BEST PRACTICES IN UNRESECTABLE NON-SMALL-CELL LUNG CANCER

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IDEOlogy Health

Creating Aha! Moments In Healthcare

A Case: Mr. PP

HPI

Mr. PP is a 76yo gentleman who presented with a cough and a 30lb weight loss to his PCP.

PMH

DM2
HTN

SH

Married (39 years)
6 children
Heavy smoker - quit 26yrs ago

Mr. PP

Evaluation:

- ECOG PS 0
- CT/PET/MRI revealed a 5.5cm RLL lesion w/ satellite nodule and mediastinal, SCV, and hilar LAN. Brain negative.
- Path: squamous carcinoma (EBUS), Tempus NGS (*TP53, FAT1, PTEN;* MSS, TMB 13.7 Mut/Mb), PD-L1 0 (22C3)
- Stage IIIC (T3N3M0)

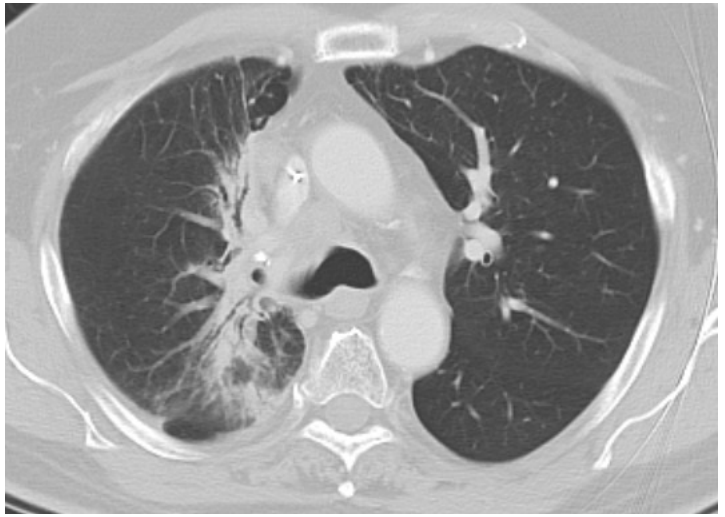
Treatment:

Received carboplatin/paclitaxel and RT f/b enrollment

on a clinical trial. Patients are randomized to durvalumab alone

atezolizumab + tiragolumab (SKYSCRAPER-03)

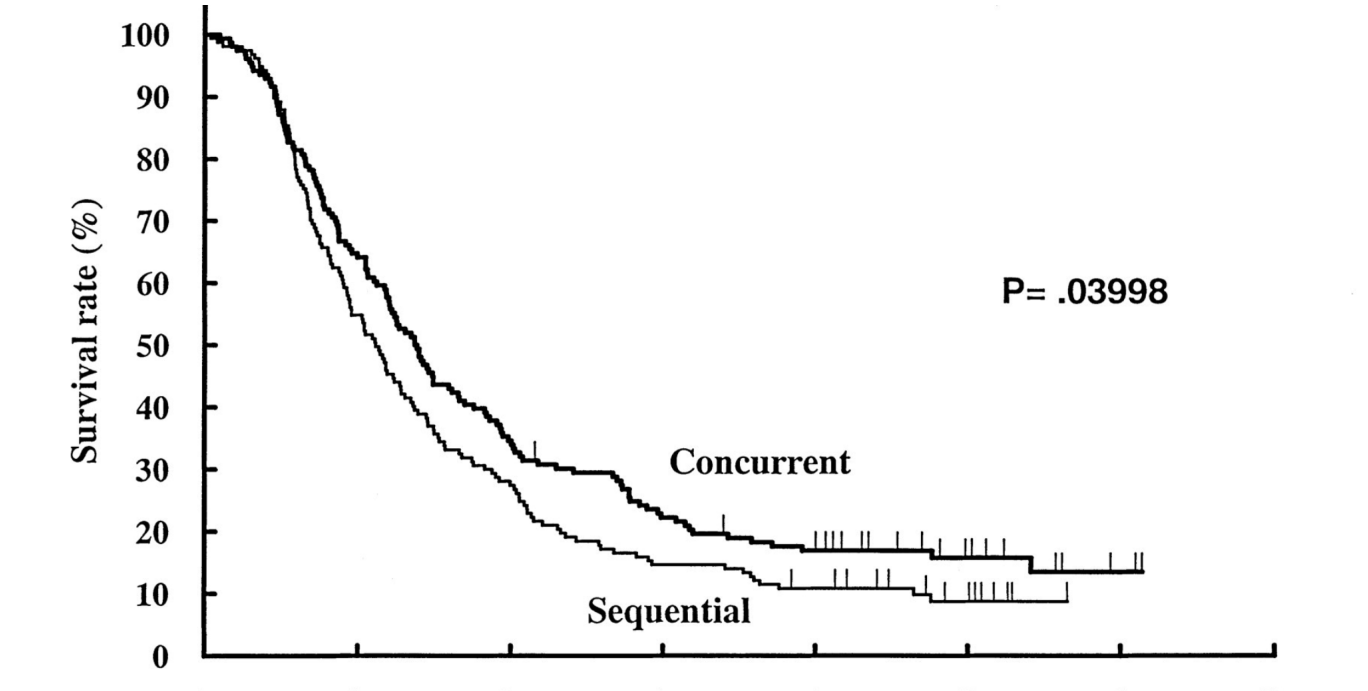
Did well on durvalumab – in surveillance



Outline

- Standard of Care for Unresectable Stage III NSCLC Before PACIFIC
- PACIFIC
- Future Development

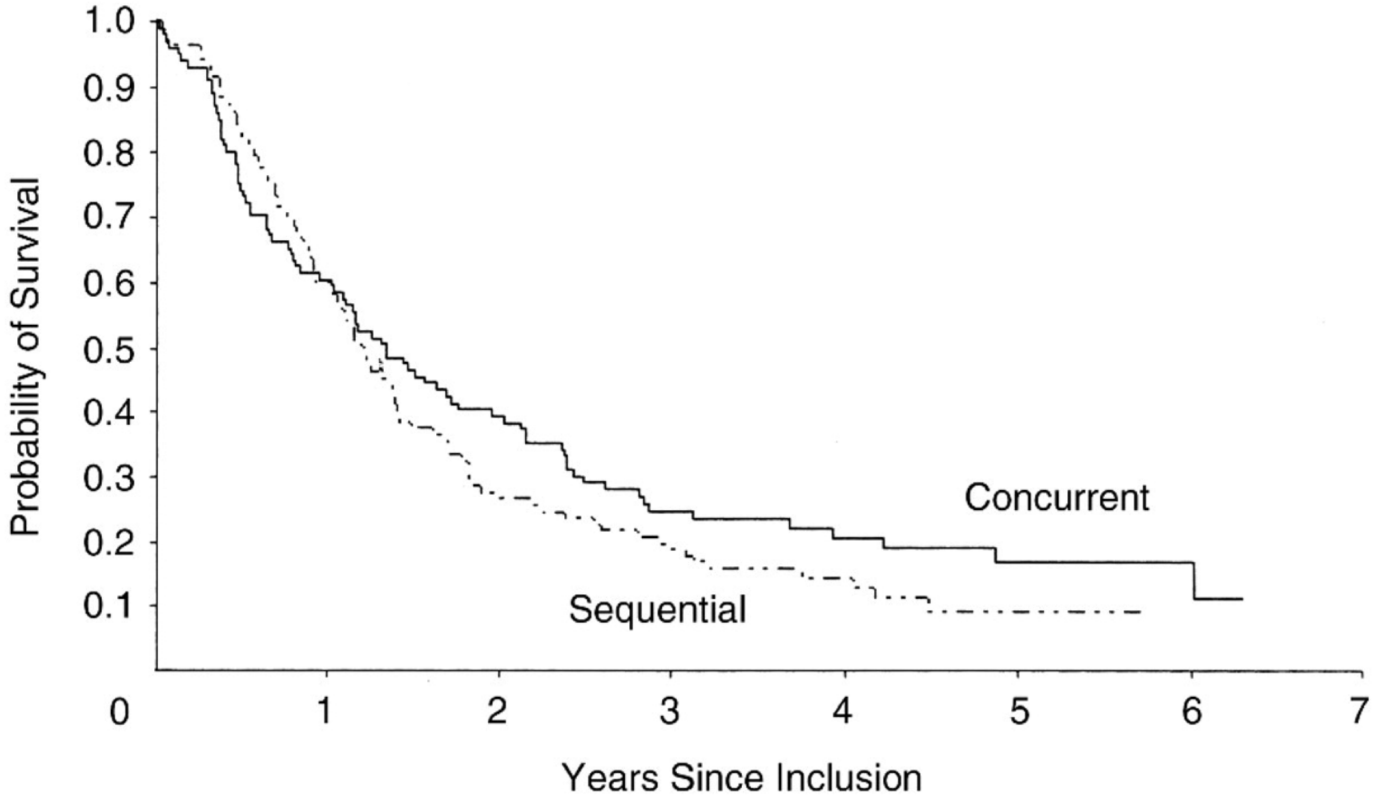
Advances in Stage III NSCLC: Concurrent v. Sequential Chemoradiation



