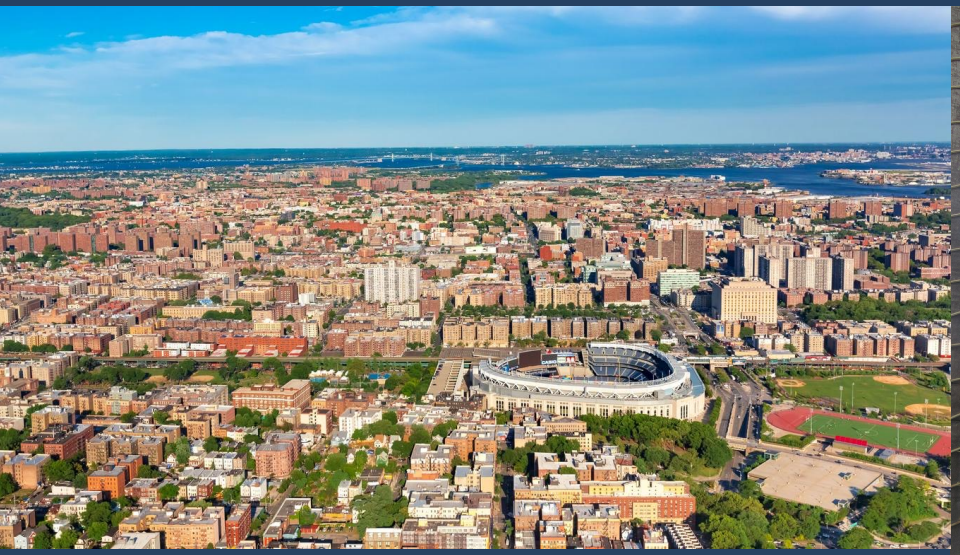
First line immunotherapy for stage 4 NSCLC with no driver

Balazs Halmos MD

Montefiore Einstein Comprehensive Cancer Center

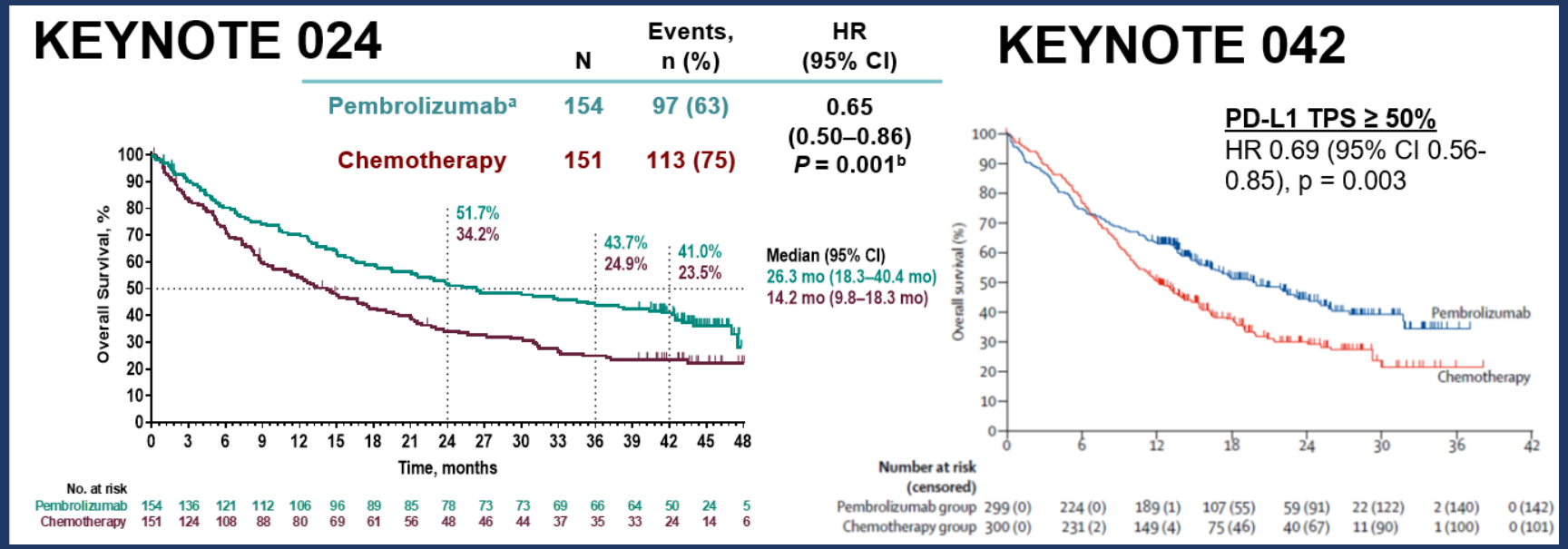


First line immunotherapy for stage 4 NSCLC with no driver

First line immunotherapy for stage 4 NSCLC with no driver

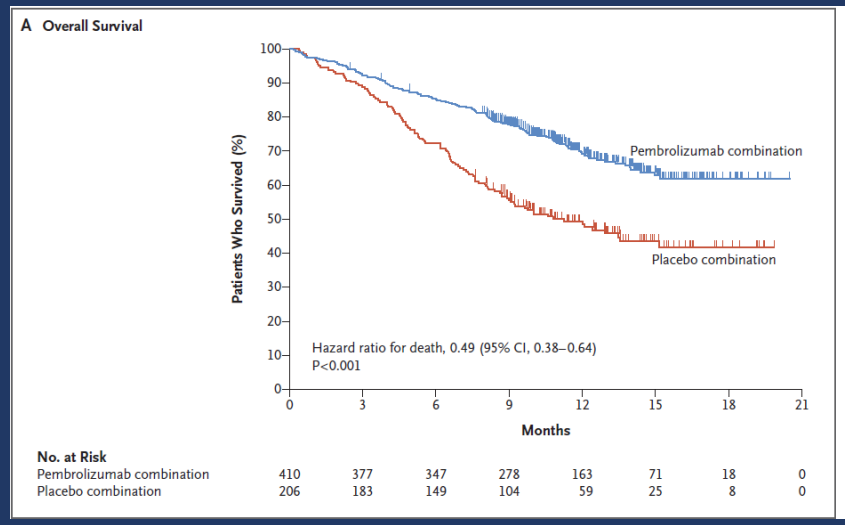
- For whom
- For whom not
- Combo IO
- What failed
- IO continuation upon progression
- Biomarkers- available/emerging
- Managing patients on IO
- What the future holds

