ASCO Update Lungenkarzinom

PD Dr. G Chakupurakal

Praxis für Hämatologie-Onkologie, Koblenz

13.07.2022

Was ist neu?

- Neoadjuvante Therapie in NSCLC
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT
- Adjuvante Therapie in NSCLC
  - Impower 010
- Fortgeschrittenes Stadium NSCLC
  - Immunchemotherapie
  - TKI
  - Post Immuntherapie
  - Leptomeningeale Metastasen
- SCLC

Was ist neu?

- **Neoadjuvante Therapie in NSCLC**
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT

Neoadjuvante Therapie in NSCLC

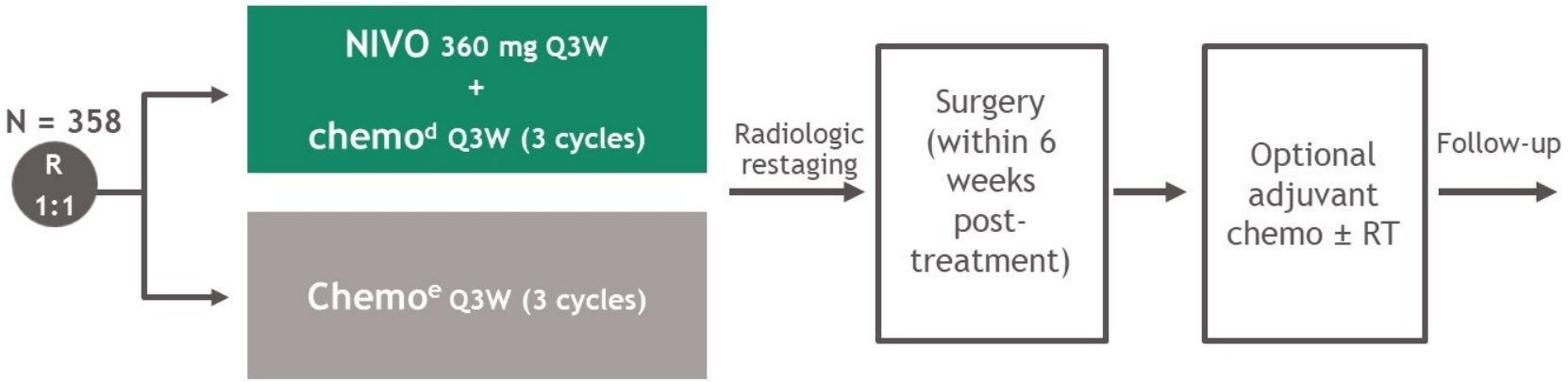
- Warum Neoadjuvanz
  - 20% der Patienten haben einen Stadium III A or N2 Erkrankung
  - 5-Jahres Uberlebensrate (OS) beträgt 36%
  - Neoadjuvante CT verbessert OS um 5% in 5 years
  - Mediane pCR mit neoadjuvanter CT ist 4% (0-16%)
- Checkmate 816- randomisierte Phase III - Studie
- Nadim II- randomisierte Phase II - Studie

CheckMate 816 study design[a,1]

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)-IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