No. of Patients Alive						
Concurrent	156	100	54	34	25	11
Sequential	158	86	43	23	16	7

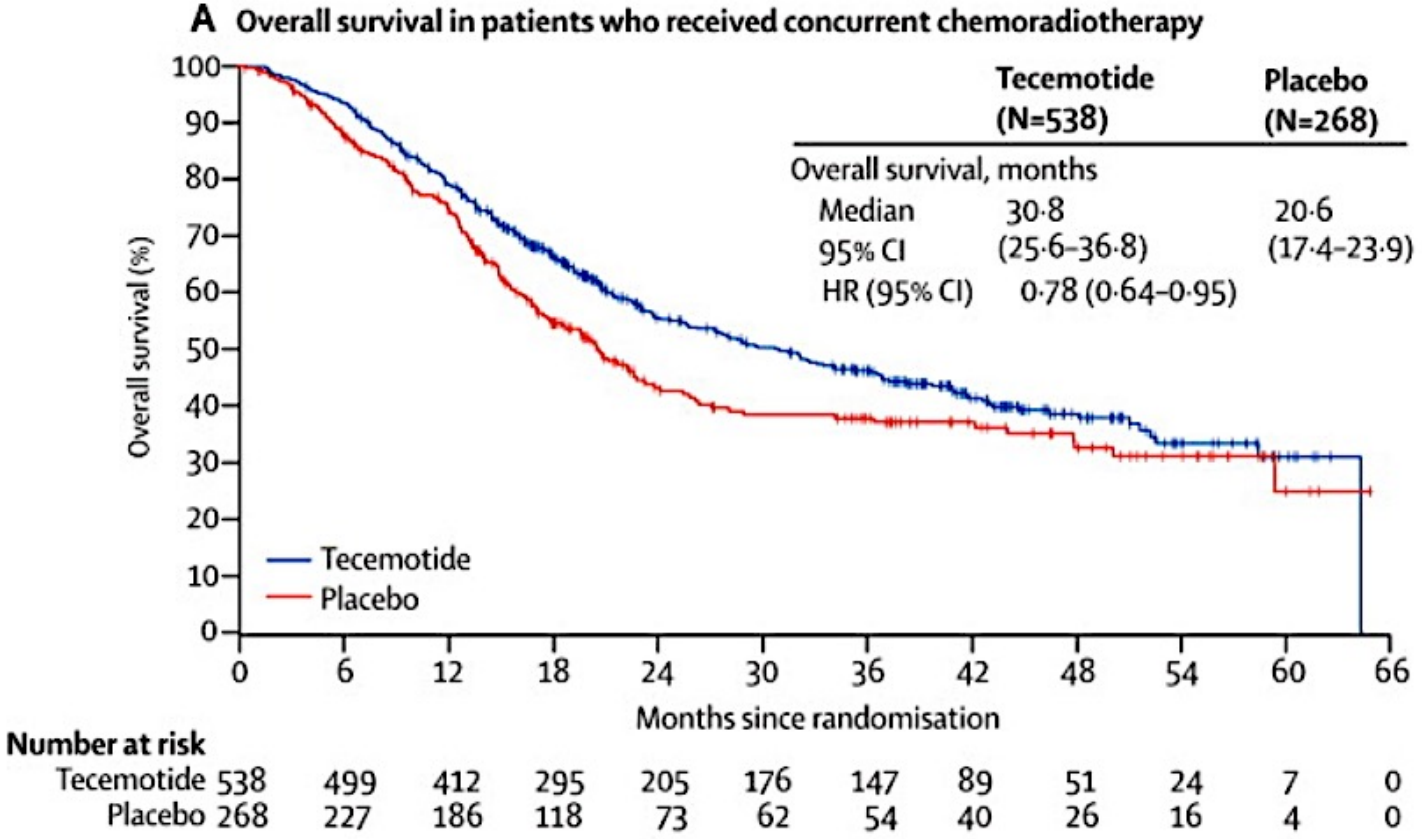
Furuse, JCO 1999

Advances in Stage III NSCLC: Concurrent v. Sequential Chemoradiation



Fournel, JCO 2005

Tecemotide (L-BLP25) v placebo after chemoradiotherapy for stage III NSCLC (START)



Butts, Lancet Onc 2013

PACIFIC

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PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Trial

- Unresectable Stage III NSCLC without progression after definitive platinum-based cCRT* (≥2 cycles)
- 18 years or older
- WHO PS score 0 or 1
- If available, archived pre-cCRT tumor tissue for PD-L1 testing†

Patients enrolled irrespective of PD-L1 status

N = 713 randomized

1–42 days post-cCRT

R

Durvalumab
10 mg/kg q2w for up to 12 months
N = 476

2:1 randomization, stratified by age, sex, and smoking history

Placebo
q2w for up to 12 months
N = 237

Primary endpoints

- PFS (BICR) using RECIST v1.1‡
- OS

Key secondary endpoints

- ORR, DoR, and TTDM (BICR) using RECIST v1.1
- Safety
- Patient-reported outcomes

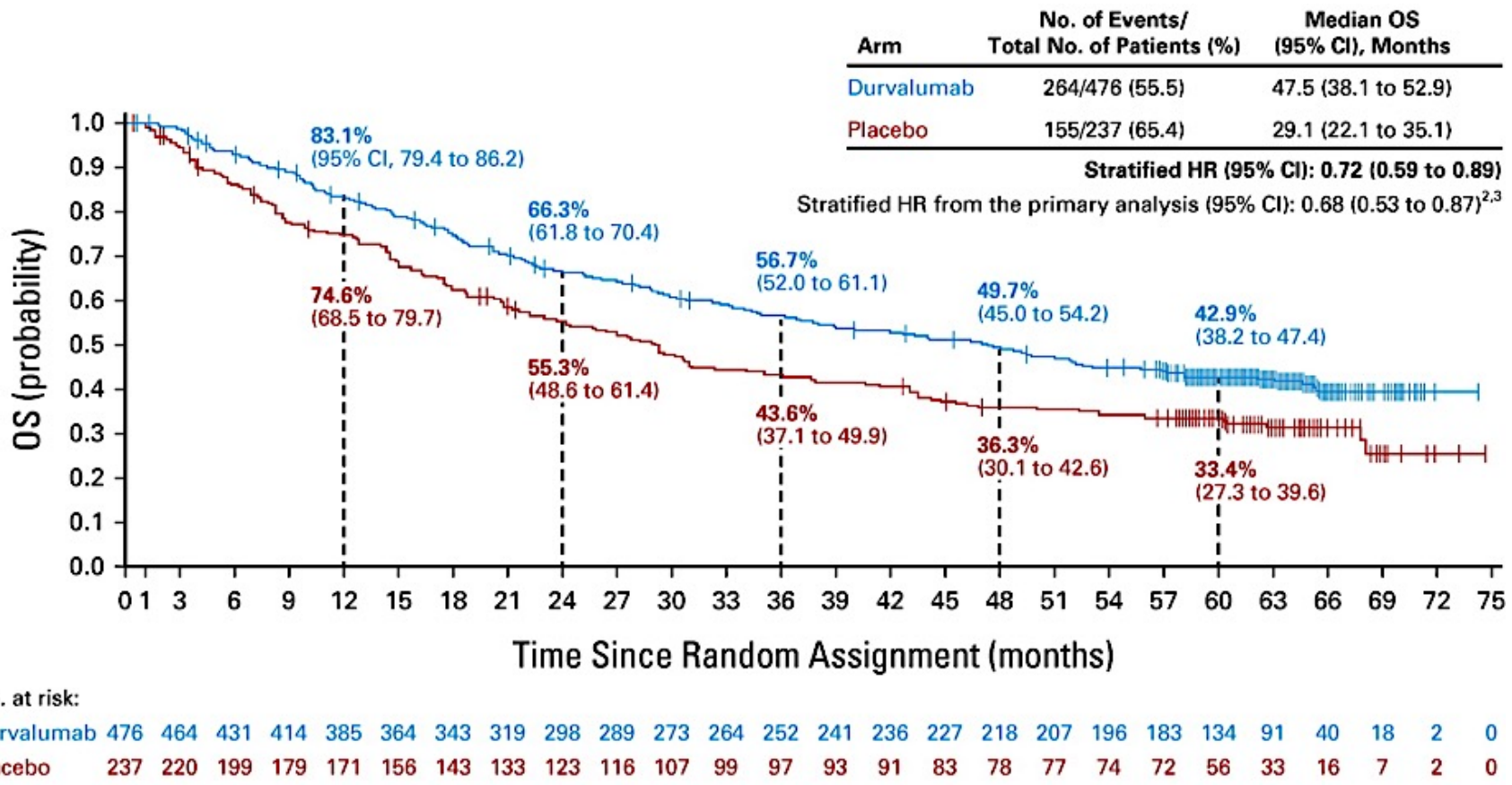
- **Updated analyses of OS and PFS, assessed ~5 years after the last patient was randomized (data cutoff: 11 January 2021; exploratory, post-hoc analysis)**
  - **Treatment effects were estimated using stratified log-rank tests in the ITT population**
  - **Medians and yearly landmark rates were estimated using the Kaplan–Meier method**