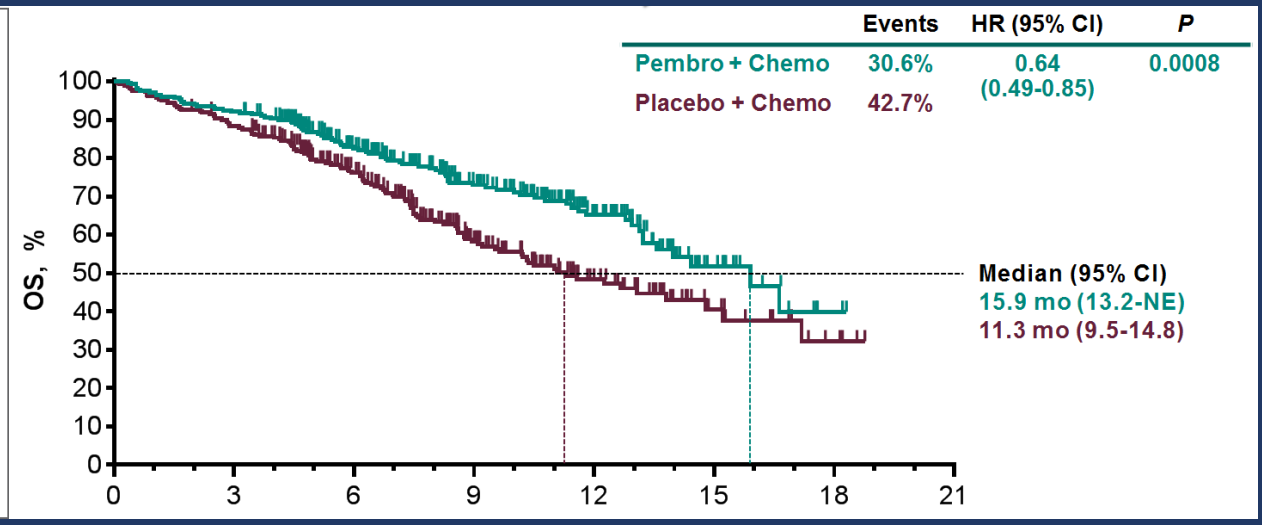
The basic landscape



Reck et al NEJM

Lopes et al ASCO

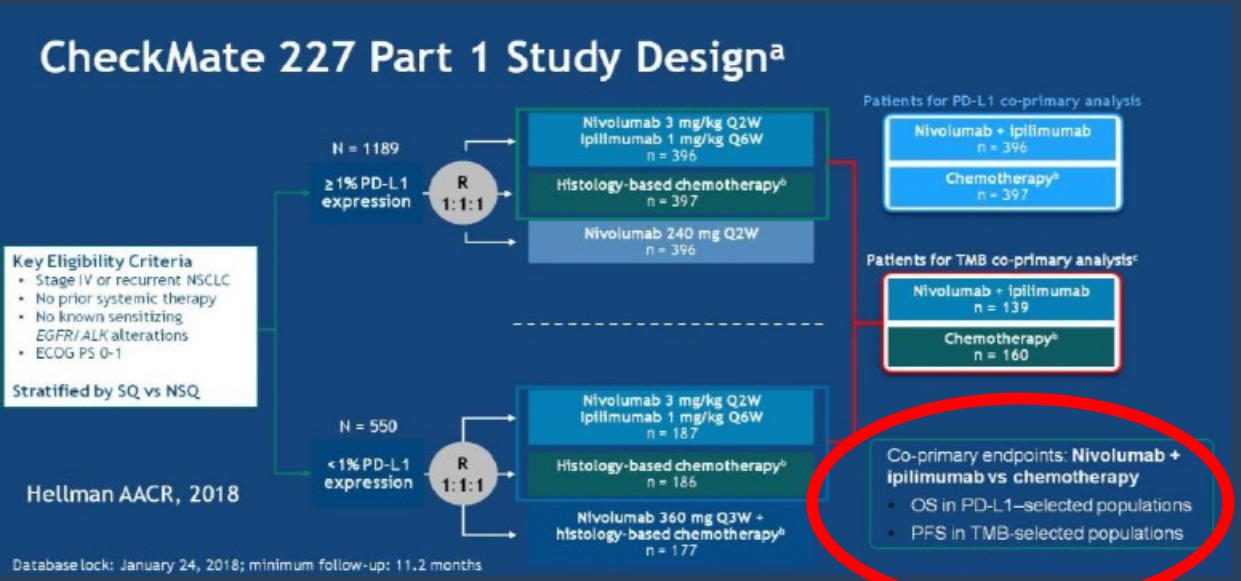


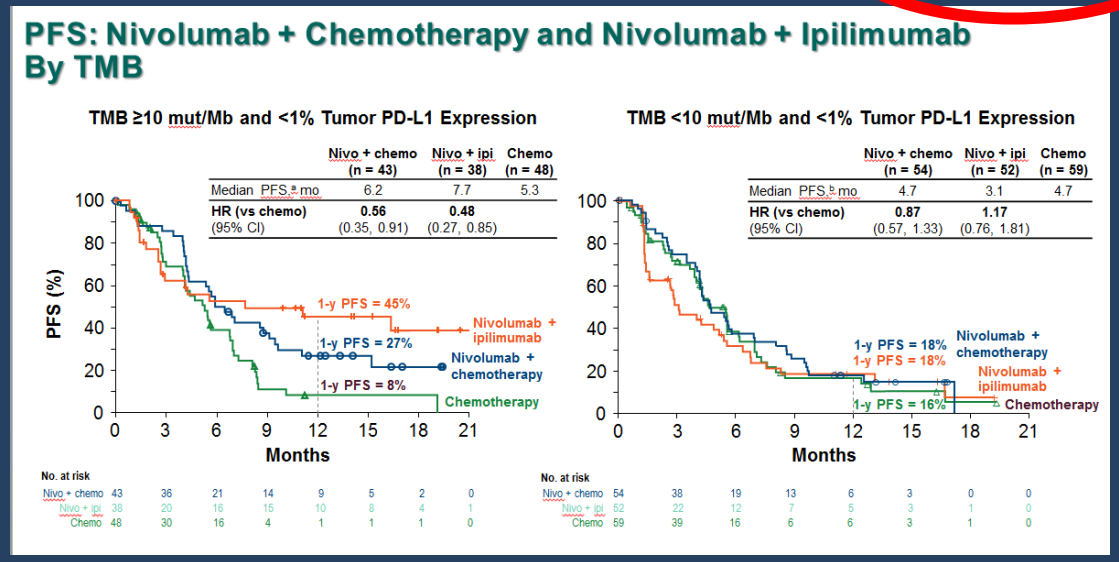


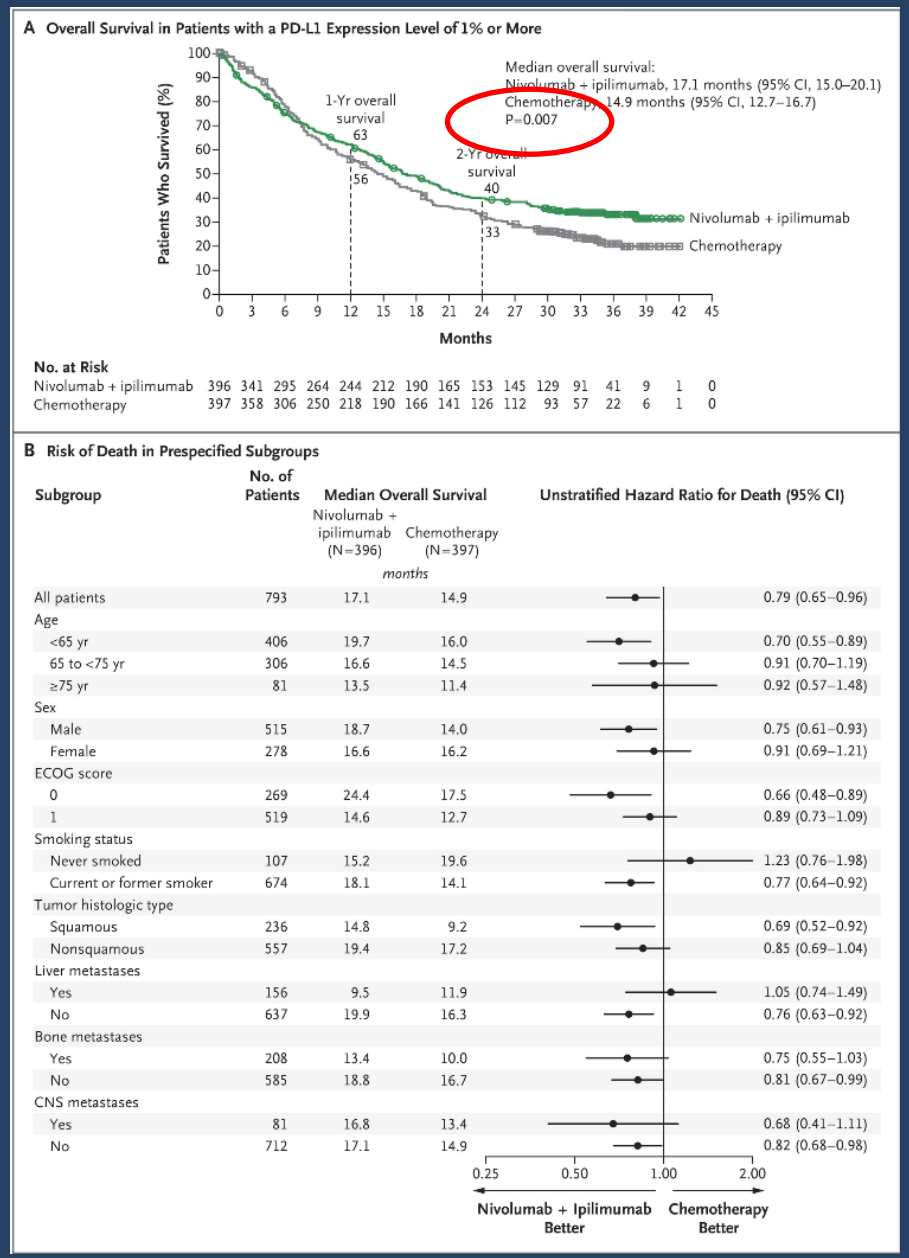
Gandhi et al NEJM

Paz-Ares et al NEJM

Combination immunotherapy- Checkmate 227







Borghaie et al ASCO 2018/ Hellman NEJM

Checkmate 9LA

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

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

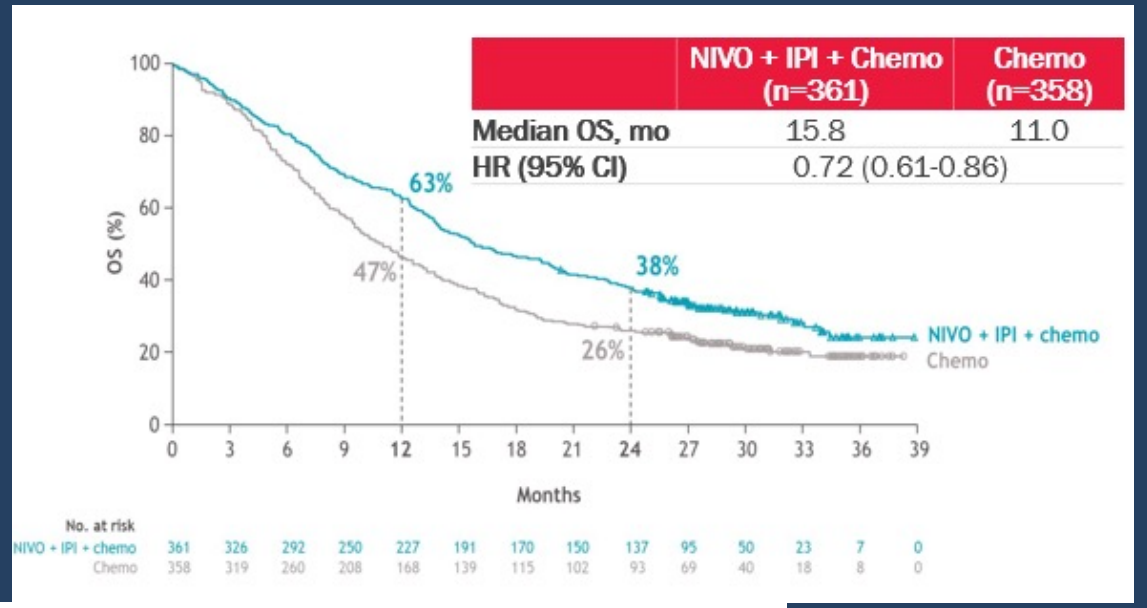
R 1:1

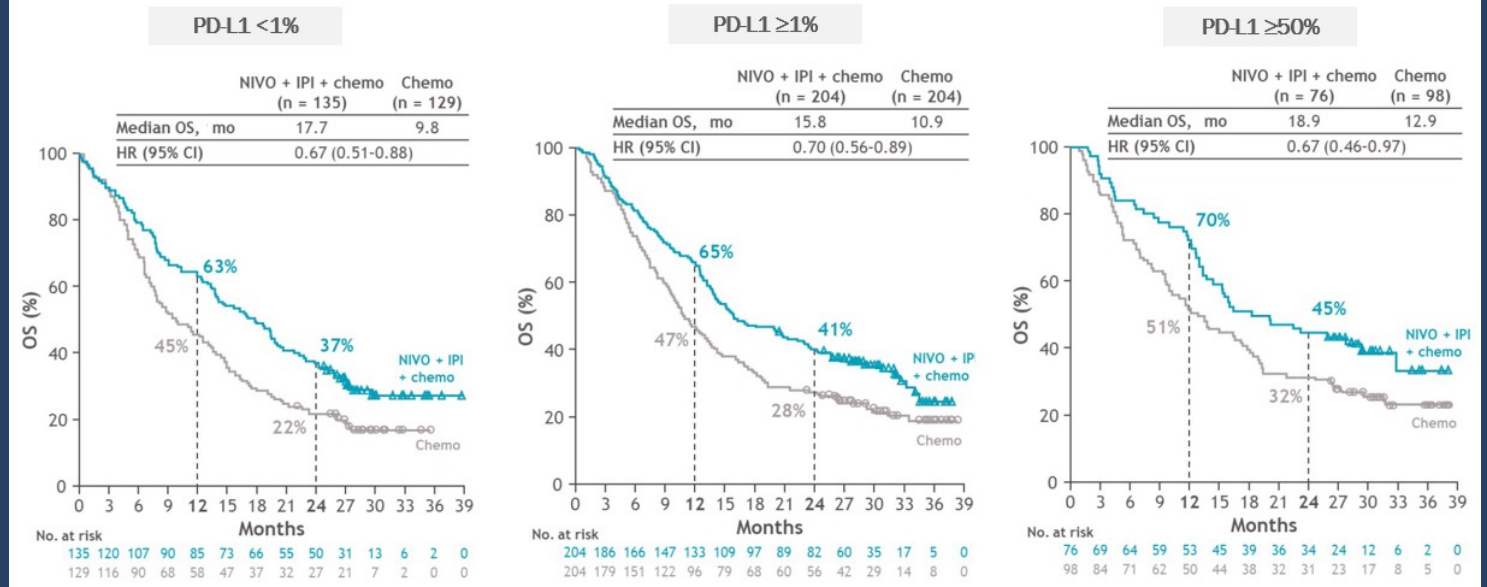
NIVO + IPI + Chemo (2 cycles) n=361

Chemo (4 cycles) n=358

- **Primary endpoint**: OS
- **Secondary endpoints**: PFS by BICR, ORR by BICR, efficacy by tumor PD-L1 expression

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





Reck et al ASCO 2021

New kid on the block
POSEIDON

POSEIDON Study Design

Phase 3, global, randomised, open-label, multicentre study in 1L mNSCLC

Stage IV NSCLC

N=1013 (randomised)

- *EGFR*/*ALK*wt
- ECOG PS 0 or 1
- Treatment-naïve for metastatic disease
- Tumour biopsy* and baseline plasma sample (for ctDNA)

Stratification factors

- PD-L1 expression (TC ≥50% vs <50%)
- Histology (NSQ vs SQ)
- Disease stage (IVA vs IVB)

R 1:1:1

- **T+D+CT†** q3w 4 cycles → **T** (week 16 only) + **D** q4w until PD
- **D+CT†** q3w 4 cycles → **D** q4w until PD
- **Platinum-based CT†** q3w up to 6 cycles

Primary endpoints

D+CT vs CT:

- PFS‡
- OS

Key secondary endpoints

T+D+CT vs CT:

- PFS‡
- OS

- **Durvalumab** 1500mg ± **limited-course tremelimumab** 75mg + **CT** q3w for **4 cycles**
  - One additional dose of tremelimumab post-CT (week 16; 5th dose)
- Followed by **durvalumab q4w maintenance** until PD, and optional pemetrexed q4w§

Peters, S et al, WCLC 2022

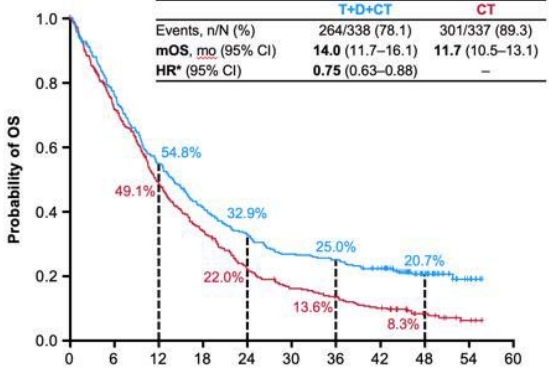
PARIS 2022 ESMO congress

Overall Survival Update

Durable long-term OS benefit for T+D+CT vs CT with HR 0.75 and estimated 25.0% alive at 3 yrs vs 13.6%

T+D+CT vs CT

	T+D+CT	CT
Events, n/N (%)	264/338 (78.1)	301/337 (89.3)
mOS, mo (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.75** (0.63–0.88)	–

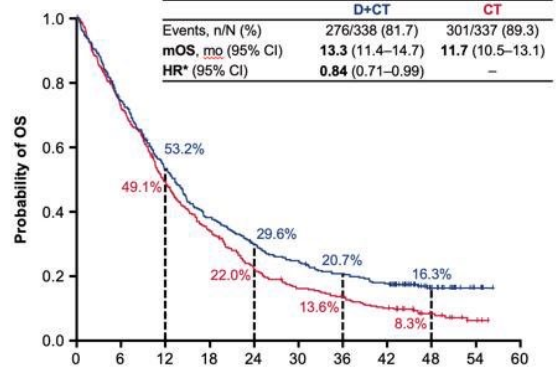


No. at risk

T+D+CT	338	256	183	137	109	89	83	70	32	6	0
CT	337	236	160	111	71	51	42	31	14	5	0

D+CT vs CT

	D+CT	CT
Events, n/N (%)	276/338 (81.7)	301/337 (89.3)
mOS, mo (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.84** (0.71–0.99)	–



No. at risk

D+CT	338	247	176	126	97	81	67	57	26	5	0
CT	337	236	160	111	71	51	42	31	14	5	0

Median follow-up in censored patients at DCO: 46.5 months (range 0.0–56.5)

mOS, median OS

*HR <1 favours D(±T)+CT vs CT (stratified analysis); DCO, 11 Mar 2022

NCCN guidelines- a maze
And this just for TPS>50%!

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

PD-L1 ≥50% First-line Therapy

ADENOCARCINOMA, LARGE CELL, NSCLC NOS

Preferred
- Pembrolizumab (category 1)[46,47]
- (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[48,49]
- Atezolizumab (category 1)[50]
- Cemiplimab-rwlc (category 1)[51]

Other Recommended
- Carboplatin + paclitaxel + bevacizumab[c,d] + atezolizumab (category 1)[52]
- Carboplatin + albumin-bound paclitaxel + atezolizumab[53]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[54]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 2B)[56]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[57]

SQUAMOUS CELL CARCINOMA

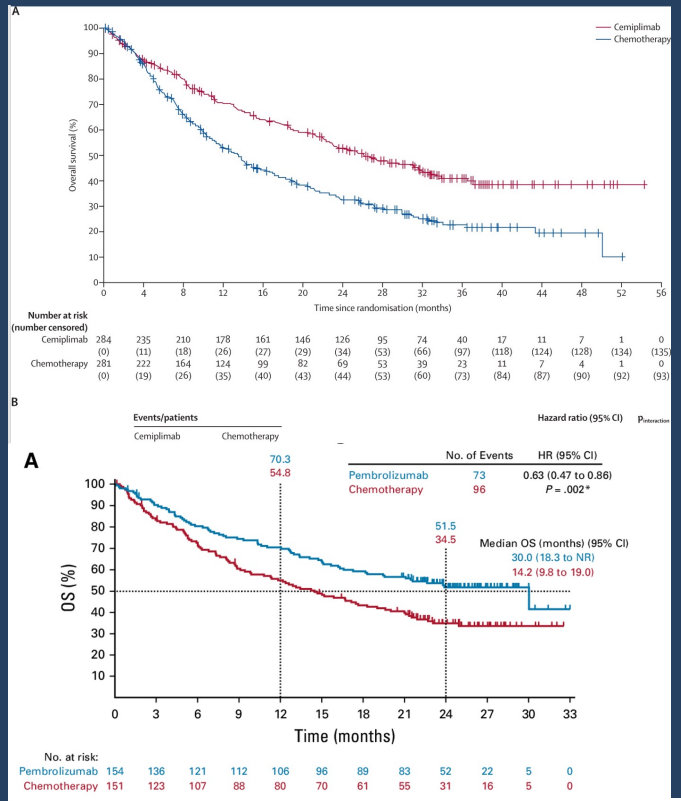
Preferred
- Pembrolizumab (category 1)[46,47]
- Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[58]
- Atezolizumab (category 1)[50]
- Cemiplimab-rwlc (category 1)[51]

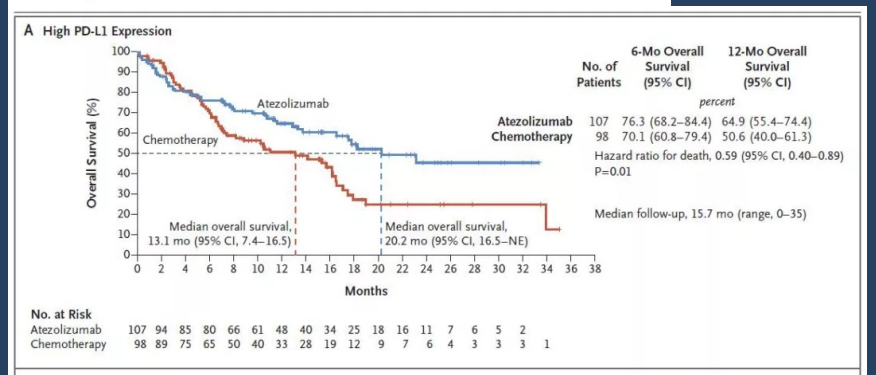
Other Recommended
- Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[53]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[56]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine (category 2B)[56]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[57]

PD-L1 ≥1-49% First-line Therapy
Continuation Maintenance

High TPS score- which IO to use? Pembro? Cemi? Atezo?



