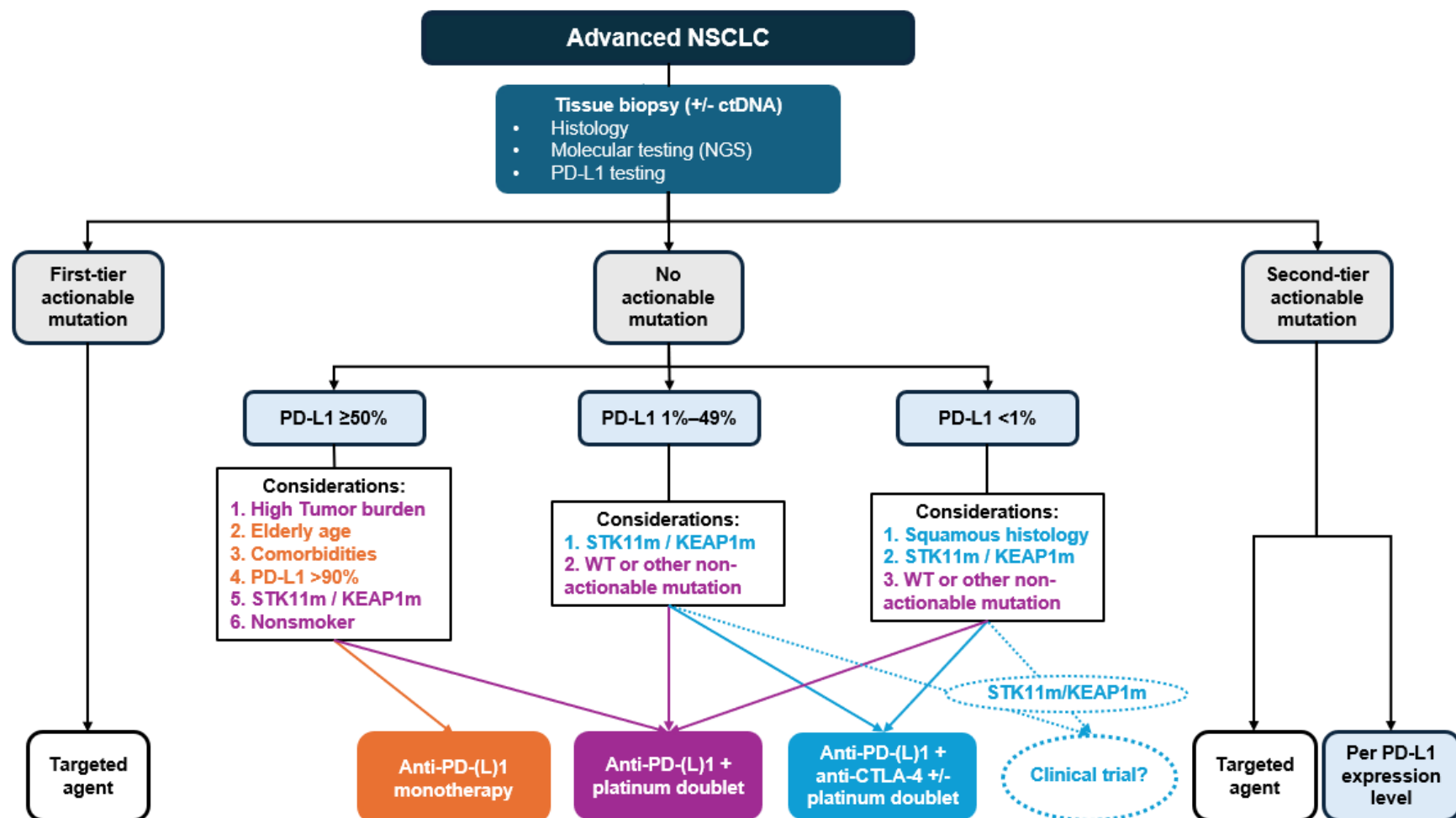
Discussion

- Do you routinely look for *STK11/KEAP1* on the report?
- Has a result ever changed your first-line regimen?
- Would you wait for results to choose?

Are we testing for STK11 and KEAP1?