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; DoR, duration of response; ITT, intent-to-treat; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PS, performance status; q2w, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization

Dr. David R. Spigel

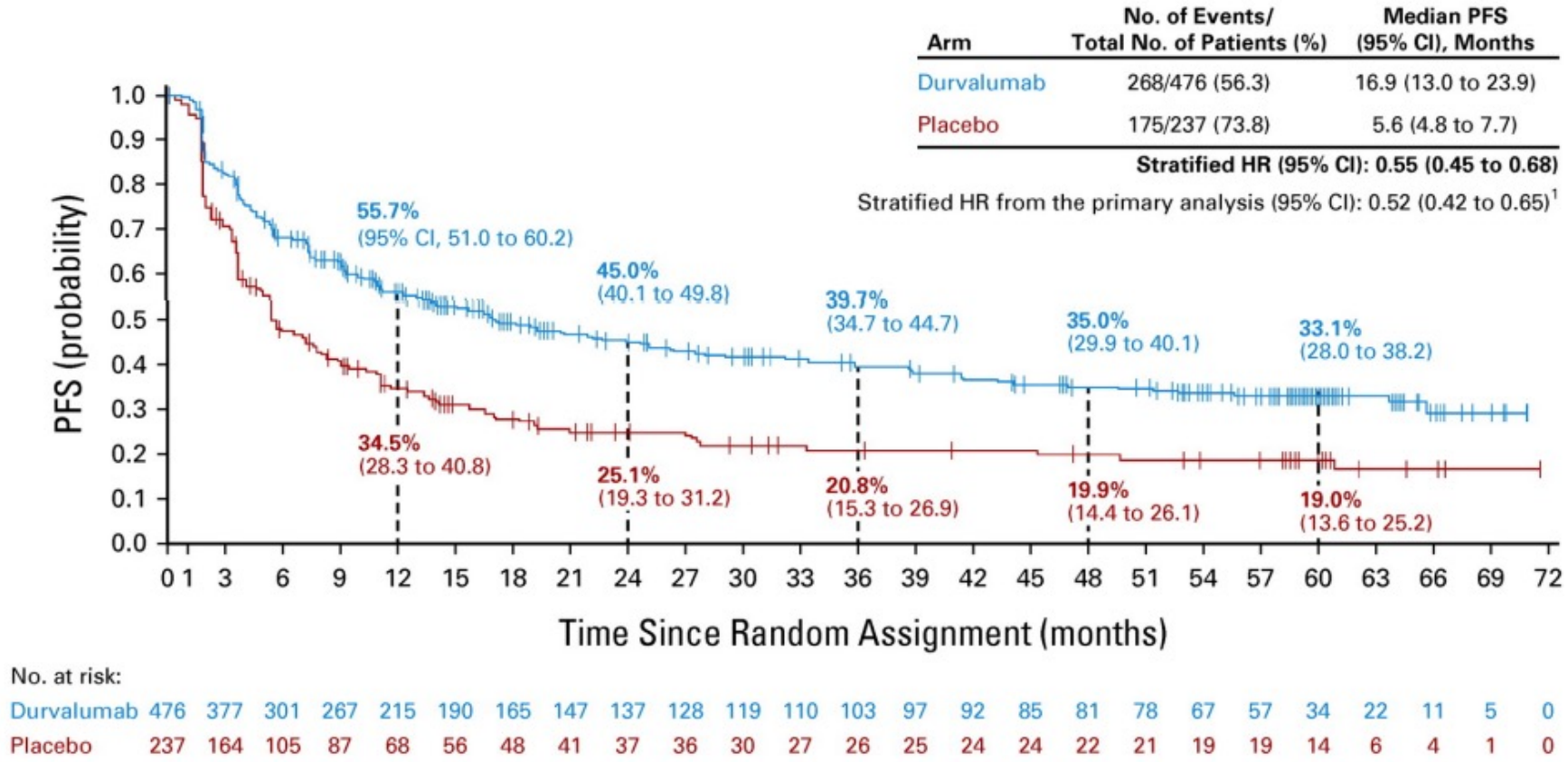
NCT02125461. *Radiation dosage typically 60–66 units of gray in 30–33 fractions. †Using the Ventana SP263 immunohistochemistry assay. ‡Defined as the time from randomization to the date of objective disease progression or death by any cause in the absence of progression

PACIFIC OS



Spigel, JCO 2022

PACIFIC PFS



Spigel, JCO 2022

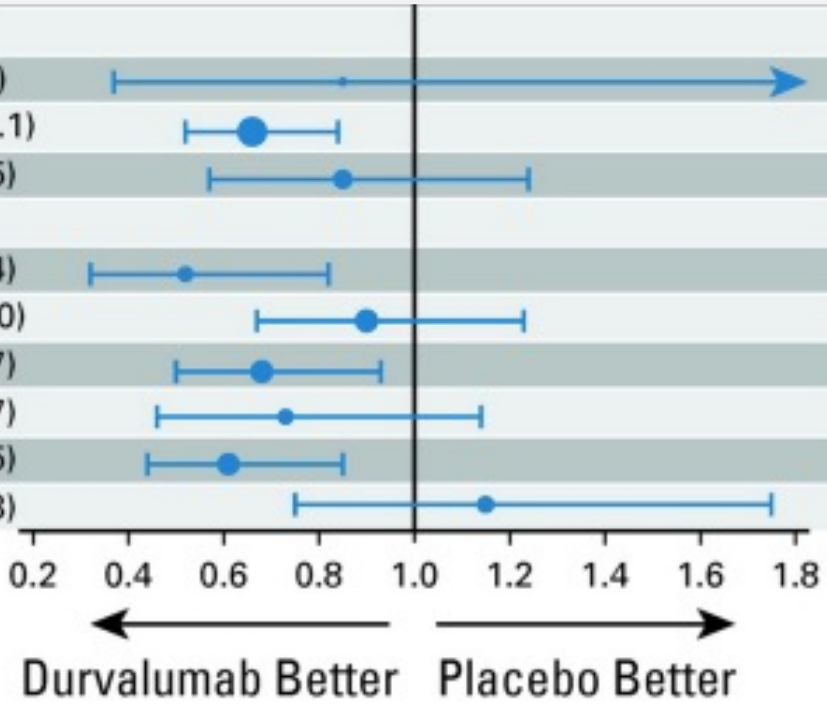
PACIFIC: AEs (All Grade)

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	145 (30.5)	222 (94.9)	61 (26.1)
Cough	167 (35.2)	2 (0.4)	59 (25.2)	1 (0.4)
Fatigue	114 (24.0)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Radiation pneumonitis†	96 (20.2)	7 (1.5)	37 (15.8)	1 (0.4)
Diarrhea	88 (18.5)	3 (0.6)	46 (19.7)	3 (1.3)
Pyrexia	72 (15.2)	1 (0.2)	22 (9.4)	0
Nausea	68 (14.3)	0	31 (13.2)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Pneumonia	63 (13.3)	21 (4.4)	18 (7.7)	9 (3.8)
Pneumonitis†	60 (12.6)	9 (1.9)	18 (7.7)	4 (1.7)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Upper respiratory tract infection	59 (12.4)	1 (0.2)	24 (10.3)	0
Pruritus	59 (12.4)	0	12 (5.1)	0
Rash	58 (12.2)	1 (0.2)	18 (7.7)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	26 (11.1)	8 (3.4)

Antonia, NEJM 2018

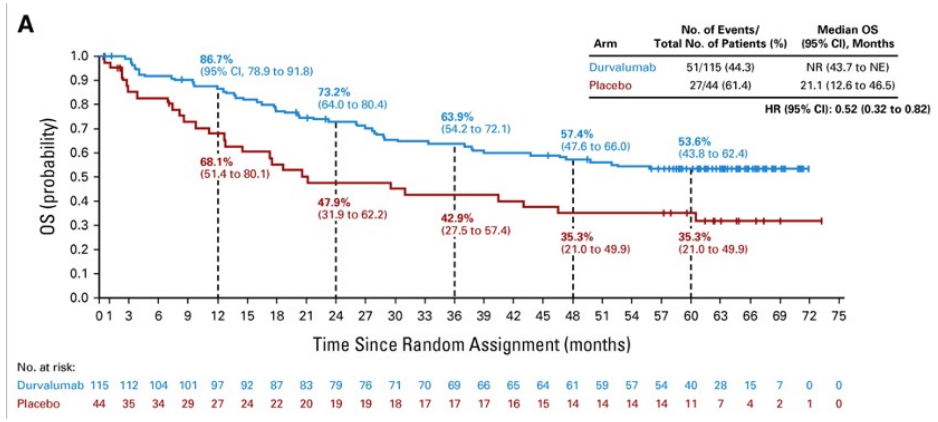
PACIFIC *EGFR*, *ALK*, and PD-L1 Subsets

EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)

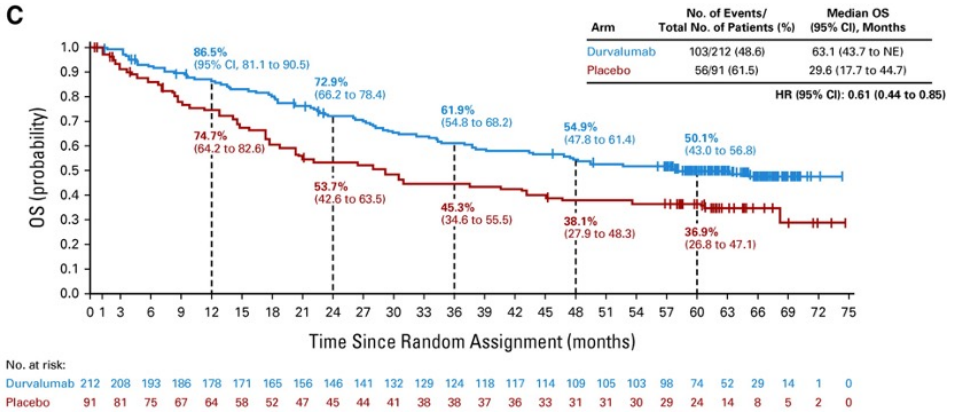


Spigel, JCO 2022

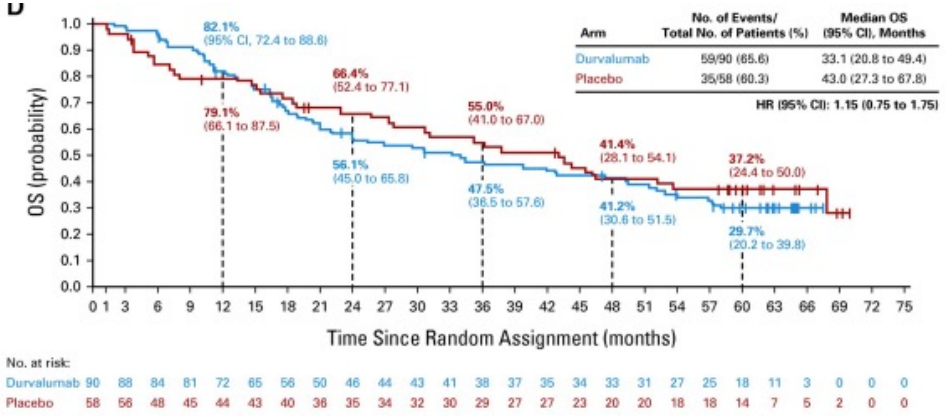
PACIFIC PD-L1 Subsets



PD-L1 >25%



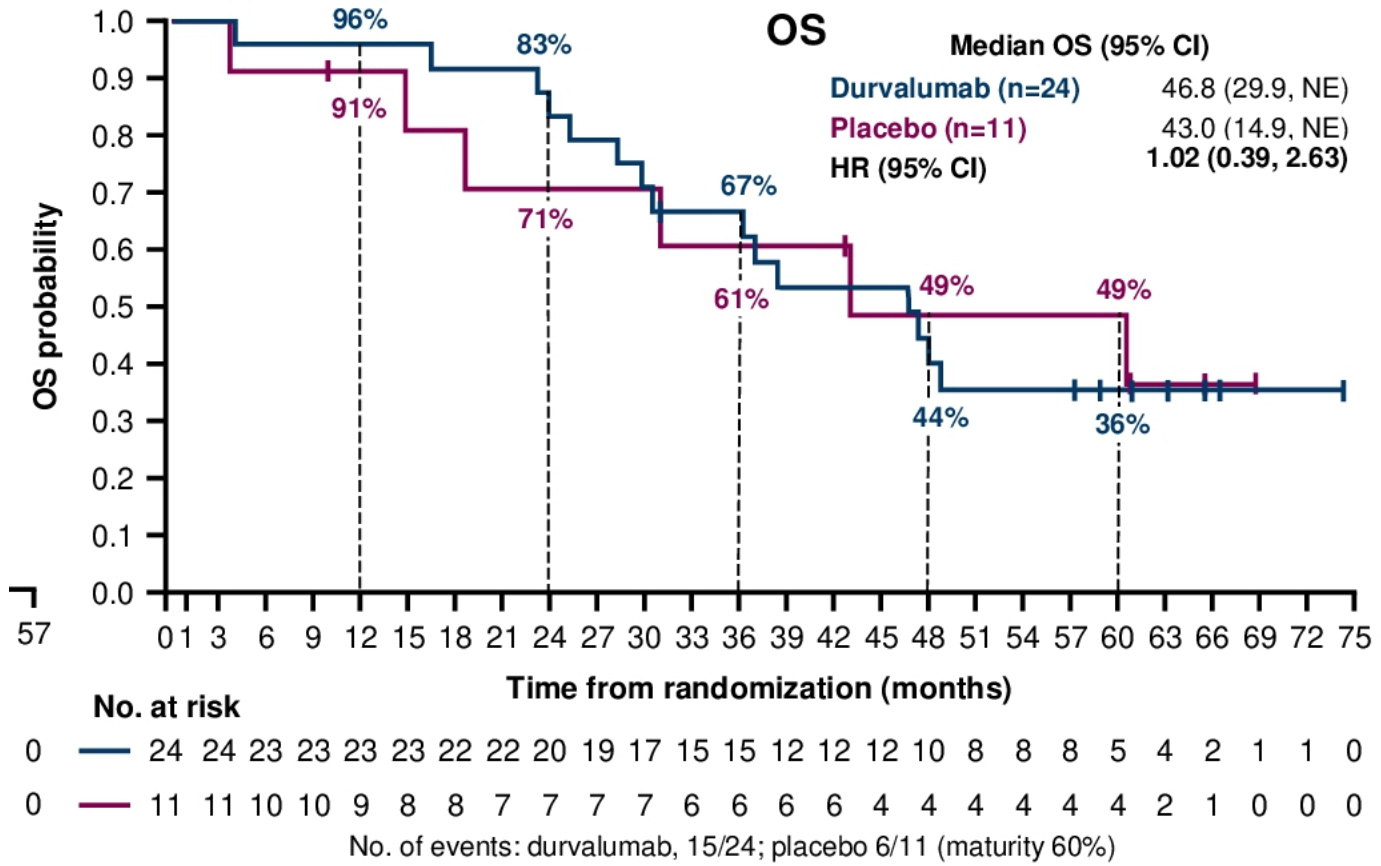
PD-L1 >1%



PD-L1 <1%

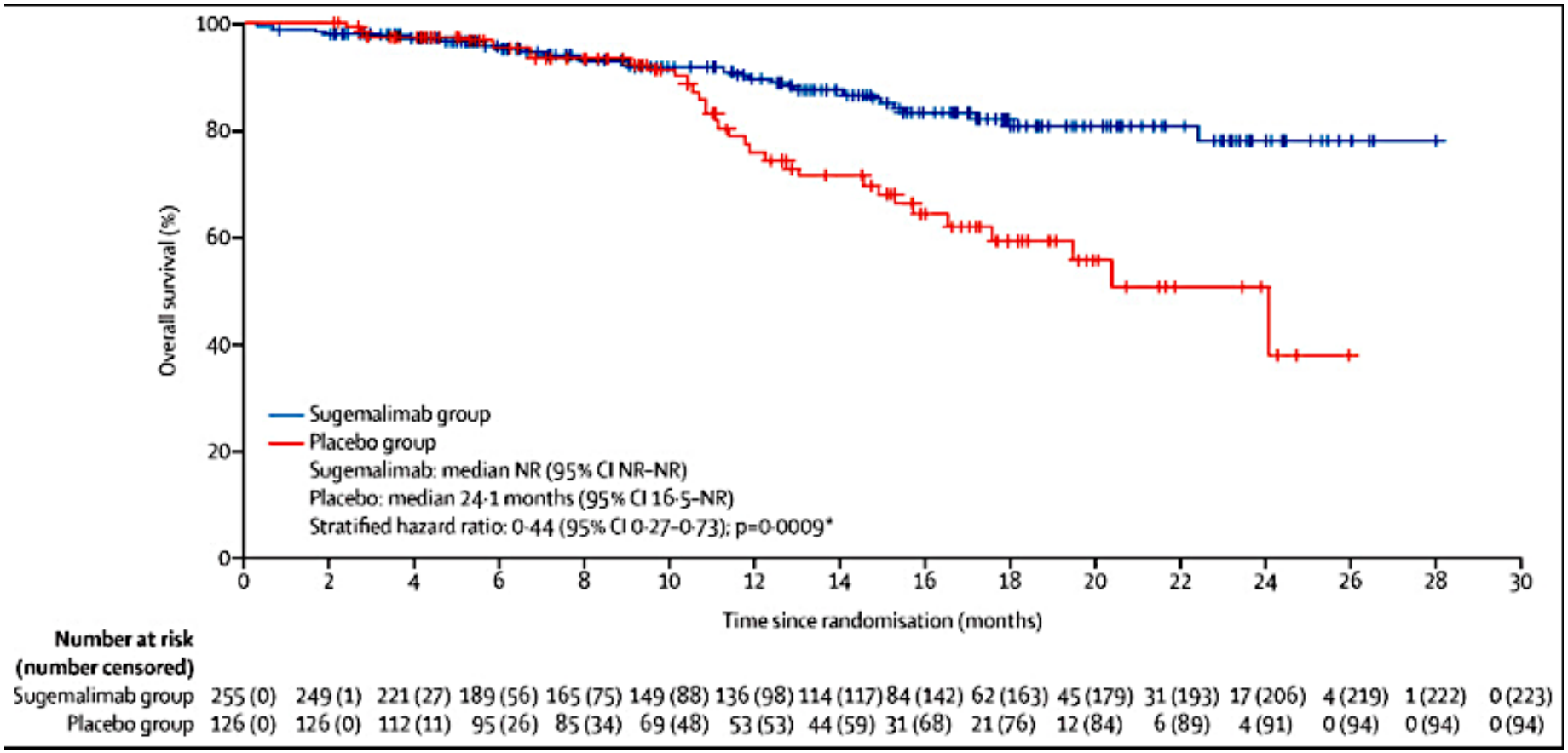
Spigel, JCO 2022

PACIFIC *EGFR* Subset (*post hoc*)