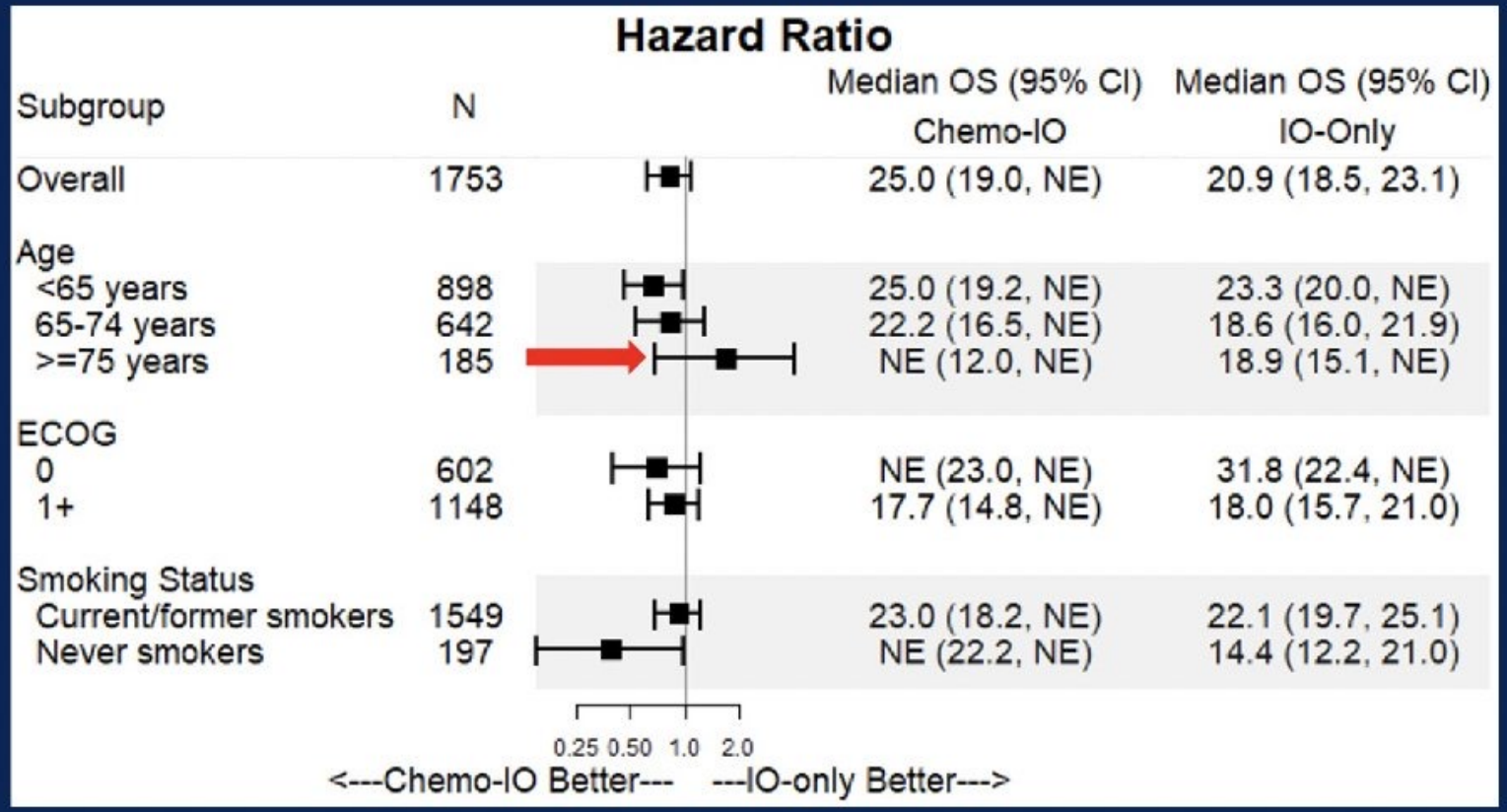


Convenience
Cost
Availability

IO vs chemo-IO for TPS>50%?

OS in NSCLC PD-L1 ≥50% in selected subgroups

FDA



Abbreviations: Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group Performance Status; IO=immunotherapy; NE=not estimable; NSCLC=non-small-cell lung cancer; OS=overall survival; PD-L1=programmed death ligand-1.

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

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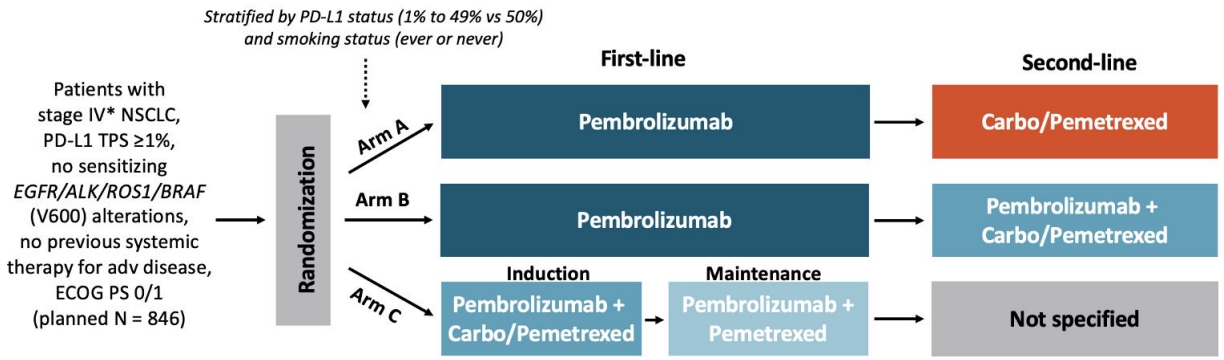
KNOWLEDGE CONQUERS CANCER

IO vs chemo-IO?

- INSIGNA (EA5163/S1709)



EA5221/ACHIEVE Study

Do you have advanced non-small cell lung cancer and are aged 70 or older?

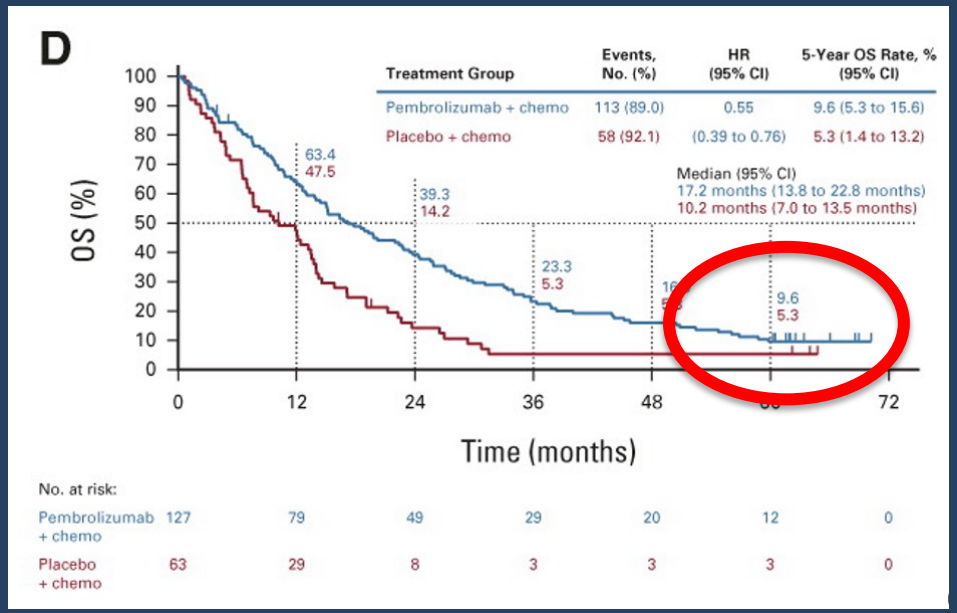
If so, you may be able to participate in this study of a potential new treatment.

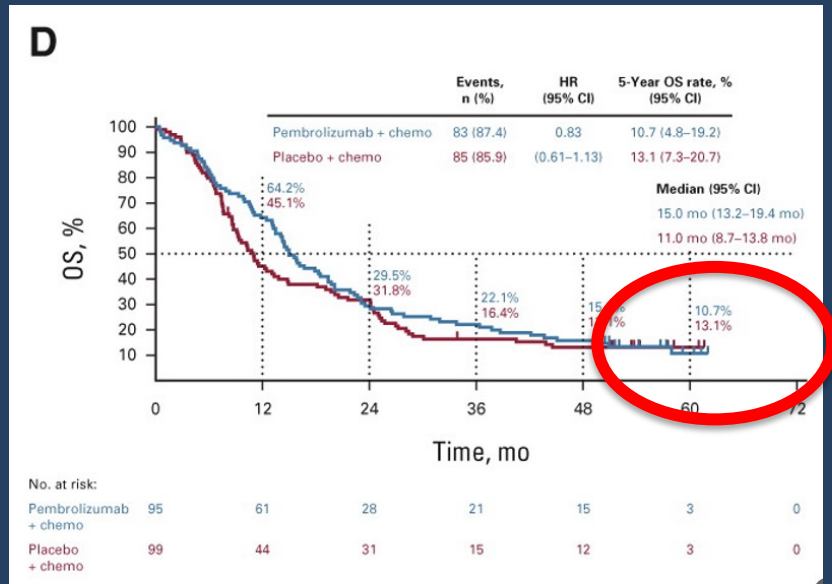
Chemotherapy Combined with Immunotherapy vs. Immunotherapy Alone for Older Adults with Advanced Lung Cancer

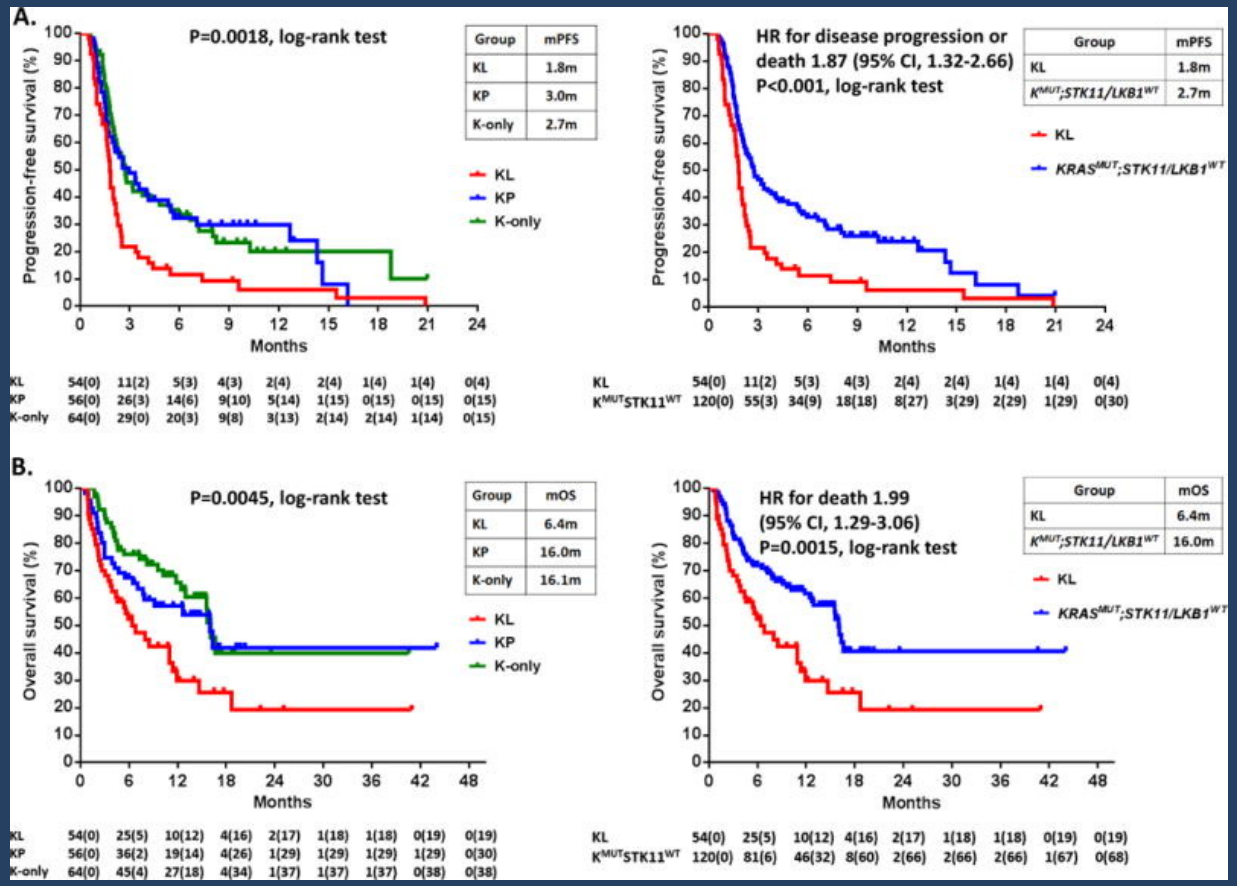
WHY consider participating in this study?

- Research studies are an important way to test the effectiveness of new therapies and approaches for treating lung cancer.
- The usual approach (the care most people get) to treat lung cancer is with surgery, radiation, chemotherapy, immunotherapy, or sometimes a combination of these treatments.
  - Generally, patients 70 years of age or older who have advanced non-small cell lung cancer (NSCLC) are treated with immunotherapy alone or chemotherapy with immunotherapy.
- EA5221/ACHIEVE aims to find out if adding chemotherapy to immunotherapy helps older patients with lung cancer live longer while also maintaining a good quality of life.