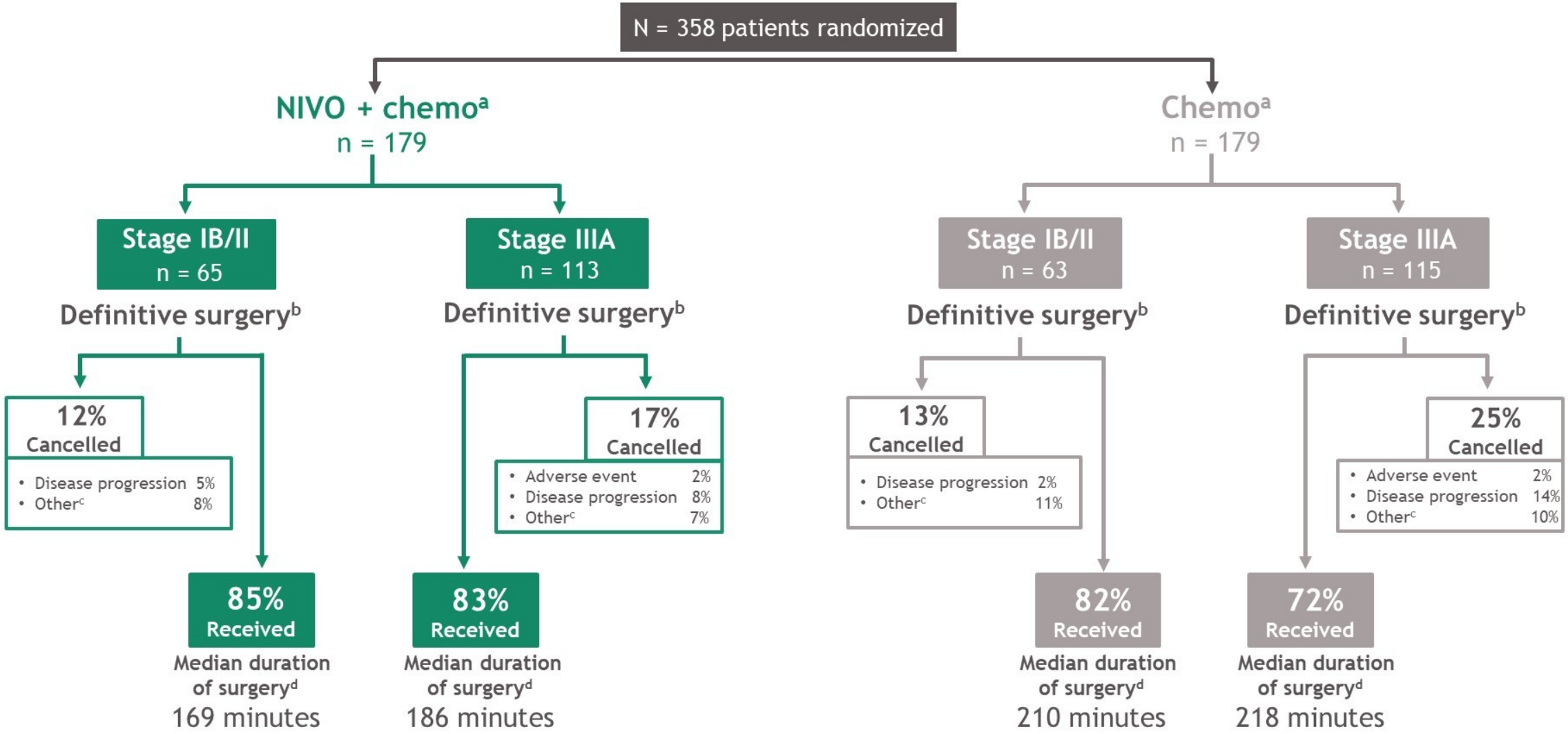
Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