Naidoo, ASCO 2022

GEMSTONE-301



Zhou, Lan Onc 2022

FUTURE DEVELOPMENT IN UNRESECTABLE STAGE III NSCLC

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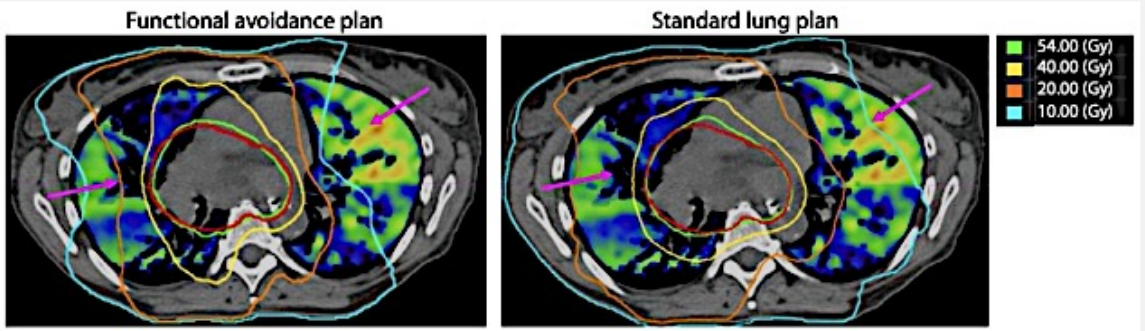
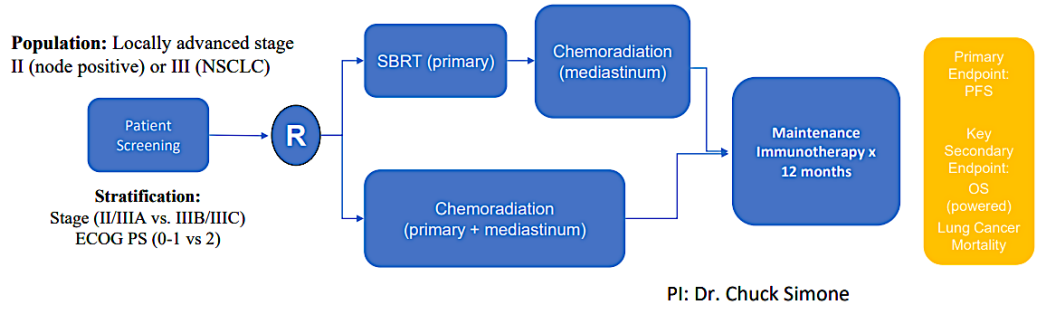
Advances in Radiation

- Proton Therapy (RTOG 1308)
- Esoph sparing/Ventilation Mapping
- FLASH
- RT + Drug Synergies