	Assay	Company	STK11	KRAS	KEAP1	Sample type
Decentralized (in-house) assays	TruSight Oncology 500 ¹	Illumina	+	+	+	FFPE
	TruSight Oncology 500 High-Throughput ¹	Illumina	+	+	+	FFPE
	TruSight Oncology 500 ctDNA assay v2 ²	Illumina	+	+	+	ctDNA
	TruSight Tumor 170 ³	Illumina	+	+	-	FFPE
	AmpliSeq Focus ⁴	Illumina	-	+	-	FFPE
	AmpliSeq Comprehensive Panel ⁵	Illumina	+	+	-	FFPE
	OncoPrint™ Focus Assay ⁶	ThermoFisher	-	+	-	FFPE
	OncoPrint™ Comprehensive Assay ⁷	Thermo Fisher	+	+	-	FFPE
	OncoPrint™ Precision Assay ⁸	Thermo Fisher	-	+	-	FFPE
	OncoPrint™ Dx Target Test ⁹	Thermo Fisher	-	+	-	FFPE
Centralized (outsourced)	Archer™ FUSIONPlex™ Lung v2 Panel ¹⁰	Integrated DNA Technologies	-	+	-	FFPE
	AmoyDx® HANDLE Classic NGS Panel ¹¹	Amoy Diagnostics	+	+	+	FFPE
	Guardant360® CDx ¹²	Guardant Health	+	+	+	ctDNA
	FoundationOne® CDx ¹³	Foundation Medicine	+	+	+	FFPE
	FoundationOne® Liquid CDx ¹⁴	Foundation Medicine	+	+	+	ctDNA
	Caris	Caris Life	+	+	+	FFPE
	TEMPUS	TEMPUS	+	+	+	FFPE

Current guidelines and pathways do not include STK11 and KEAP1



Take home messages

- STK11 and KEAP1 are tumor suppressor genes involved in maintaining metabolic homeostasis under normal conditions. In non–small cell lung cancer, their inactivation contributes to tumor initiation, progression, and metastasis.
- Mutations in both STK11 and KEAP1 occur more commonly in smokers and carry distinct clinical implications depending on concurrent alterations in genes such as TP53 and KRAS.
- These mutations confer resistance to immune checkpoint inhibitors and are associated with an immune-cold or immune-depleted tumor microenvironment.
- Therapeutic strategies to overcome the immunosuppressive phenotype of STK11- and KEAP1-mutant NSCLC are currently under investigation and dual PD-(L)1 blockade + CTLA-4 inhibition has the potential to abrogate resistance.
- In first-line dual IO trials (POSEIDON, CheckMate 9LA, CheckMate 227), exploratory analyses suggest the greatest relative benefit in STK11/KEAP1/KRAS-mutant and PD-L1-negative disease; prospective biomarker-selected data (TRITON) are needed before STK11/KEAP1 testing routinely drives regimen choice.

Acknowledgements

Dana-Farber Cancer Institute

Julia Rotow Jaclyn LoPiccolo
Jia Luo Prabhsimranjot Singh
Jacob Sands Elliot Brea
Narjust Florez Alice Shaw
Paul Marcoux Jennifer Marks
Federica Pecci David Jackman
Valentina Santo Edoardo Garbo
Eleonora Gariazzo
Mihaela Aldea
Kenneth Kehl
Alice Shaw
Pasi Janne
David Barbie

CCGD/MIT

Yvonne Y. Li
Andrew Cherniack
Hersh Gupta
Renato Umeton

Brigham and Women's Hospital

Lynette Sholl
Scott Rodig
Igor Odintsov
James Lindsay
Mizuki Nishino
Hyesun Park

Harvard TH Chan

David Christiani
Xinan Wang
Xihong Lin

Memorial Sloan Kettering Cancer Center

Adam Schonfeld
Arielle Elkrief
Rohit Thummalapalli
Alissa Cooper
Matthew Hellman

MD Anderson Cancer Center

Ferdinandos Skoulidis
Marcelo Negrao
Mehmet Altan
Natalie Vokes
John Heymach



Penn Medicine

Charu Aggarwal, MD, MPH, FASCO

Leslye M. Heisler Professor of Lung Cancer Excellence

Section Chief, Thoracic and Head & Neck Medical Oncology

Director, Precision Oncology Innovation, Penn Center for Cancer Care Innovation (PC3I)