[a]NCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

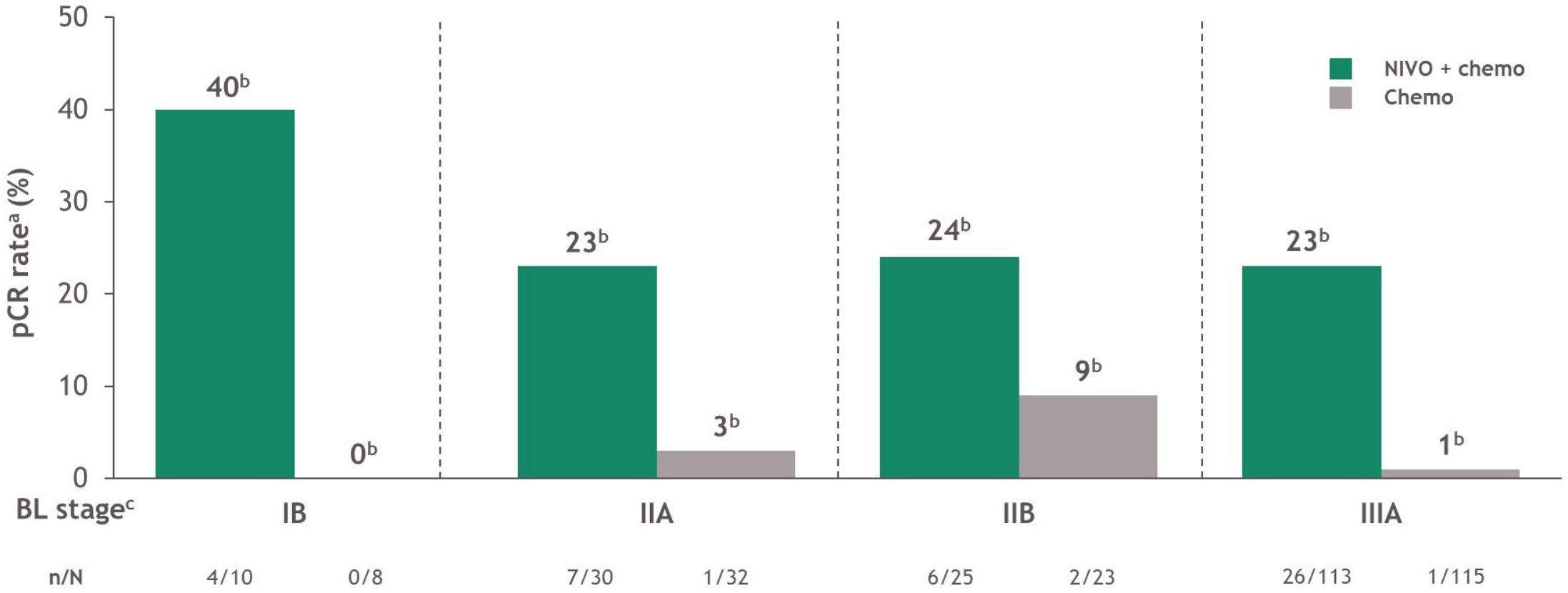
1. Forde PM, et al. Oral presentation at the AACR Annual Meeting; April 8-10, 2021; virtual. Abstract 5218.

Surgery summary: by baseline stage of disease



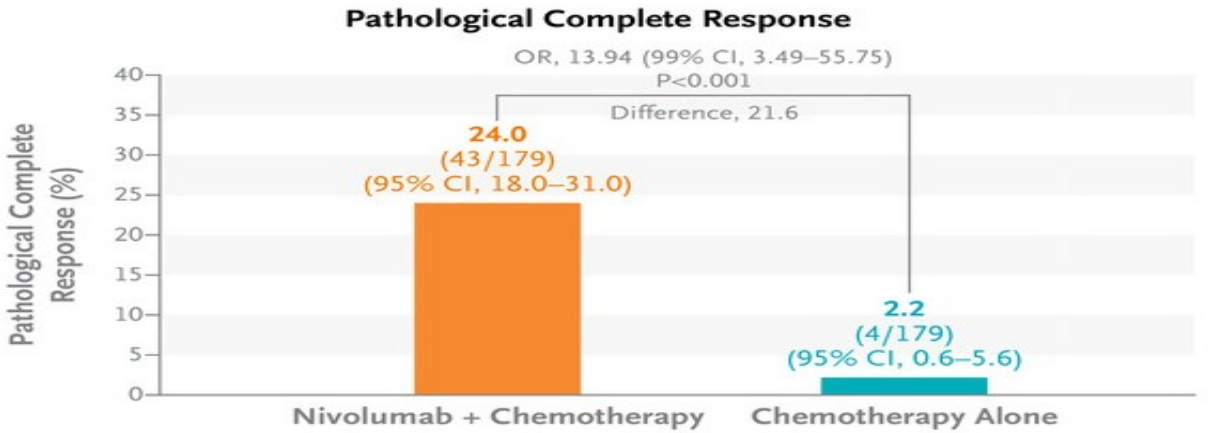
[a]1 patient with stage IV in each arm; [b]Patients with definitive surgery not reported: NIVO + chemo, 3% (stage IB/II), 0 (stage IIIA); chemo, 5% (stage IB/II), 3% (stage IIIA); [c]Other reasons included patient refusal, unresectability, and poor lung function; [d]Patients (n) with reported duration of surgery: NIVO + chemo, 46 (stage IB/II), 76 (stage IIIA); chemo, 47 (stage IB/II), 74 (stage IIIA); IQR for median duration of surgery: NIVO + chemo, 126.0-275.0 (stage IB/II) and 134.5-245.5 (stage IIIA); chemo, 150.0-267.0 (stage IB/II) and 147.0-290.0 (stage IIIA).