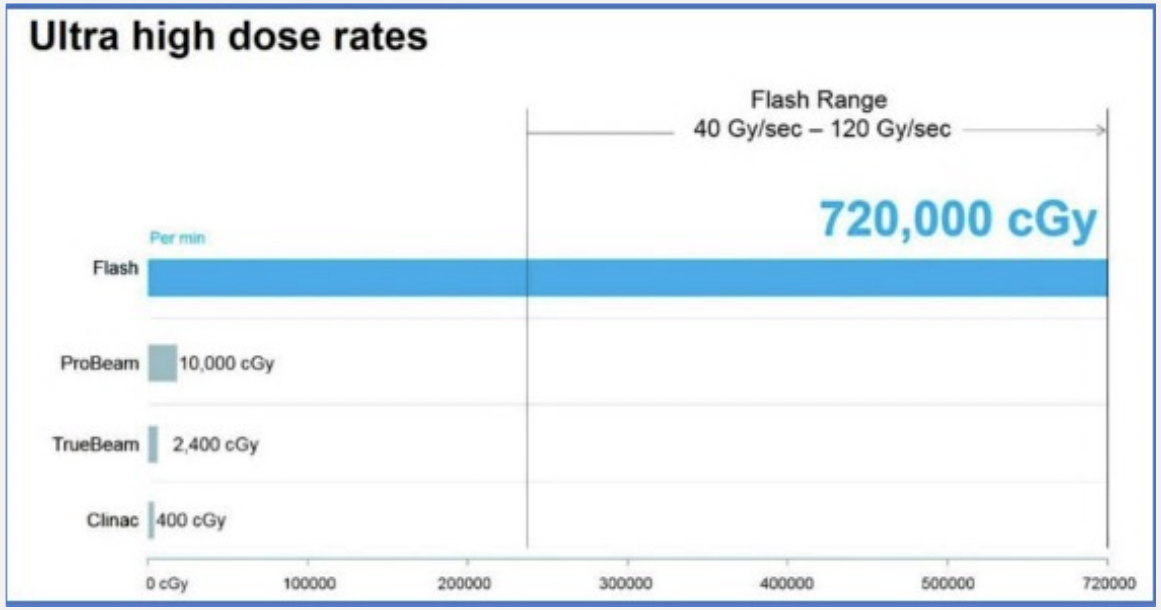


NRG ONCOLOGY™ LU008 Schema: Phase III



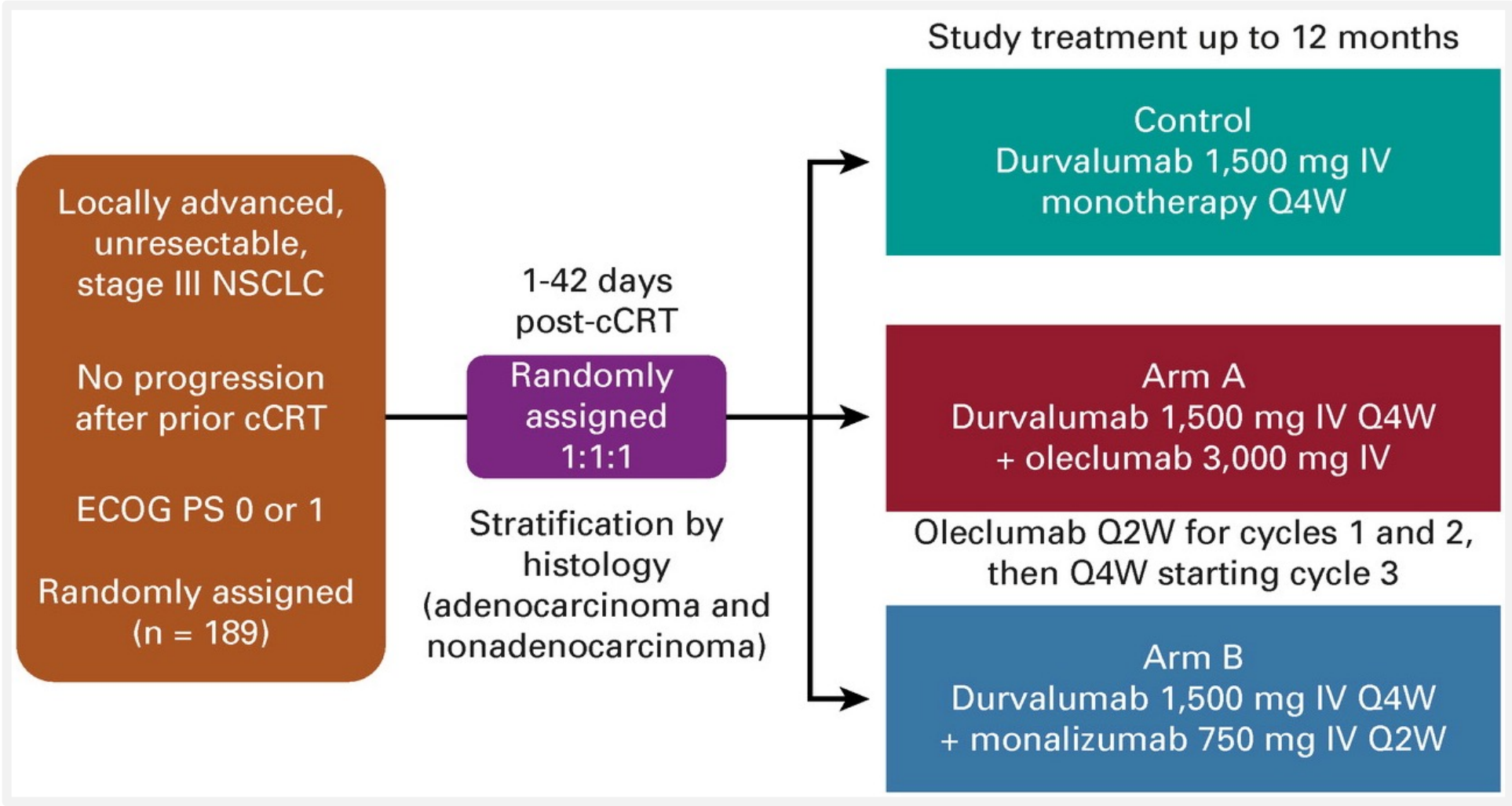
PI: Dr. Chuck Simone

- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
- Experimental arm: SBRT to the primary (standard BED ≥100 Gy dose regimen) → chemoradiation to mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
  - **SBRT to primary tumor:**
    - 3 fractions to 54 Gy (BED10 of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED10 of 112.5 Gy) [peripheral or central]
    - 5 fractions to 50 Gy (BED10 of 100 Gy) [central] or to 60 Gy (BED10 of 132 Gy) [peripheral or central]



Vinogradskiy, IJRO 2021
Fauvodon, Sci Trans Med 2014

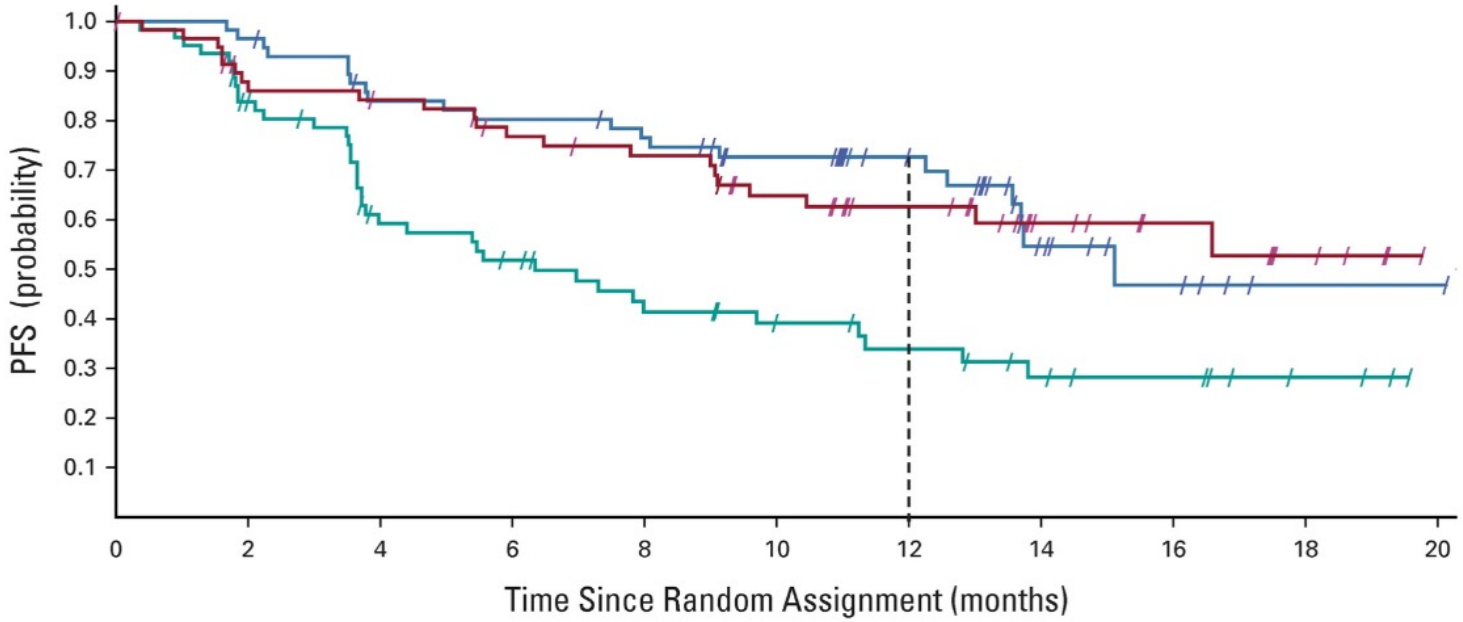
Advances in Immunotherapy: COAST



Herbst, JCO 2022

COAST PFS

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

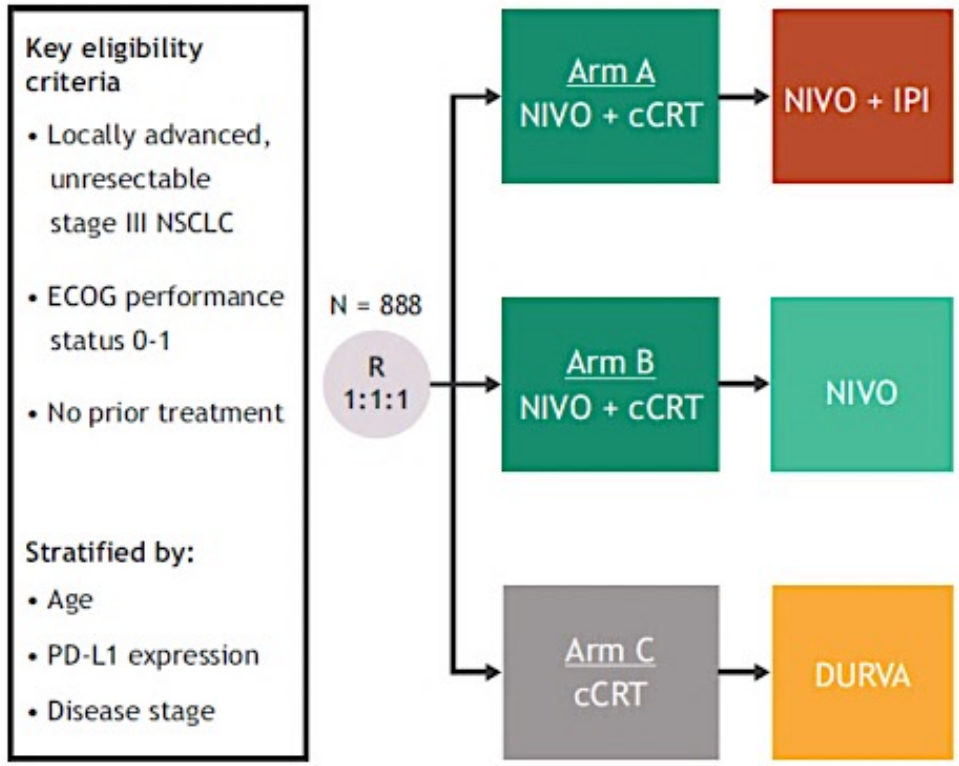


No. at risk:											
Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

Herbst, JCO 2022

Checkmate 73L

A phase 3 study comparing nivolumab plus concurrent CRT followed by nivolumab ± ipilimumab versus cCRT followed by durvalumab for previously untreated, locally advanced stage III NSCLC