University of Pennsylvania

@CharuAggarwalMD

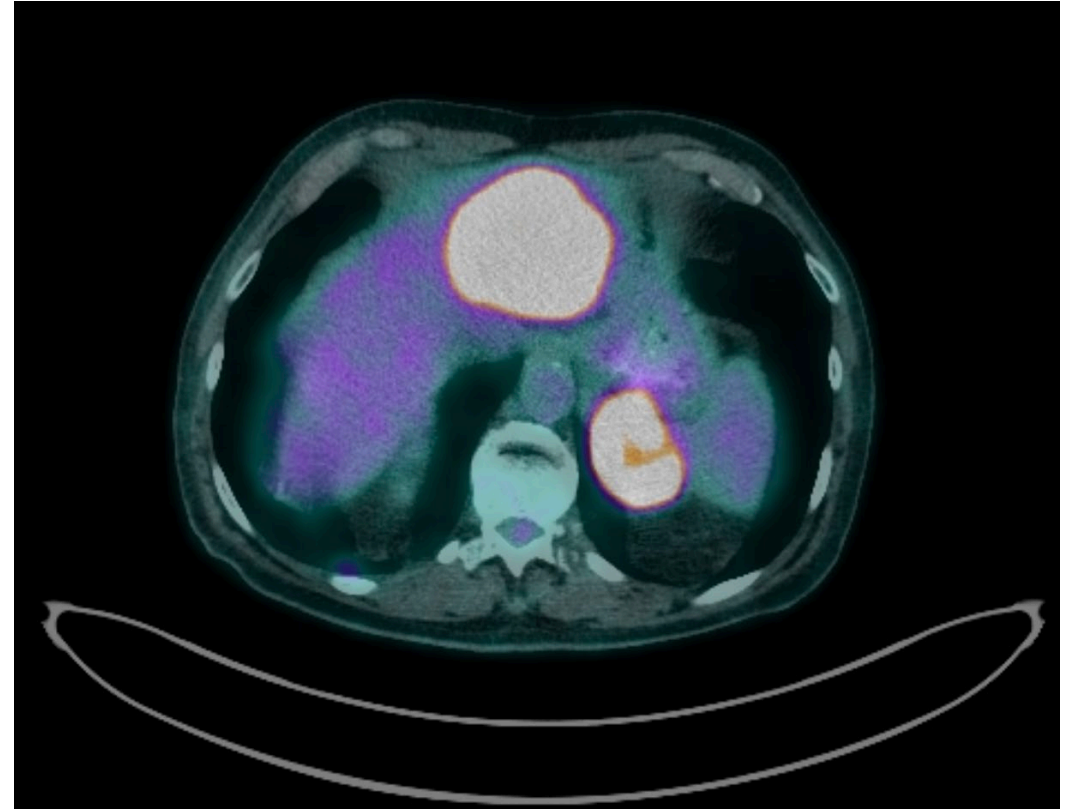
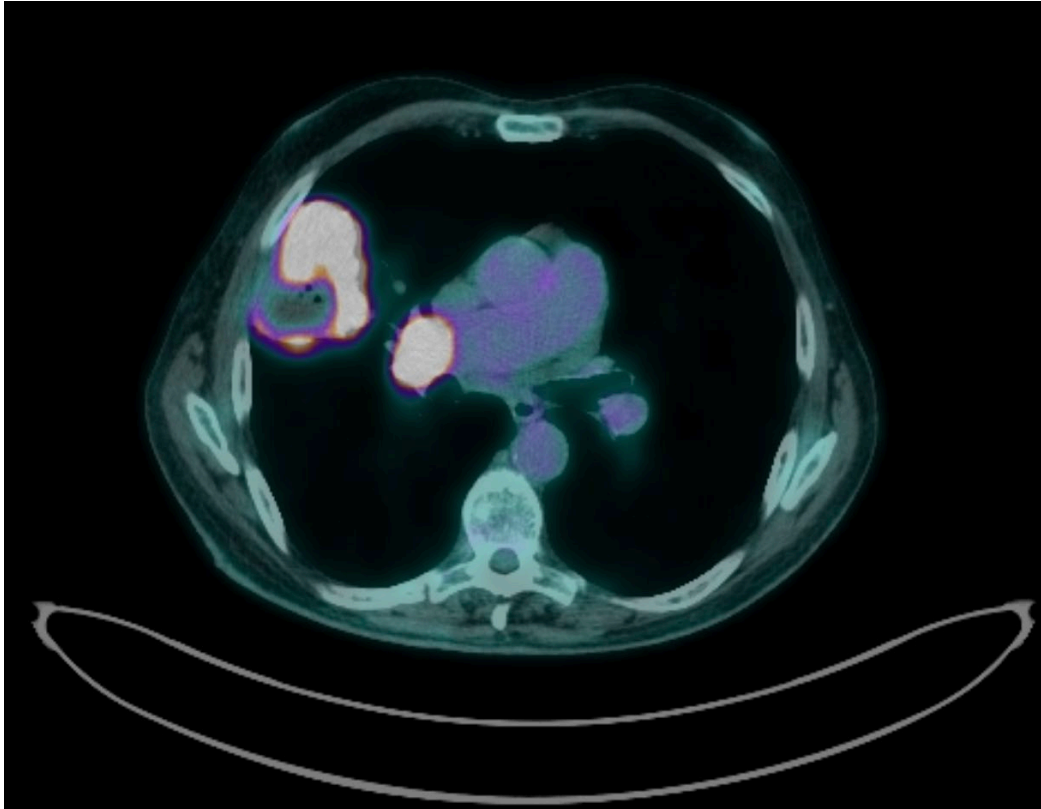