TPS score <1%/STK11/KEAP1- chemoIO

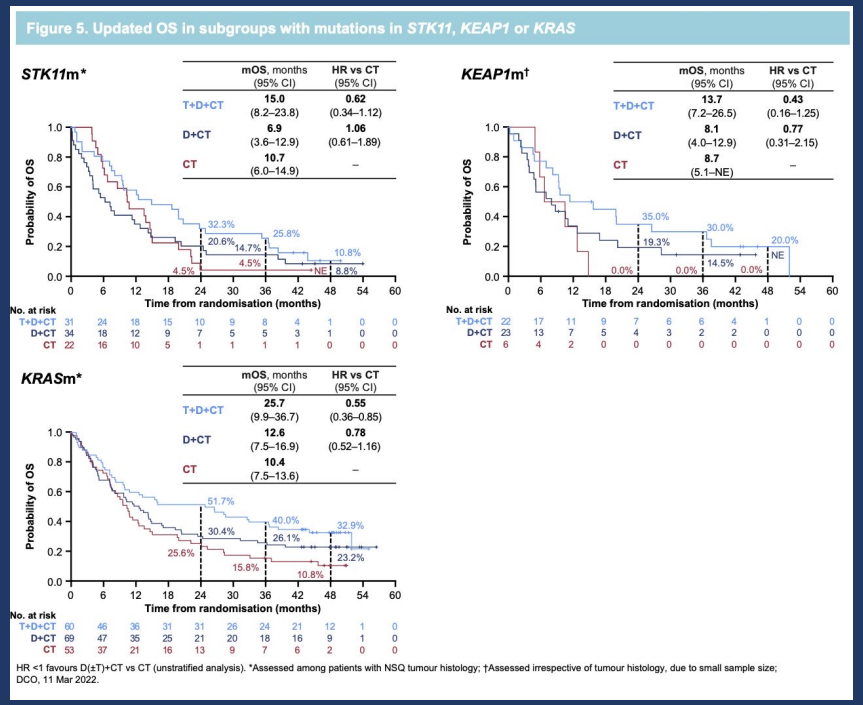






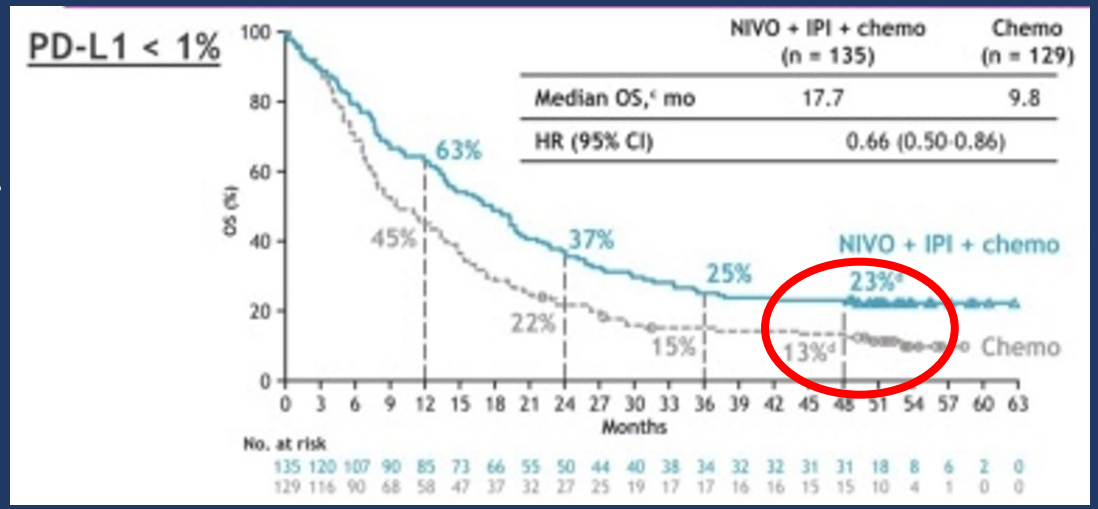
Skoulidis et al

CTLA-4 inhibitor – finally getting called to work?

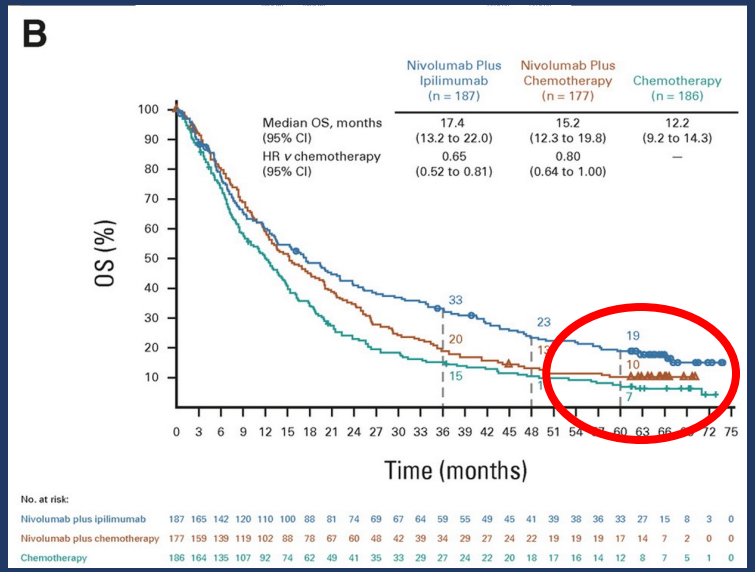


POSEIDON for the rescue

CM9LA- 4yrs on

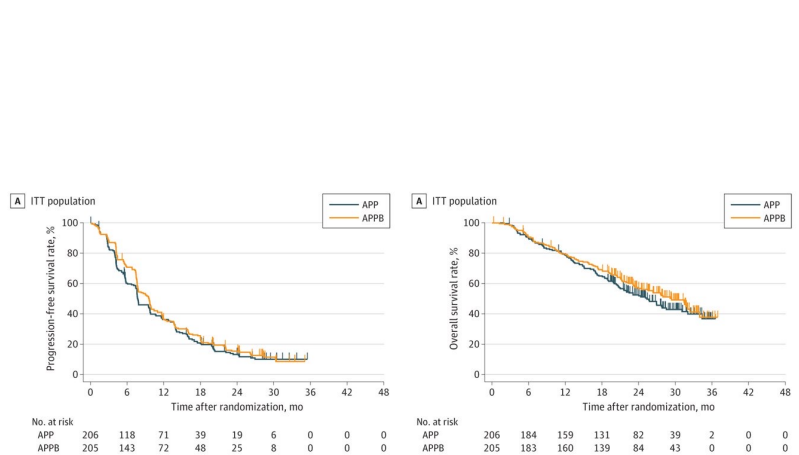


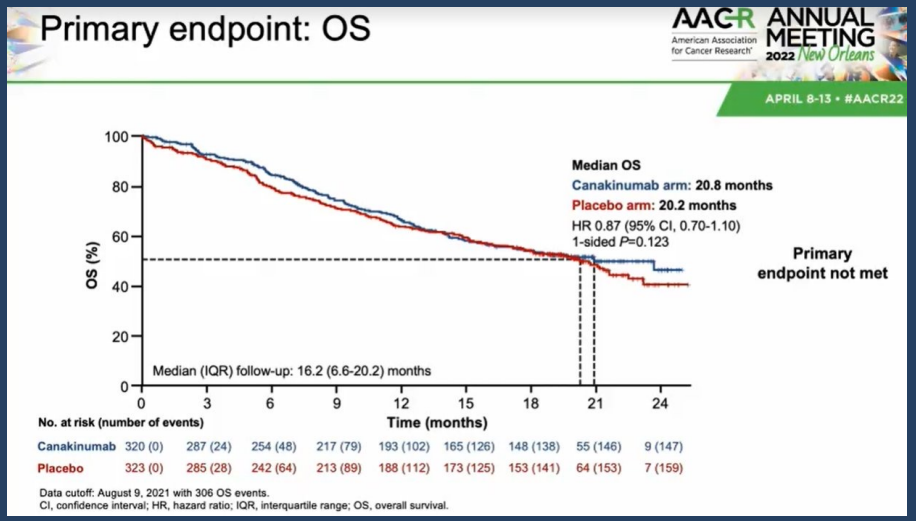
CM227- 5 years on



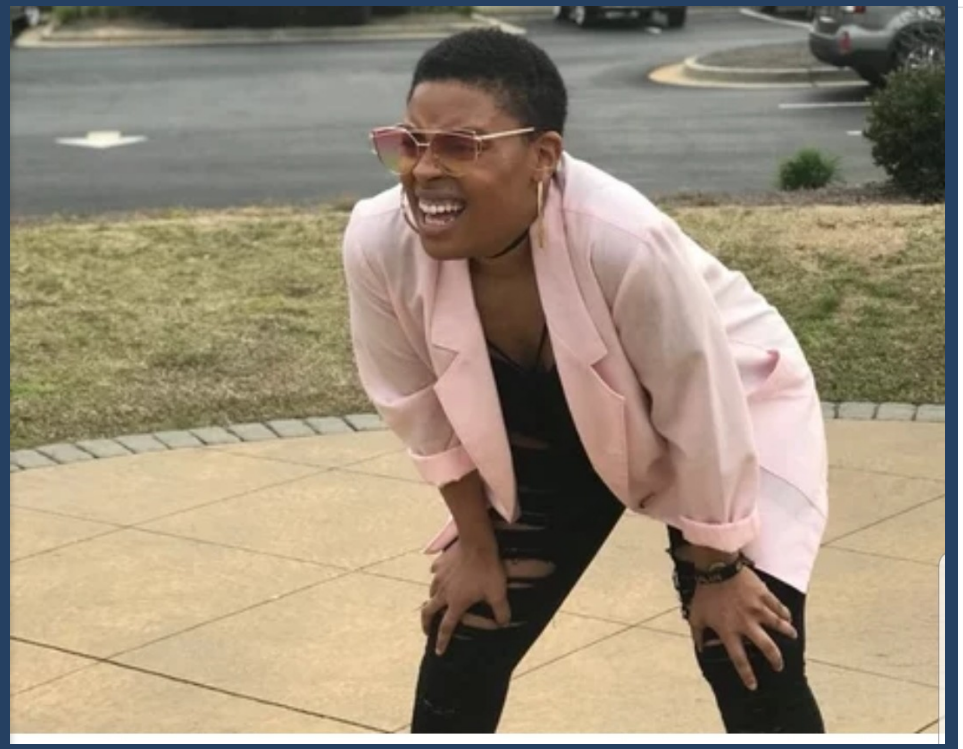
What failed?

Bevacizumab





Canakinumab



PARP

5:32
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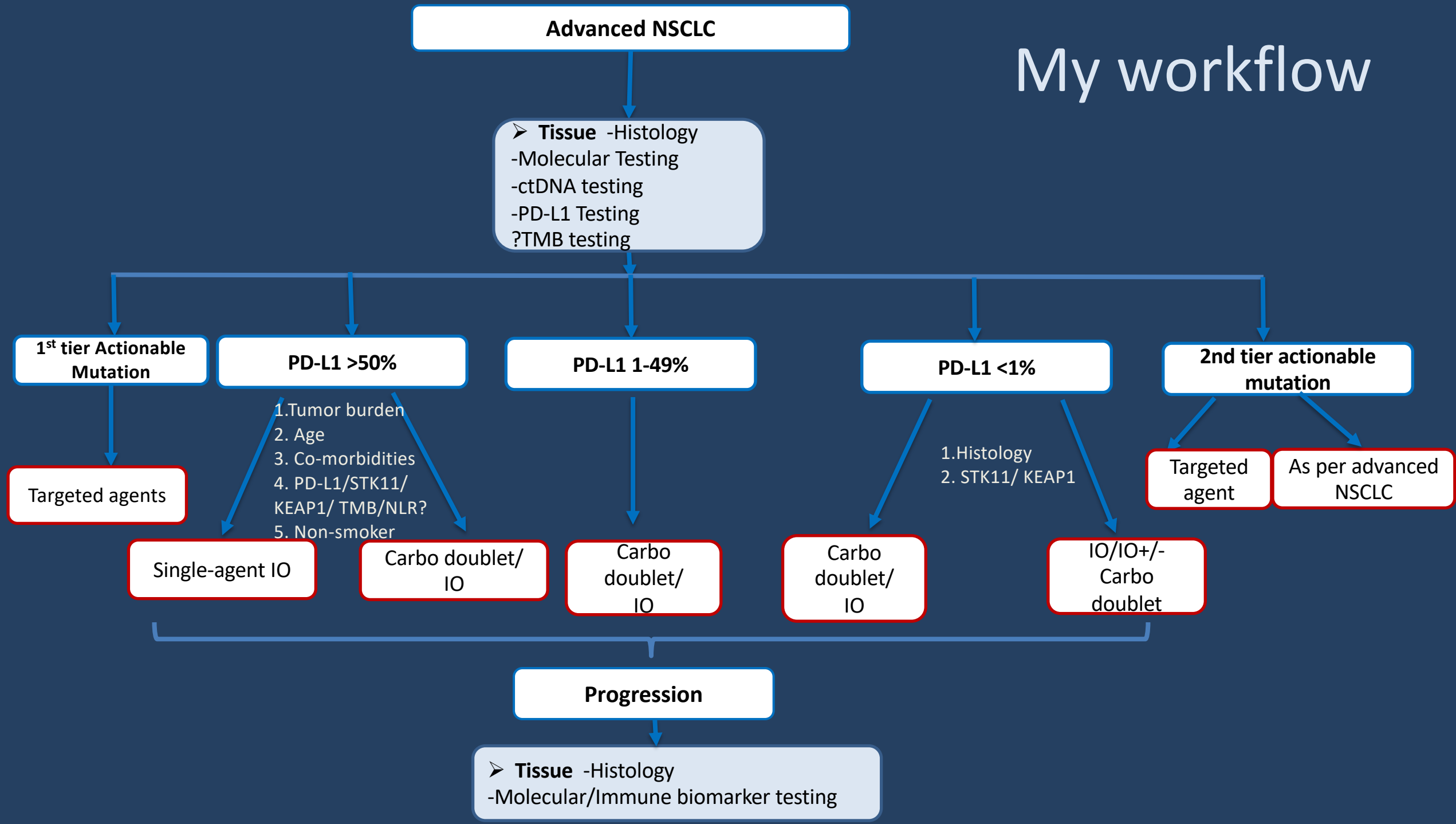
Merck Announces KEYLYNK-008 Trial Evaluating (pembrolizumab) Plus (olaparib) for Patients With Metastatic Squamous Non-Small Cell Lung Cancer to Stop for Futility

December 07, 2023 06:45 AM Eastern Standard Time

RAHWAY, N.J.--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced that it will stop the Phase 3 KEYLYNK-008 trial evaluating KEYTRUDA, Merck's anti-PD-1 therapy, in combination with maintenance LYNPARZA, a PARP inhibitor, for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC). Merck is discontinuing the study based on the recommendation of an independent Data Monitoring Committee (DMC), which reviewed data from a planned interim analysis (IA3). At the interim analysis 3, KEYTRUDA in combination with chemotherapy followed by KEYTRUDA plus LYNPARZA did not demonstrate an improvement in overall survival (OS), one of the study's dual primary endpoints, compared to KEYTRUDA in combination with chemotherapy followed by KEYTRUDA plus placebo.