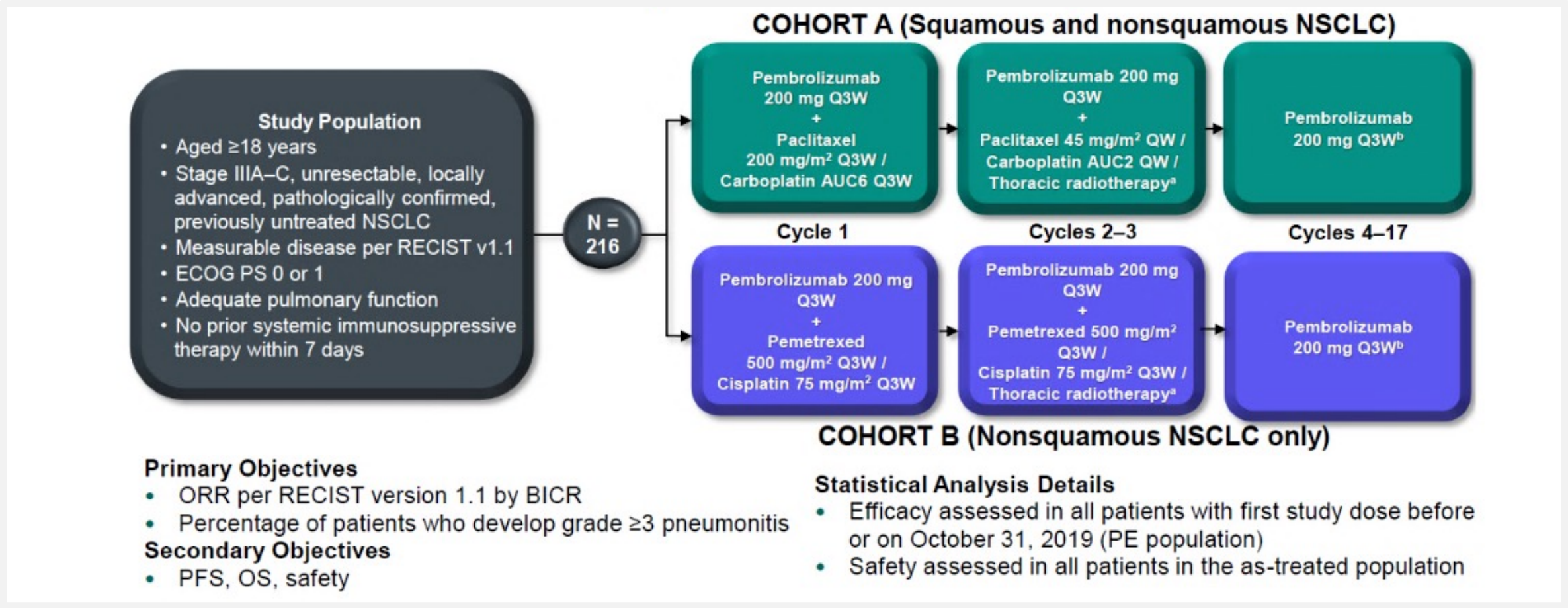


Primary endpoints:

NIVO + cCRT followed by NIVO + IPI (Arm A) vs cCRT followed by DURVA (Arm C)

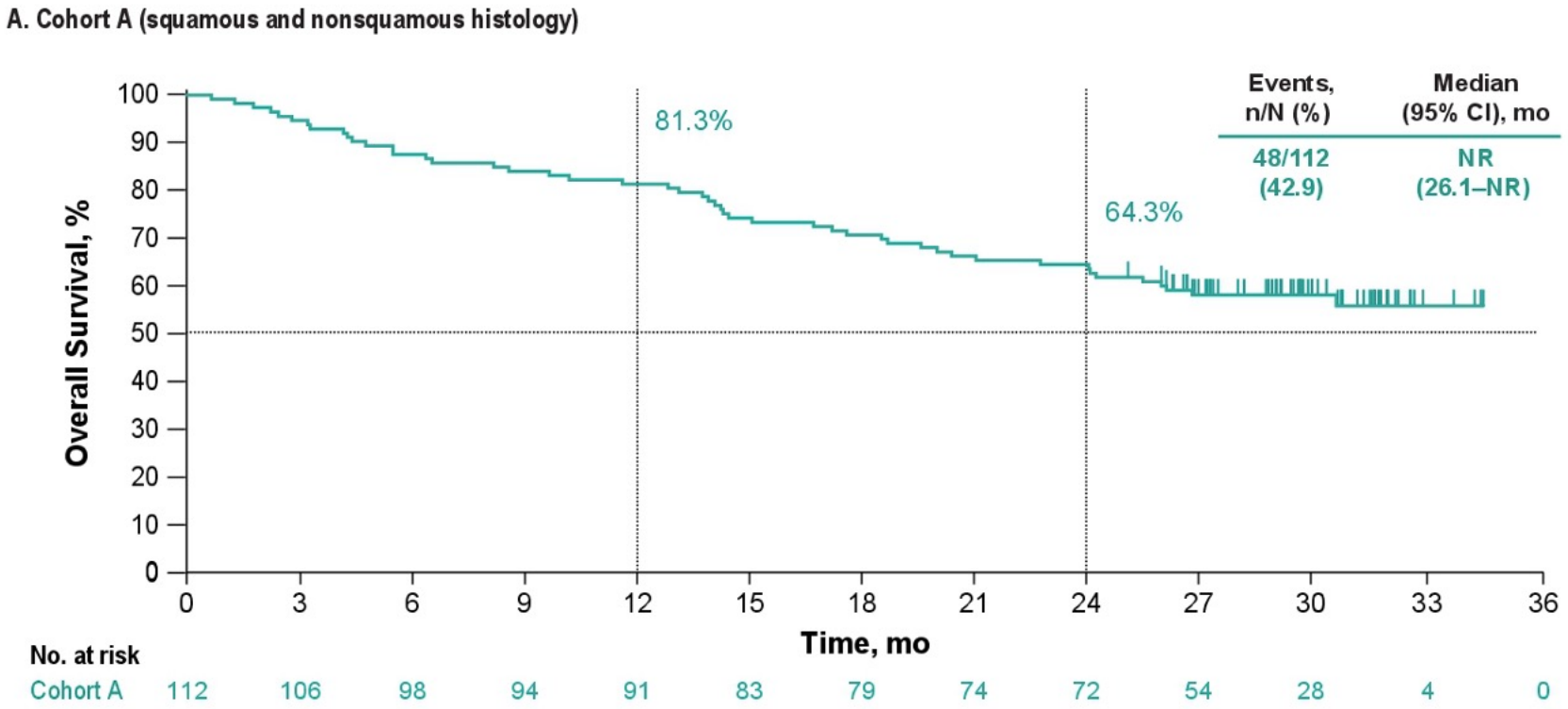
- PFS
- OS

KEYNOTE 799



Reck, ASCO 2022

KEYNOTE 799 – Overall Survival



Reck, ASCO 2022

KEYNOTE 799 – Safety

Table 4. Adverse event summary

AE, n (%)	Cohort A[a] (n = 112)	Cohort B[b] (n = 102)
Grade ≥3 pneumonitis[c]	9 (8.0)	7 (6.9)
Treatment-related AEs	105 (93.8)	99 (97.1)
Grade 3–5	72 (64.3)	52 (51.0)
Occurring in >10% of patients in either cohort		
Neutropenia	18 (16.1)	10 (9.8)
Anemia	12 (10.7)	4 (3.9)
Led to death	4 (3.6)[d]	1 (1.0)[e]
Led to discontinuation of any treatment component	38 (33.9)	21 (20.6)
Immune-mediated AEs and infusion reactions[f]	58 (51.8)	46 (45.1)
Grade 3–5	18 (16.1)	9 (8.8)
Occurring in >5% of patients in either cohort		
Pneumonitis	7 (6.3)	6 (5.9)
Led to death	4 (3.6)[d]	1 (1.0)[e]
Led to discontinuation of any treatment component	21 (18.8)	12 (11.8)

[a]Squamous and nonsquamous histology.
[b]Nonsquamous histology only.
[c]Coprimary endpoint; includes immune-mediated AE of "pneumonitis" and the Medical Dictionary for Regulatory Activities (MedDRA) preferred term of "radiation pneumonitis".
[d]4 patients died due to treatment-related pneumonitis.
[e]1 patient died due to treatment-related interstitial lung disease.

Reck, ASCO 2022

Ongoing Phase III Trials in Unresectable NSCLC

NCT03521154 (LAURA)

Osimertinib after ChemoRT in EGFRm

NCT04513925 (SKYSCRAPER-03)

Atezolizumab + Tiragolumab (Anti-TIGIT Ab) v. Durvalumab after ChemoRT

NCT04951635

Almonertinib (3rd-Gen EGFR Inhibitor) after ChemoRT in EGFRm

NCT05221840 (PACIFIC-9)

Oleclumab (Anti-CD73 Ab) + Durvalumab v. Monalizumab (NKG2A Ab) + Durvalumab after ChemoRT

NCT03519971

Concurrent Durvalumab and ChemoRT

Ongoing Phase III Trials in Unresectable NSCLC

NCT05211895 (PACIFIC-8)