76 year old male with 40 pack year smoking history

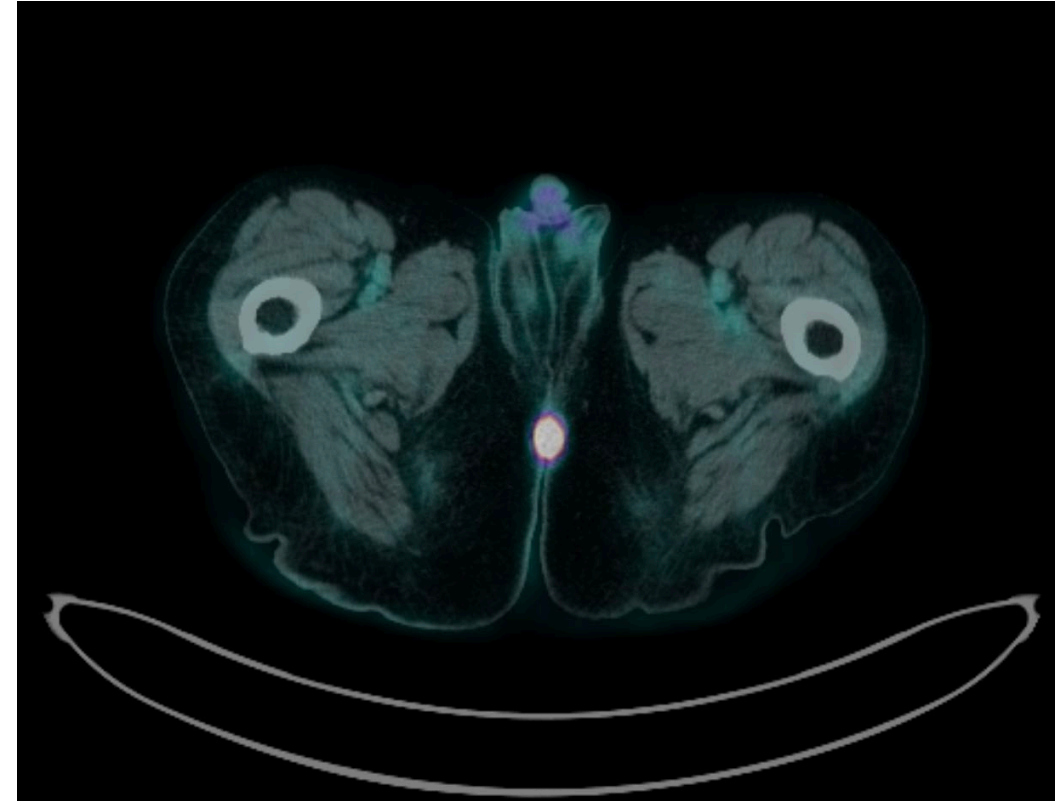
Underwent a low-dose CT Chest, which was notable for a new RUL 6.8 x 5 cm lesion and 3 smaller subpleural RLL lesions and several enlarged mediastinal and paratracheal lymph nodes

PET CT was performed: with evidence of FDG avid right lung disease and extensive mediastinal mets and liver and adrenal mets