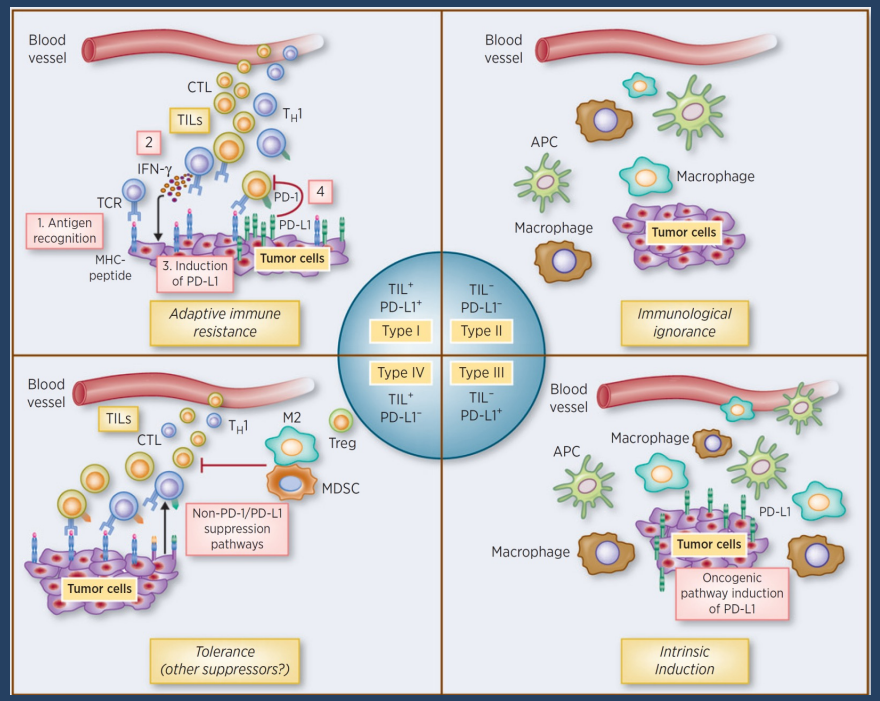
My workflow


Advanced NSCLC
➢ Tissue -Histology
-Molecular Testing
-ctDNA testing
-PD-L1 Testing
?TMB testing
1st tier Actionable Mutation
PD-L1 >50%
PD-L1 1-49%
PD-L1 <1%
2nd tier actionable mutation
Targeted agents
1.Tumor burden
2. Age
3. Co-morbidities
4. PD-L1/STK11/ KEAP1/ TMB/NLR?
5. Non-smoker
1.Histology
2. STK11/ KEAP1
Targeted agent
As per advanced NSCLC
Single-agent IO
Carbo doublet/ IO
Carbo doublet/ IO
Carbo doublet/ IO
IO/IO+/- Carbo doublet
Progression
➢ Tissue -Histology
-Molecular/Immune biomarker testing

Biomarkers to guide choices

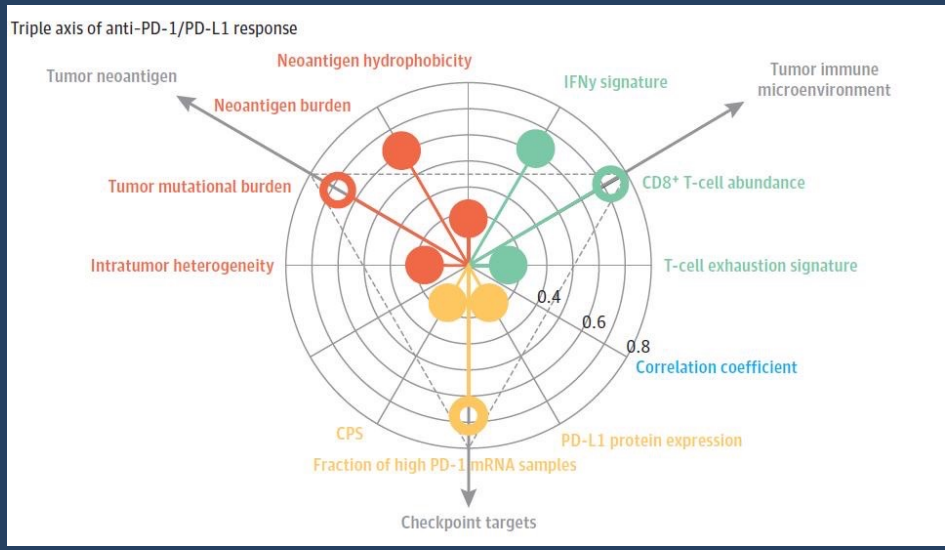
Warm tumor

Cold tumor

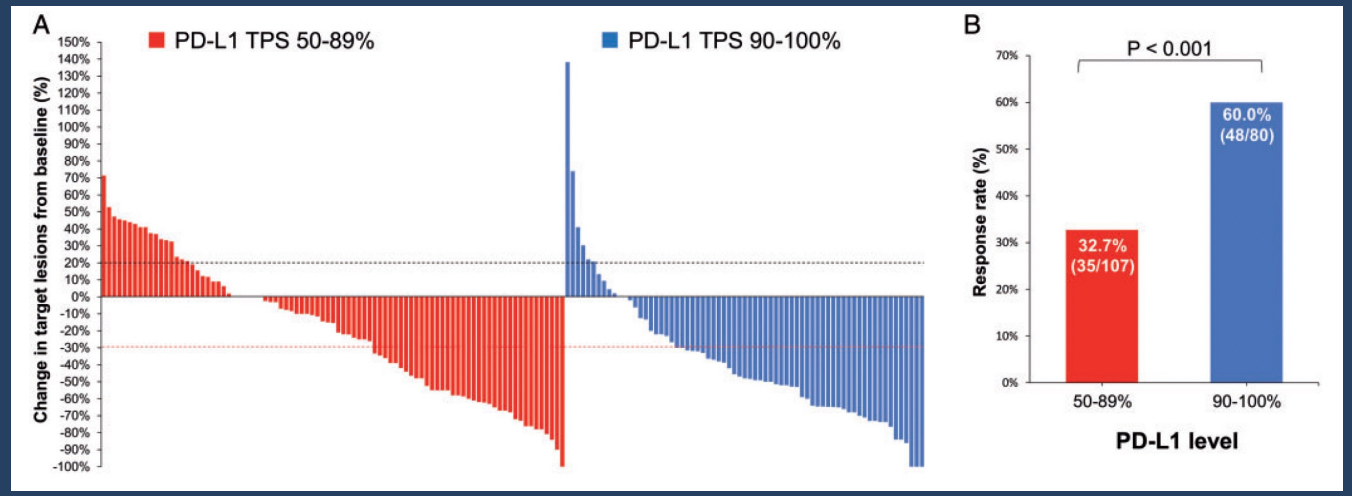


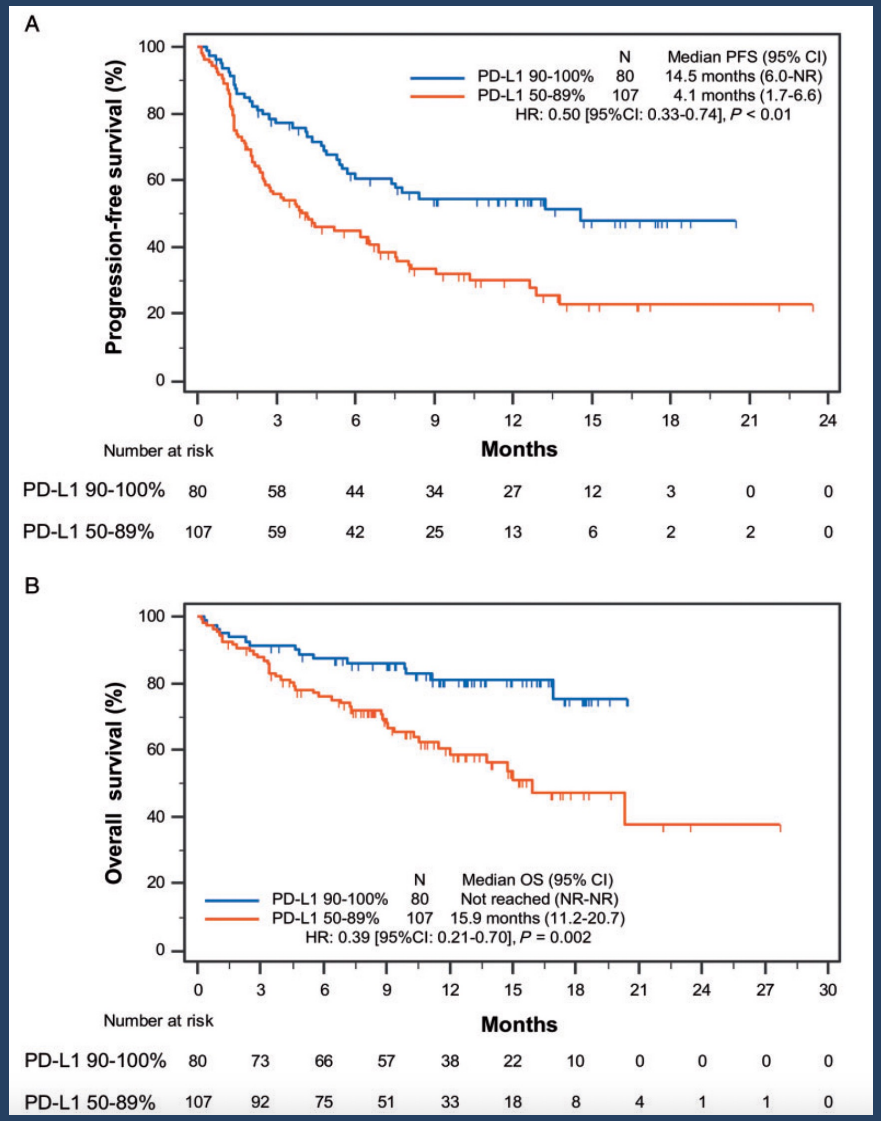
Teng MW et al. *Cancer Res.* 2015;75:2139-2145.

- PD-L1 IHC
  - TPS
  - TC/IC
- TMB
  - Tissue TMB
  - Blood TMB
- Other genomic factors
  - STK11/KEAP1
  - EGFR/ALK/ROS
- Inflammatory signatures
  - NLR
  - Teff/TIL
- Proteomics
- ctDNA dynamics



Can we enrich even more with PD-L1 TPS?



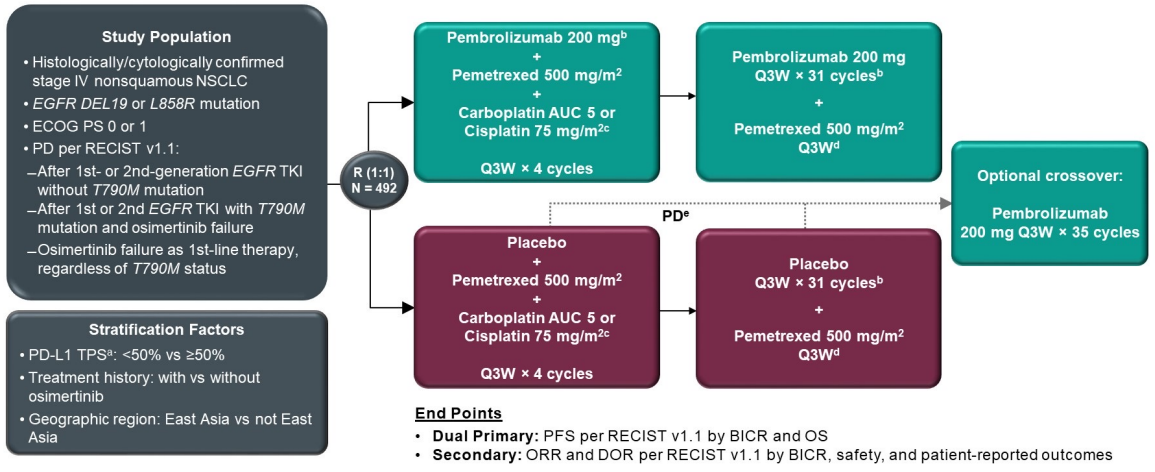


1. Aguilar EJ, Ricciuti B, Gainor JF, et al. Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression. *Annals of Oncology*. 2019 Oct 1;30(10):1653-9.

Important to know what does not work!

Do no harm!

KEYNOTE-789: Phase 3 Randomized Study (NCT03515837)

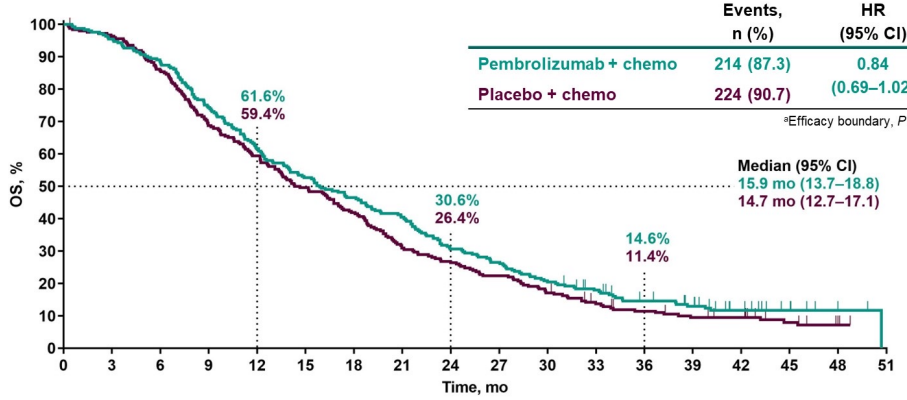


End Points

- **Dual Primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR and DOR per RECIST v1.1 by BICR, safety, and patient-reported outcomes

[a]PD-L1 expression was centrally assessed using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA). [b]If a patient has documented PD but is benefiting clinically, they may receive pembrolizumab monotherapy to complete a total of 35 pembrolizumab administrations. [c]Carboplatin or cisplatin therapy is at the investigator's choice. [d]Maintenance pemetrexed may continue past 35 cycles until reaching a discontinuation criterion if the patient is receiving benefit; however, pembrolizumab or saline placebo are limited to 35 cycles. [e]Patients could crossover at any time during the treatment. To be eligible for crossover, PD must have been verified by BICR.