Durvalumab + Domvanalimab (Anti-TIGIT Ab) after ChemoRT

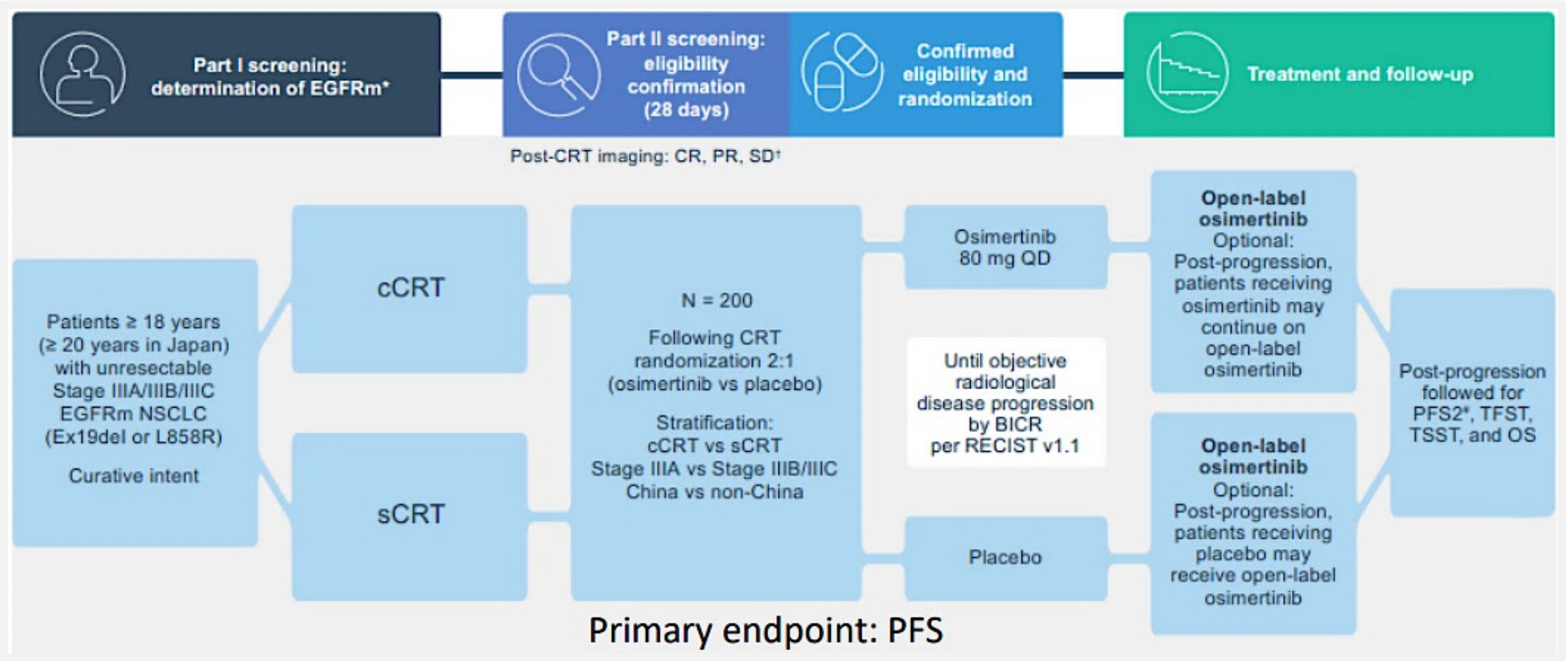
NCT04866017

Tislelizumab (Anti-PD1) + Ocimerlimab (Anti-TIGIT Ab) v. Tislelizumab v. Durvalumab after ChemoRT

NCT04380636 (KEYLYNK-012)

Pembrolizumab + Concurrent ChemoRT followed by Pembrolizumab +/- Olaparib

LAURA



Lu, ESMO 2020

ctDNA and Disease Monitoring

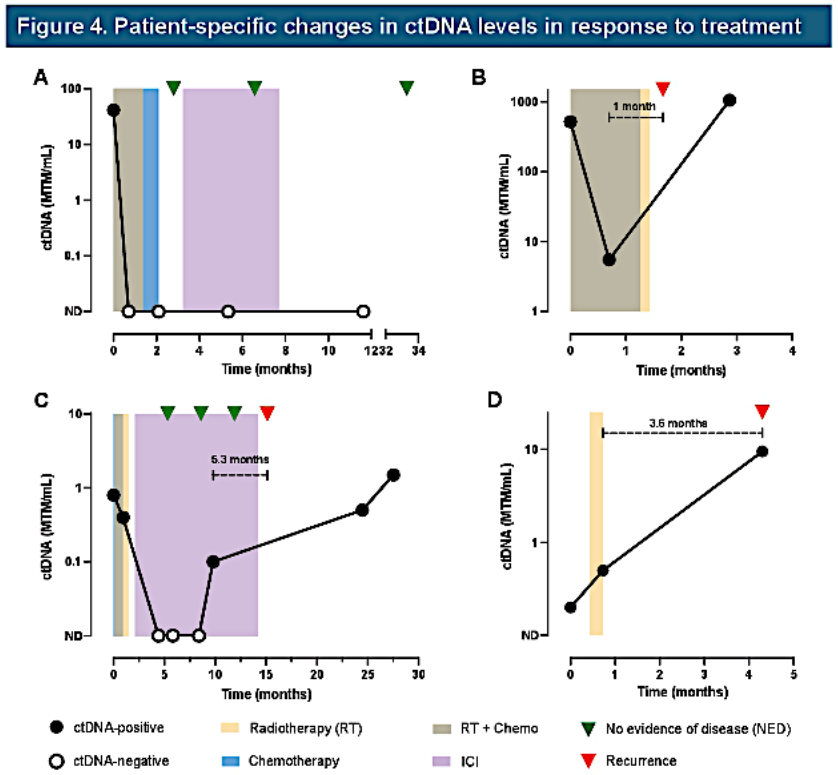
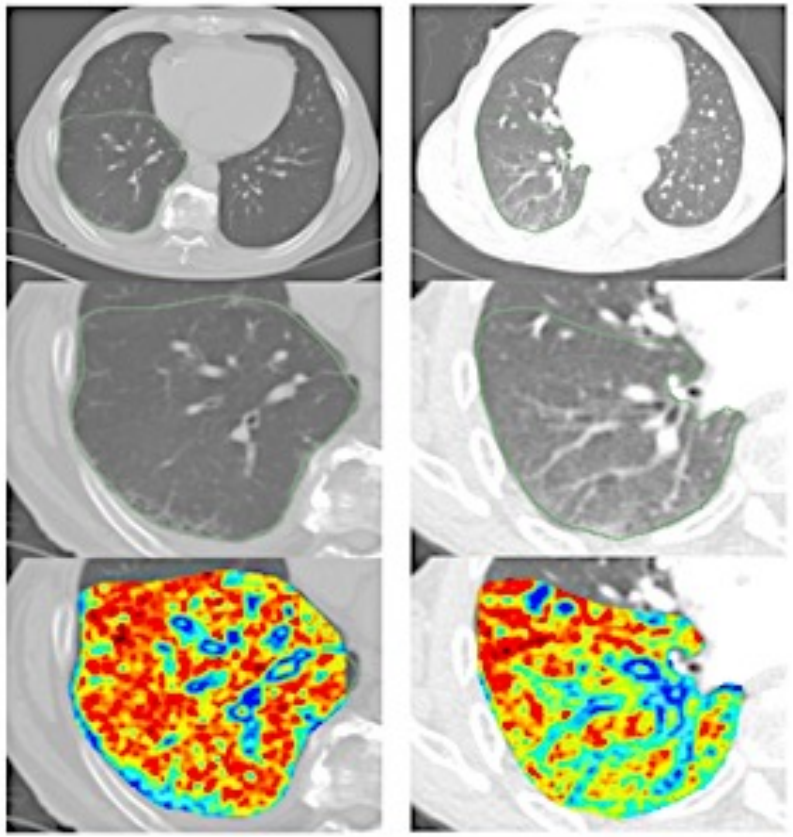


Figure 4. For stage I-III NSCLC patients undergoing RT+/- chemotherapy, ctDNA serves as a prognostic biomarker for disease progression. **A**. ctDNA clearance indicates response to RT+/- chemotherapy. **B-D**. ctDNA detection at the end of treatment or during follow-up period precedes radiographic disease recurrence. RT: radiotherapy; ICI: immune checkpoint inhibitors.

- ctDNA detection in patients with stage I-III NSCLC undergoing definitive RT +/- chemotherapy/immunotherapy is feasible and showed a baseline detection rate of 82%.
- Post-definitive RT ctDNA status is highly prognostic of DRFS at single time point (HR=19.9; p=0.007) and longitudinally (p=0.0002; sensitivity=100%, specificity=100%).
- ctDNA can detect disease progression with an average lead-time of 5.4 months over radiographic imaging. When monitored serially, ctDNA detection at any time point is a preditor of recurrence and can identify patients who may benefit from treatment intensification.
- In univariate and multivariate analyses, ctDNA detection at post-RT time point was a strong prognostic factor associated with DRFS.

Lebow, ASCO 2022

Radiomics and Pneumonitis



(above): Segmented pneumonitis regions and heat map of Haralick entropy feature in the post-treatment CT scans for IOP (first column) and RTP (second column) patients. The texture heat maps appear to suggest higher textural entropy values for IOP compared with the RTP.

Delasos, ASCO 2022

Summary

- CRT f/b Durvalumab is SOC in Unresectable Stage III NSCLC
- IO requires careful selection and monitoring for pneumonitis
- PD-L1 Prediction of IO Benefit is Unclear
- Many Ongoing Studies: Concurrent IO and CRT, New IO Combinations, and Osimertinib instead of IO in Patients with *EGFRm*