Case Presentation – PET



Case Presentation – PET



Cough - moderate productive for yellow sputum, denies hemoptysis
Denies headaches, vision changes, dizziness, focal weakness
Does feel more fatigued than usual, but still independent of ADLs
Notes stress of diagnosis, has begun smoking 1-5 cigarettes in last 1-2 weeks
Denies any focal pain

Lung, Right Upper Lobe, RUL Mass, Biopsy:

Poorly differentiated non-small cell carcinoma

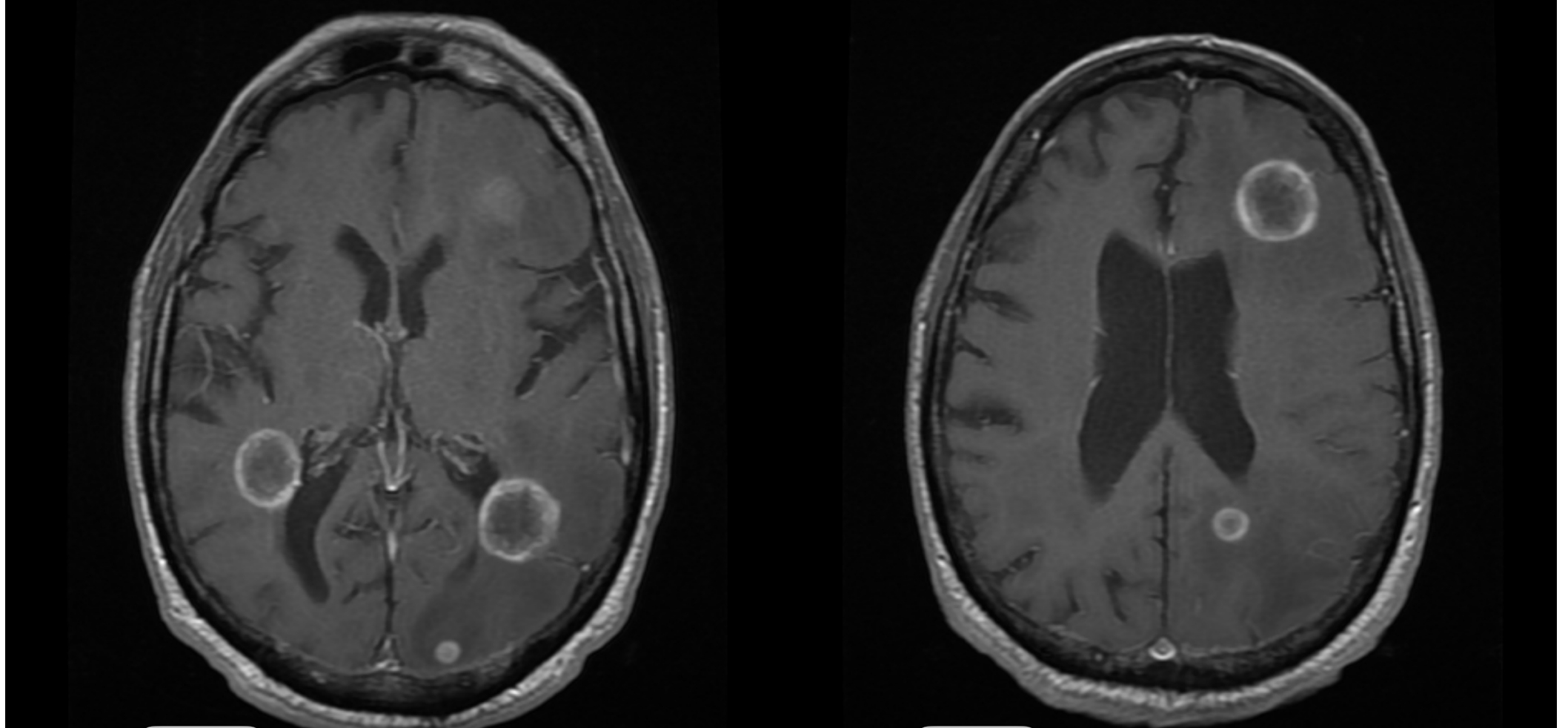
Background shows extensive necrotic material with acute and chronic inflammation

The tumor cells are positive for CK7, TTF-1, and negative for CK20, p40, chromogranin and CD56

PDL1 Negative
TP53 MT, STK11 Mutation Present

How would you treat this patient?

Case Presentation – MRI



PDL1 50%

TP53 MT, STK11 Mutation Present

How would you treat this patient?