Overall Survival at FA



	Events, n (%)	HR (95% CI)	*P* value[a]
Pembrolizumab + chemo	214 (87.3)	0.84 (0.69–1.02)	0.0362
Placebo + chemo	224 (90.7)		

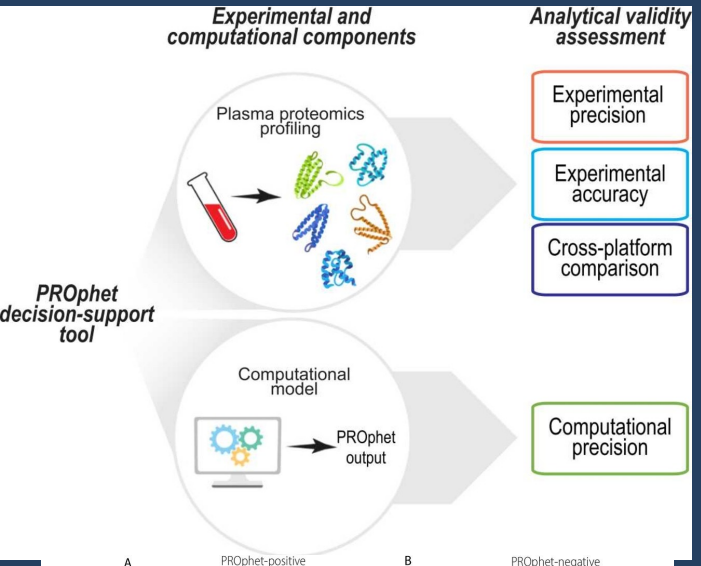
[a]Efficacy boundary, $P = 0.0117$ for OS (FA).

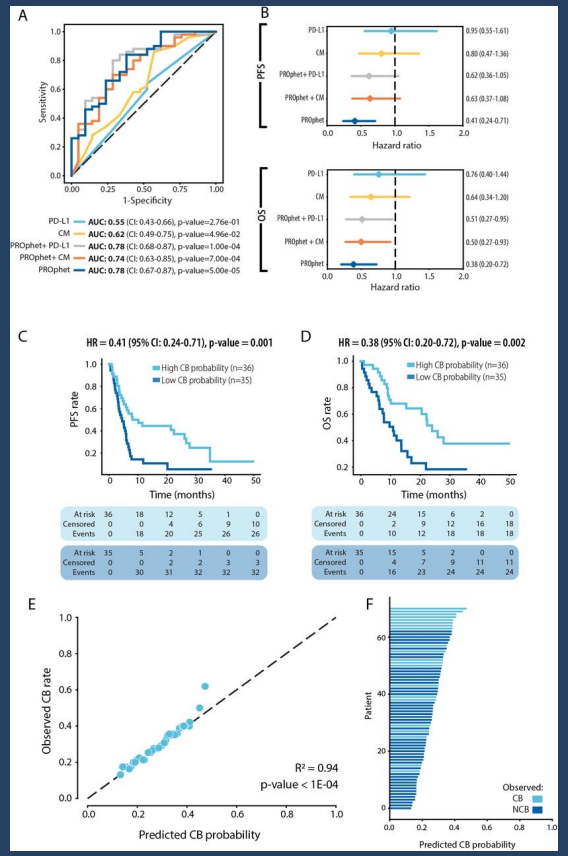
No. at risk																		
Pembrolizumab + chemo	245	234	217	182	151	129	114	99	75	65	50	40	29	23	13	7	3	0
Placebo + chemo	247	237	211	169	146	122	103	76	65	55	42	31	24	19	17	10	3	0

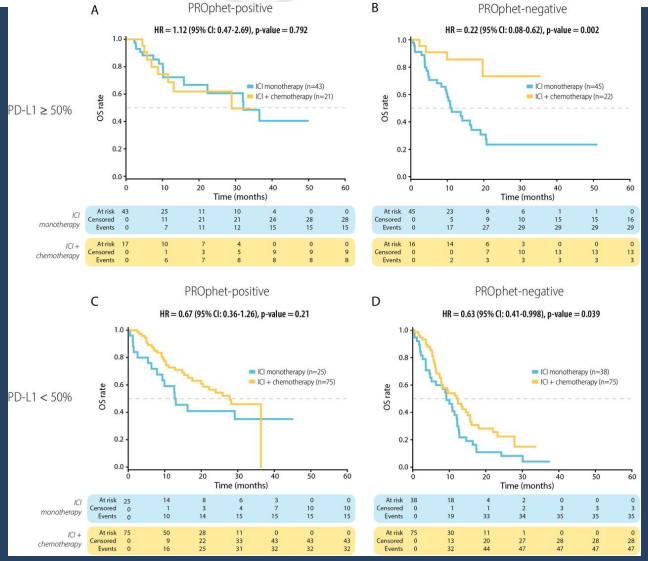
Median (range) time from randomization to data cutoff: 42.0 (29.5–53.9) months.
Data cutoff date: January 17, 2023.

Emerging biomarkers

PROphet- proteomics

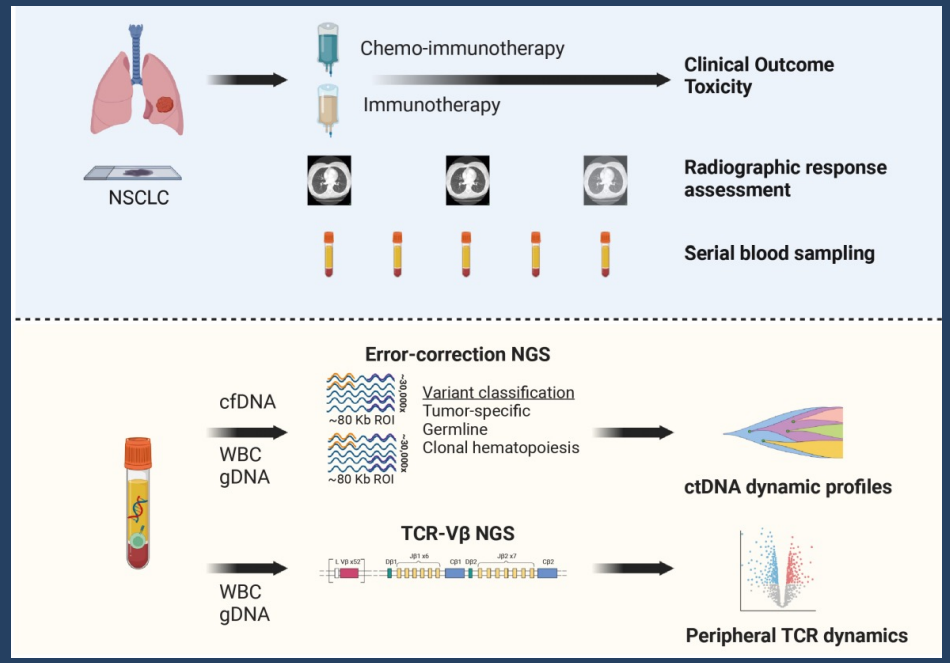


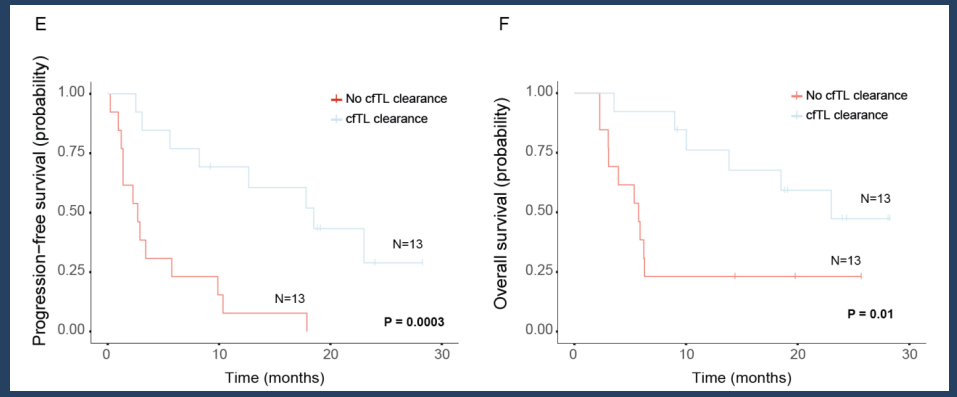




Christopoulos et al BioRxiv

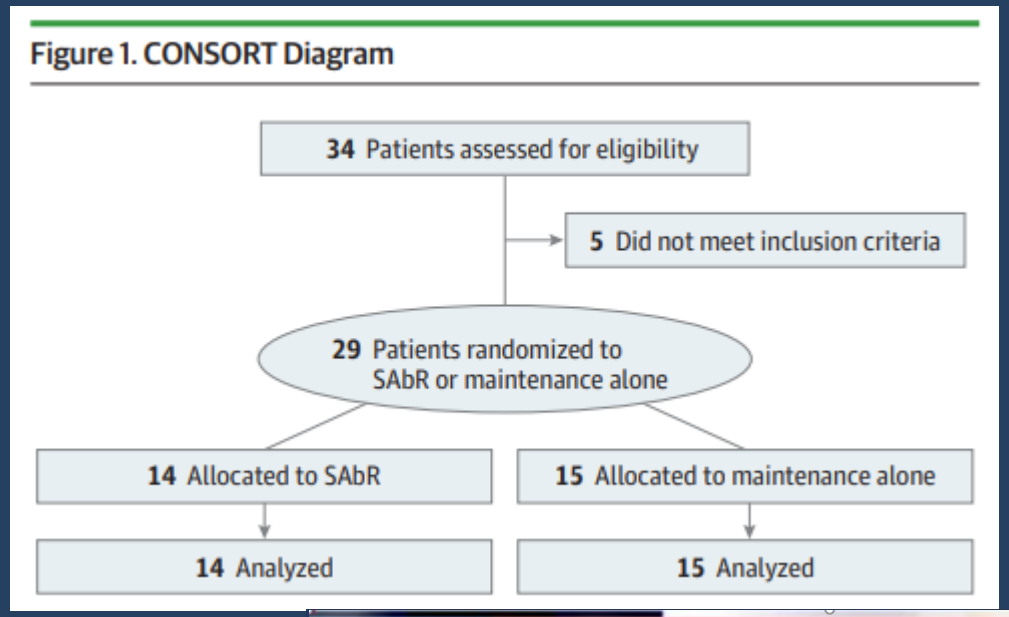
ctDNA dynamics

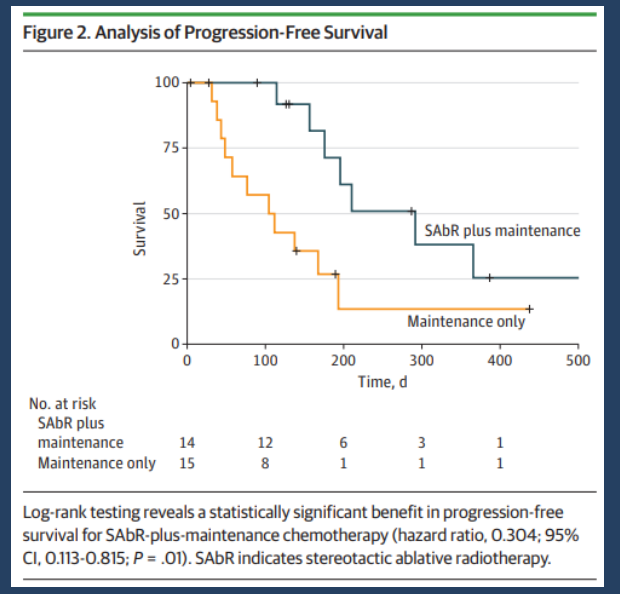




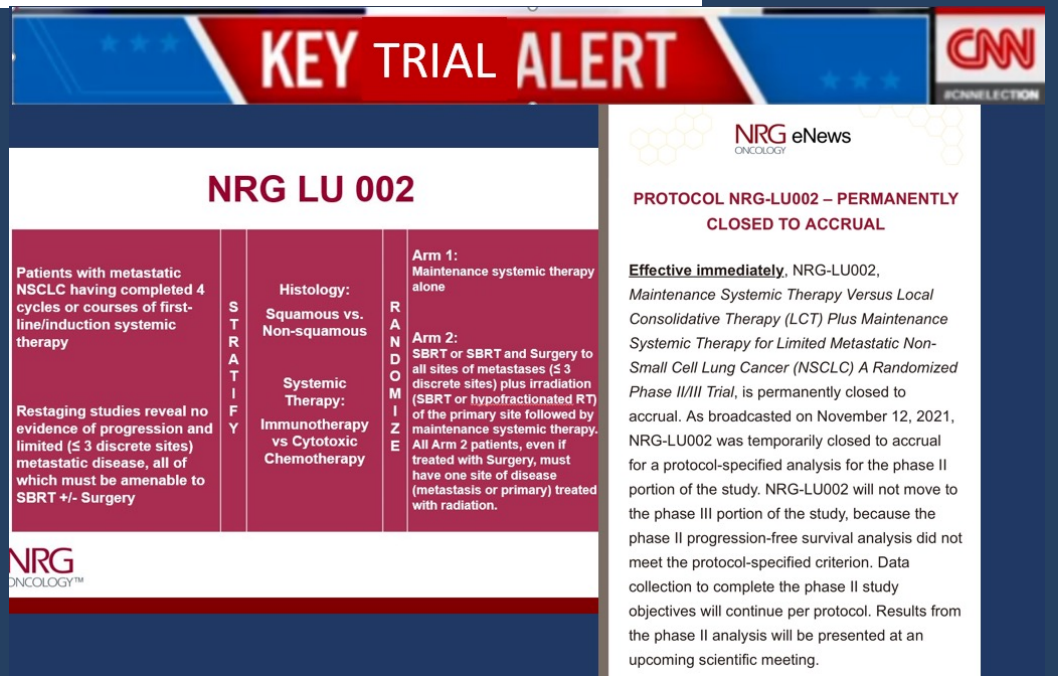
Murray et al CCR 2023

Consolidation XRT for oligomets?





Iyengar et al
JAMA Onc



IO beyond progression?

S1800A Schema—Randomized Phase II trial

NCT03971474

Stratified by 1) PD-L1 expression, 2) histology, 3) intent to receive ramucirumab in standard of care arm

Primary endpoint: OS

Secondary endpoints: RR, DCR, DoR, PFS, Toxicities

ARM A
Investigator's Choice Standard of Care
docetaxel + ramucirumab; docetaxel; gemcitabine; pemetrexed (nonSCC only)

Randomization

R (1:1)
N= 130

ARM B
Pembrolizumab
200 mg Q3W for up to 35 cycles
+
Ramucirumab
10 mg/kg Q3W

Key eligibility: 1) Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined, with PD on at least 84 days after initiation of ICI and platinum-based doublet therapy; 2) ECOG 0-1; 3) all patients met eligibility to receive ramucirumab

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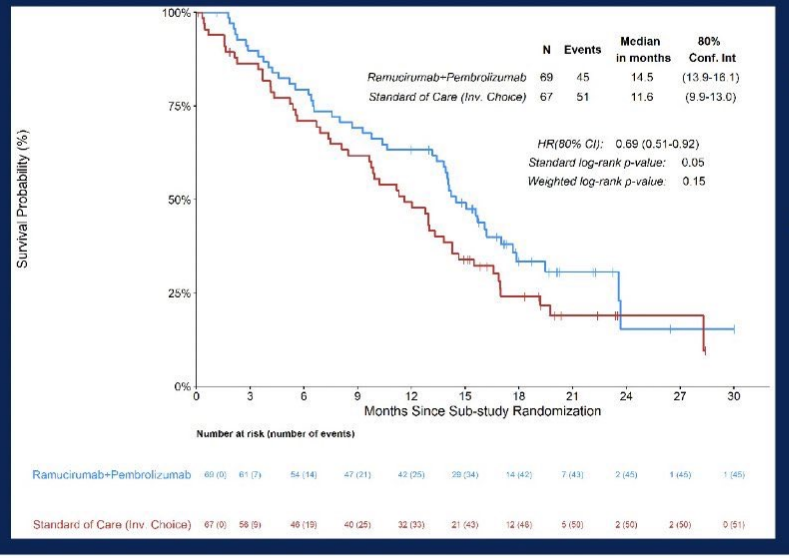
ASCO KNOWLEDGE CONQUERS CANCER

Overall survival



- Median OS for RP 14.5 months v. SOC 11.6 months
- HR= 0.69; SLR p-value 0.05

Standard of care therapy received:
- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

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ASCO KNOWLEDGE CONQUERS CANCER

SWOG CANCER RESEARCH NETWORK

NCI National Clinical Trials Network
a National Cancer Institute program

S2302: Pragmatica - Lung: A Prospective Randomized Study of Ramucirumab (LY3009806; NSC 749128) Plus Pembrolizumab (MK-3475; NSC 776864) Versus Standard of Care for Participants Previously Treated with Immunotherapy for Stage IV or Recurrent Non-Small Cell Lung Cancer

Primary Objective:

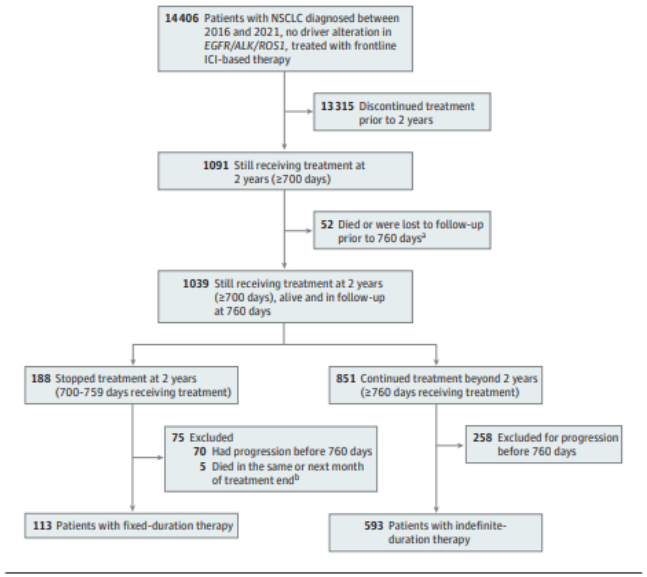
- To compare overall survival (OS) in participants previously treated with platinum-based chemotherapy and immunotherapy for Stage IV or recurrent non-small cell lung cancer (NSCLC) randomized to pembrolizumab and ramucirumab versus standard of care.

Estimated Enrollment: 700

ClinicalTrials.gov Listing: https://clinicaltrials.gov/ct2/show/NCT05633602

IO- how long to continue?

Figure 1. CONSORT Diagram

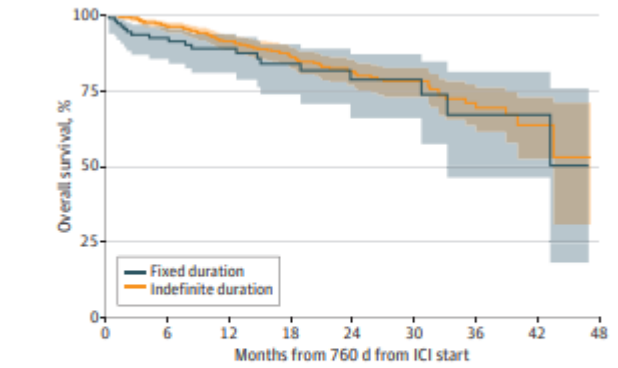


Abbreviations: NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor.

[a] Exclusion criterion applied to enable landmark Kaplan-Meier analysis starting at 760 days.

[b] Patients in the fixed-duration group were excluded if death occurred in the same month as, or the month after, their end of treatment, as these patients' treatment cessation was more likely related to death than the decision to pursue fixed-duration therapy.

Figure 2. Overall Survival



No. at risk

Fixed	113	81	62	39	25	17	7	4	1
Indefinite	593	458	340	244	167	96	46	11	1

Kaplan-Meier curve of overall survival from 2 years (760 days) from immune checkpoint inhibitor (ICI) treatment initiation in the fixed-duration cohort (stopped treatment at 2 years; 700-759 days of treatment) and indefinite-duration cohort (at least 760 days of treatment).

Table 1. Baseline Cohort Characteristics

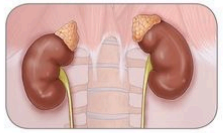
Characteristic	Patients, No. (%)[a] Fixed duration (n = 113)	Indefinite duration (n = 593)	P value[b]
Median (IQR) age, y	69 (62-75)	69 (62-76)	.66
Sex			
Female	62 (54.9)	282 (47.6)	.15
Male	51 (45.1)	311 (52.4)	
Race[c]			
Asian	0	5 (0.8)	.38
Black/African American	16 (14.2)	68 (11.5)	
White	86 (76.1)	414 (69.8)	
Other	7 (6.2)	58 (9.8)	
Missing	4 (3.5)	48 (8.1)	
ECOG performance status			
0	34 (30.1)	204 (34.4)	.68
1	56 (49.6)	254 (42.8)	
≥2	14 (12.4)	78 (13.3)	
Missing	9 (8.0)	57 (9.6)	
PD-L1, %			
0	10 (8.8)	90 (15.2)	.19
1-49	25 (22.1)	110 (18.5)	
≥50%	51 (45.1)	293 (49.4)	
Missing	27 (23.9)	100 (16.9)	
Smoking status			
Former/current	112 (99.1)	550 (92.7)	.01
Never	1 (0.9)	43 (7.3)	
Histologic type			
Nonsquamous	79 (69.9)	463 (78.1)	.15
Squamous	29 (25.7)	107 (18.0)	
NSCLC histology NOS	5 (4.4)	23 (3.9)	
Practice setting			
Community	88 (77.9)	528 (89.0)	.001
Academic	25 (22.1)	65 (11.0)	
Insurance			
Commercial	56 (49.6)	305 (51.4)	.53
Medicare/Medicaid	43 (38.1)	197 (33.2)	
Other/unknown	14 (12.4)	91 (15.3)	
Treatment			
Immunotherapy	59 (52.2)	279 (46.0)	.39
Chemoimmunotherapy	54 (47.8)	314 (53.0)	

Sun et al JAMA Onc

Immune adverse events

NEUROLOGIC
- Posterior Reversible Encephalopathy
- Neuropathy
- Guillian-Barre Syndrome
- Myelopathy
- Autoimmune Encephalitis
- Aseptic Meningitis
- Myasthenia gravis
- Transverse Myelitis
- Non-specific symptoms: headache, tremor, lethargy, memory disturbance, seizure

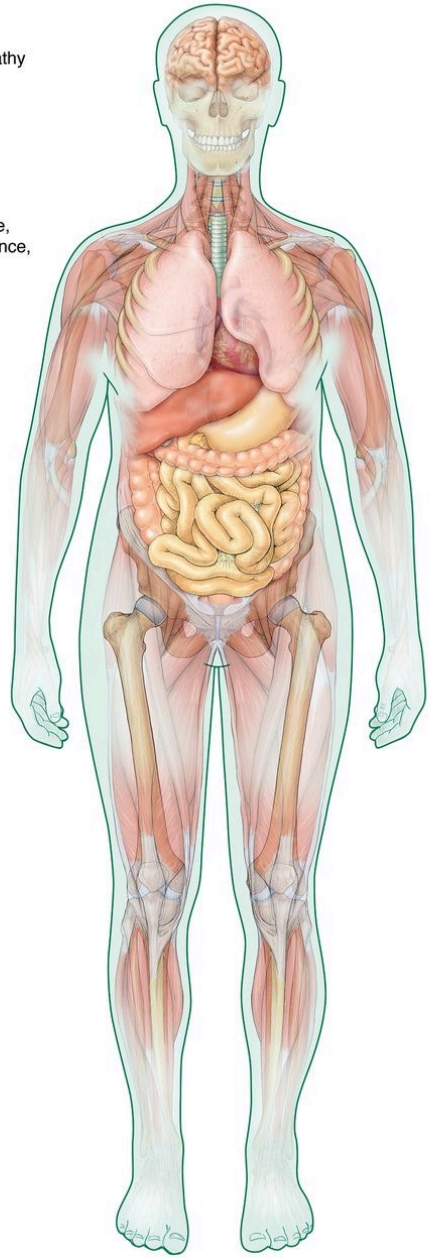
RESPIRATORY
- Cough/dyspnea
- Laryngitis
- Pneumonitis
- Bronchitis
- Pleuritis
- Sarcoid-like granulomatosis

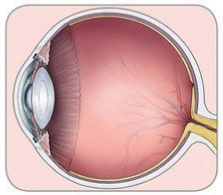
RENAL


- Tubulointerstitial nephritis
- Acute renal failure
- Lupus nephritis
- Granulomatous lesions
- Thrombotic microangiopathy

HEMATOLOGIC
- Autoimmune hemolytic anemia
- Red cell aplasia
- Thombocytopenia
- Leukopenia/Neutropenia
- Acquired hemophilia
- Myelodysplasia

DERMATOLOGIC
- Rash/Pruritis
- Mucositis
- Psoriasis
- Vitiligo
- Bullous pemphigoid
- Steven-Johnson syndrome
- DRESS syndrome



OCULAR


- Uveitis
- Conjunctivitis
- Scleritis, episcleritis
- Optic neuritis
- Blepharitis
- Retinitis
- Peripheral ulcerative keratitis
- Vogt-Koyanogi-Harada

CARDIOVASCULAR
- Myocarditis
- Pericarditis
- Pericardial effusion
- Arrhythmia
- Hypertension
- Congestive heart failure

ENDOCRINE
- Hyper or hypothyroidism
- Hypophysitis
- Adrenal insufficiency
- Diabetes

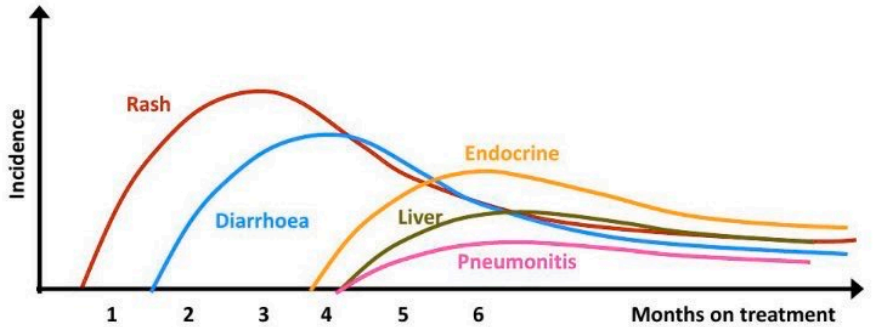
GASTROINTERSTINAL
- Diarrhea
- Gastritis
- Colitis
- Ileitis
- Pancreatitis
- Hepatitis

RHEUMATOLOGIC
- Arthralgias/Myalgias
- Inflammatory Polyarthritis
- PMR-like
- Psoriatic Arthritis
- Oligoarthritis
- Vasculitis
- Sicca Syndrome
- Sarcoidosis
- Inflammatory myositis
- Resorptive bone lesions and fractures

San Antonio Breast Cancer Symposium®, December 10-14, 2019

Toxicities with Immune checkpoint Inhibitors

- **Timing can be highly variable**
- **irAE can occur even months after the end of treatment**
- **Time course might be even more variable with novel combinations**



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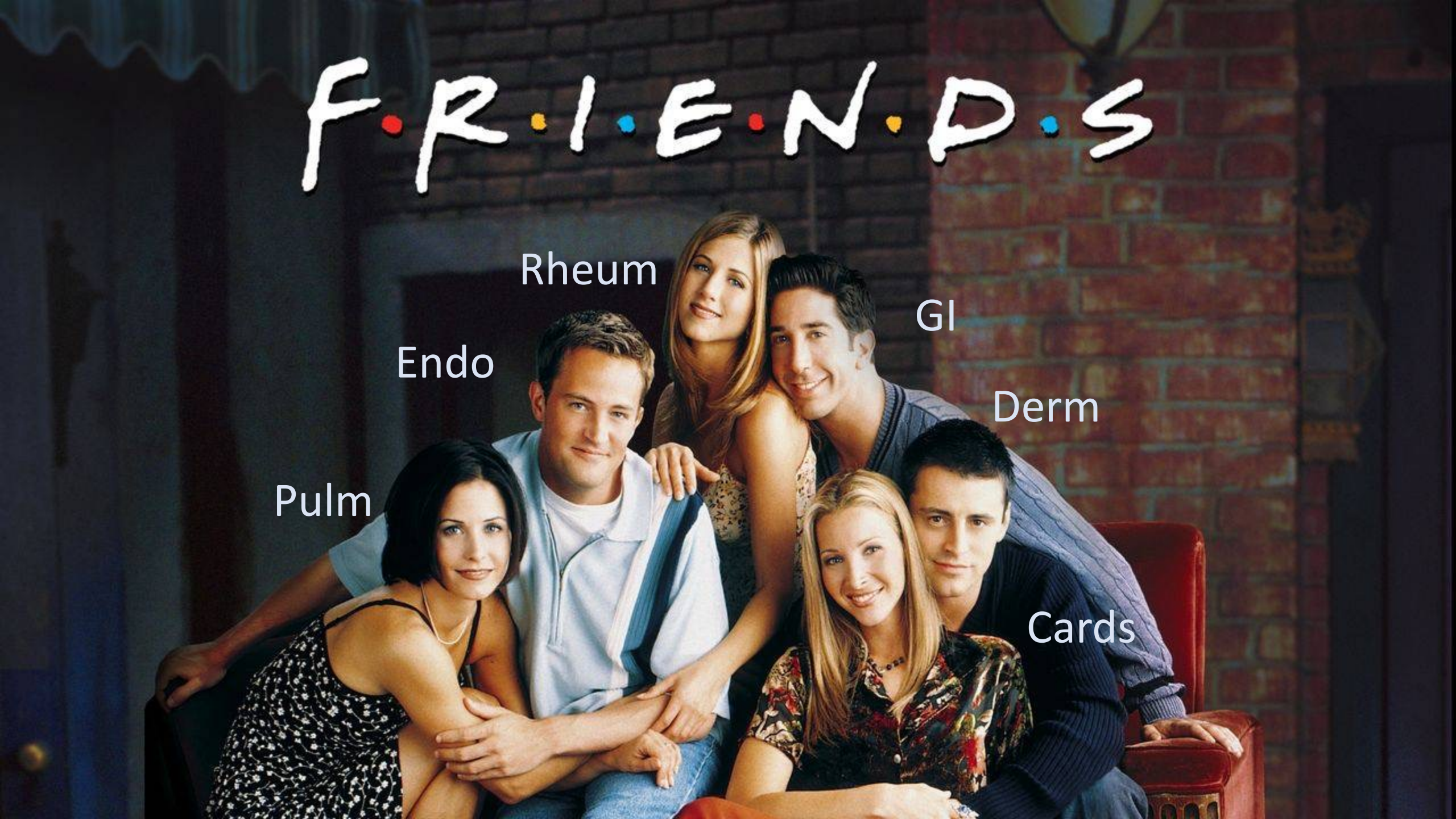
Jamal et al J of Rheumatology

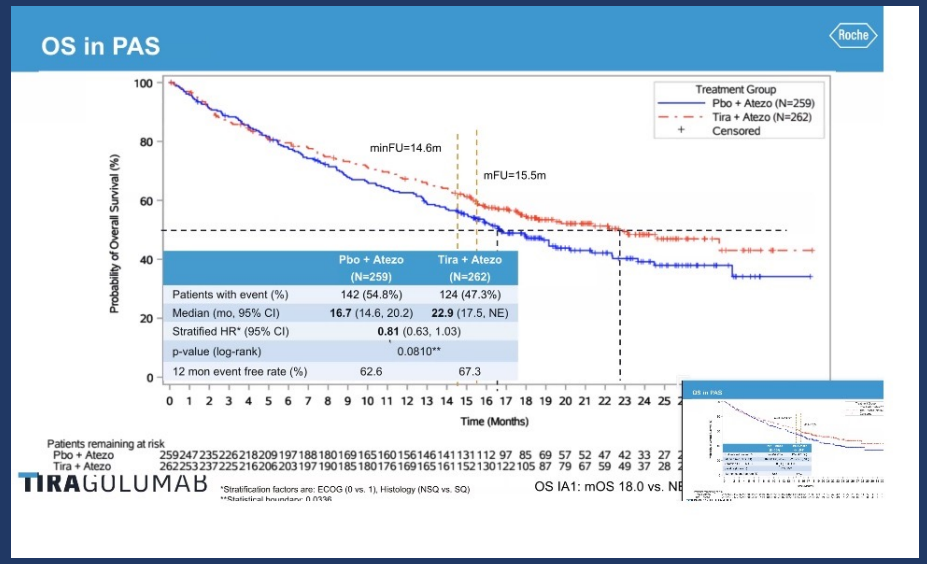
Special populations- can we use IO?

- Baseline co-morbid illness
  - Autoimmune disease
    - Organ affected
    - Severity
    - Need for immune suppressive meds
  - S/p solid organ transplant
    - Which organ
    - Immune suppression
    - Replacement strategies
- Immune paraneoplastic syndrome
  - Generally No-Go
- Prior iAE
  - How severe?
  - Which organ? How managed?
  - What if recurs?

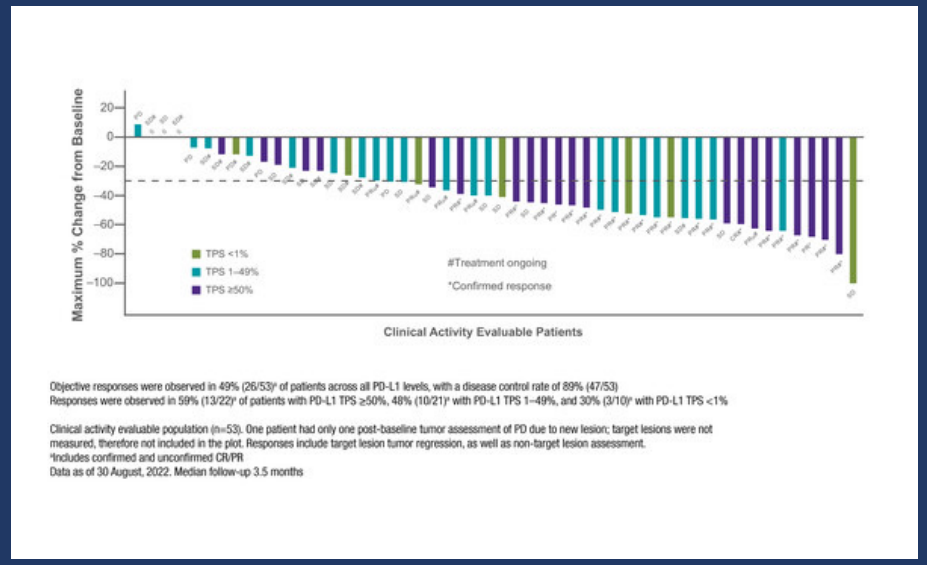

F·R·I·E·N·D·S
Rheum
GI
Endo
Derm
Pulm
Cards

What’s next?

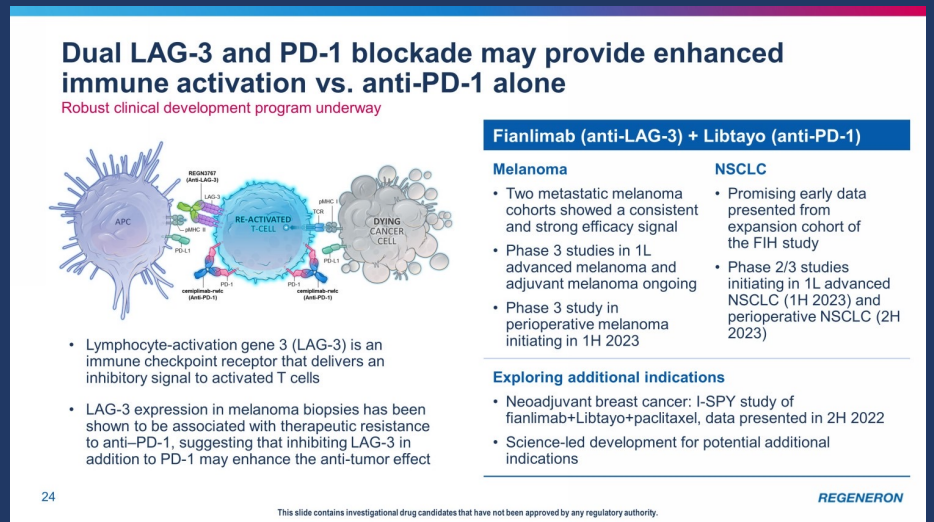
TIGIT



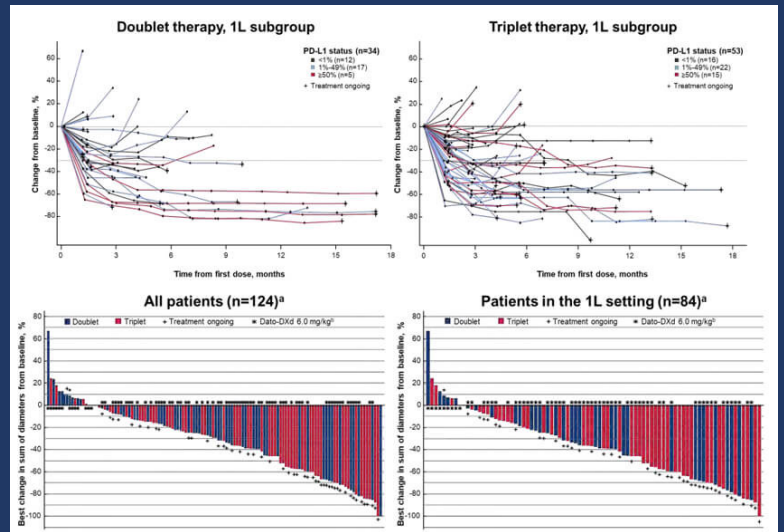
KRYSTAL-7/KRAS



LAG3

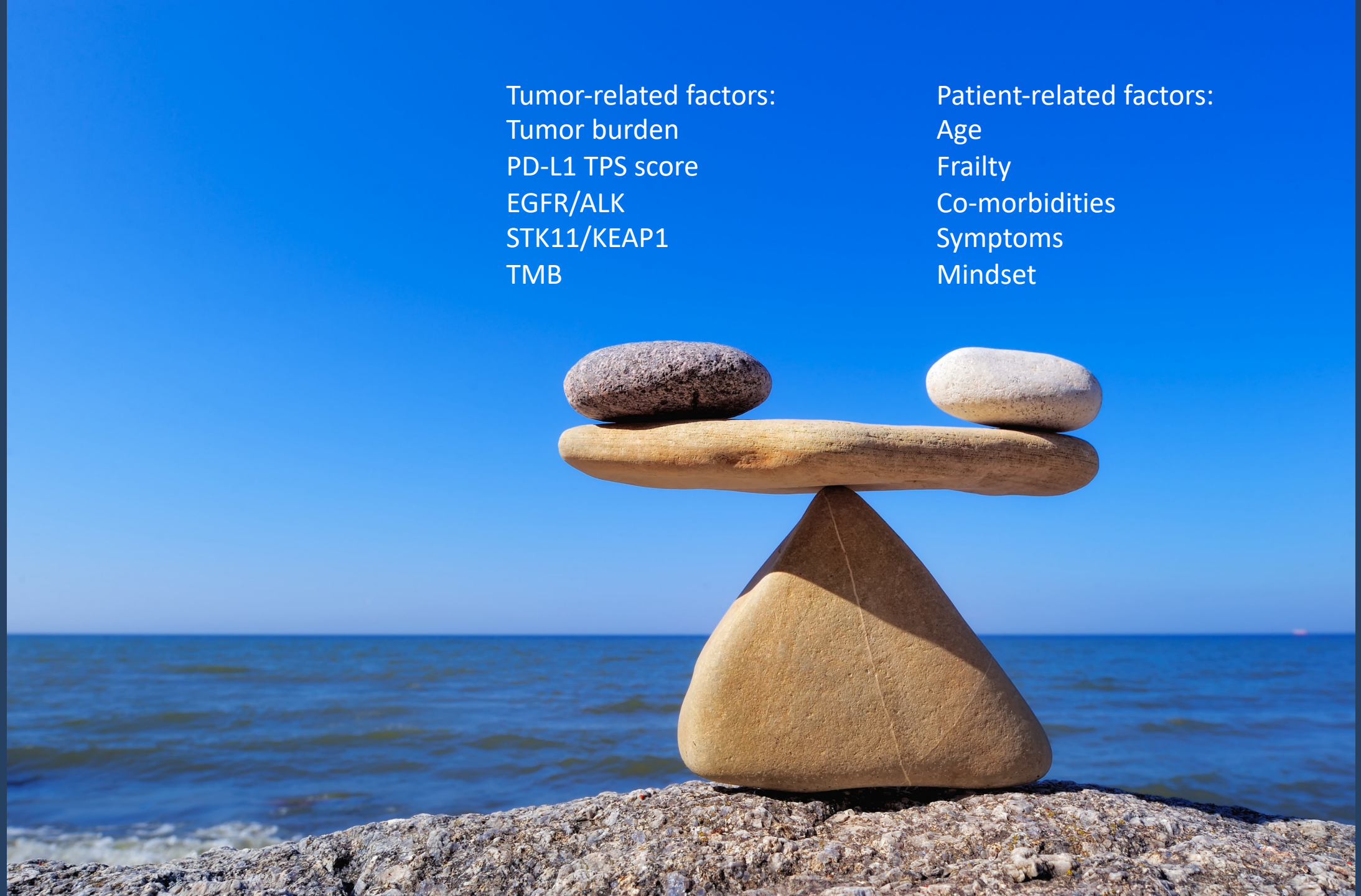


Trop2



Tumor-related factors:
Tumor burden
PD-L1 TPS score
EGFR/ALK
STK11/KEAP1
TMB

Patient-related factors:
Age
Frailty
Co-morbidities
Symptoms
Mindset

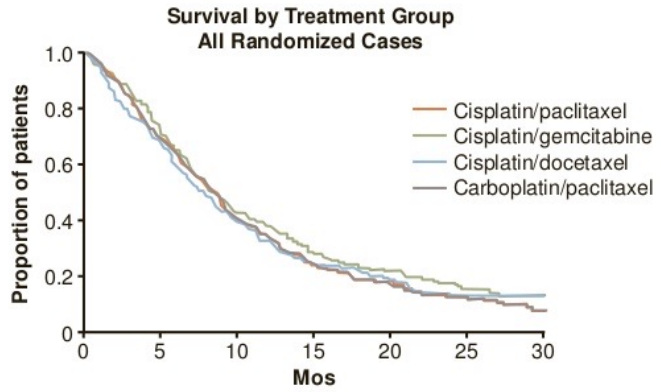


Advanced lung cancer- incurable disease

Advanced lung cancer- ~~i~~curable disease

How it started

ECOG 1594: OS



Schiller JH, et al. N Engl J Med. 2002;346:92-98.

How it is going