pCR by baseline stage of disease



- pCR improvement with NIVO + chemo vs chemo was observed regardless of radiologic down-staging[d]

[a]Per BIPR in the ITT population; neither of the 2 patients with stage IV disease (1 in each arm) achieved pCR; [b]95% CI: NIVO + chemo, chemo (stage): 12.2-73.8, 0.0-36.9 (IB); 9.9-42.3, 0.1-16.2 (IIA); 9.4-45.1, 1.1-28.0 (IIB); 15.6-31.9, 0.0-4.7 (IIIA); [c]Baseline stage of disease by CRF, TNM 7th edition used for classification; [d]pCR rate in patients with radiographic down-staging: 31% with NIVO + chemo vs 7% with chemo; pCR rate in patients without radiographic down-staging: 22% with NIVO + chemo vs 1% with chemo.



CONCLUSIONS

Among patients with resectable NSCLC, neoadjuvant nivolumab plus chemotherapy was superior to chemotherapy alone with respect to event-free survival and pathological complete response, with no increase in adverse events.

Neoadjuvant chemotherapy is feasible and results in superior pathological remissions. Further data need to be awaited to see if this translates into an OS benefit

More patients had minimally invasive surgery, R0 resection and less number of pneumonectomies

Nivolumab + chemotherapy (CT) vs CT as neoadjuvant treatment for resectable stage IIIA-B non-small cell lung cancer (NSCLC): NADIM II trial

Primary endpoint results of pathological complete response (pCR)

Mariano Provencio[1], Ernest Nadal[2], José Luis González-Larriba[3], Alex Martínez[4], Reyes Bernabé[5], Joaquim Bosch-Barrera[6], Joaquín Casal-Rubio[7], Virginia Calvo[1], Amelia Insa[8], Santiago Ponce[9], Noemí Reguart[10], Javier de Castro[11], Joaquín Mosquera[12], Raquel Benítez[13], Carlos Aguado de la Rosa[3], Ramón Palmero[2], Florentino Hernando-Trancho[3], Atocha Romero[1], Alberto Cruz-Bermúdez[1] & Bartomeu Massuti[14]

[1]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain; [2]Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain; [3]Hospital Universitario Clínico San Carlos, Madrid, Spain; [4]Hospital Universitario e Instituto de Oncología Vall d´Hebron (VHIO), Barcelona, Spain; [5]Hospital Universitario Virgen del Rocio, Seville, Spain; [6]Institut Català d'Oncologia, Girona, España; [7]Hospital Universitario de Vigo, Pontevedra, Spain; [8]Fundación INCLIVA, Hospital Clínico Universitario de Valencia, Valencia, Spain; [9]Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Hospital Clínic de Barcelona, Spain; [11]Hospital Universitario La Paz, Madrid, Spain; [12]Complejo Hospitalario Universitario A Coruña, A Coruña, Spain; [13]Genetic and Molecular Epidemiology Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain; [14]Hospital General Universitario de Alicante, Alicante, Spain.

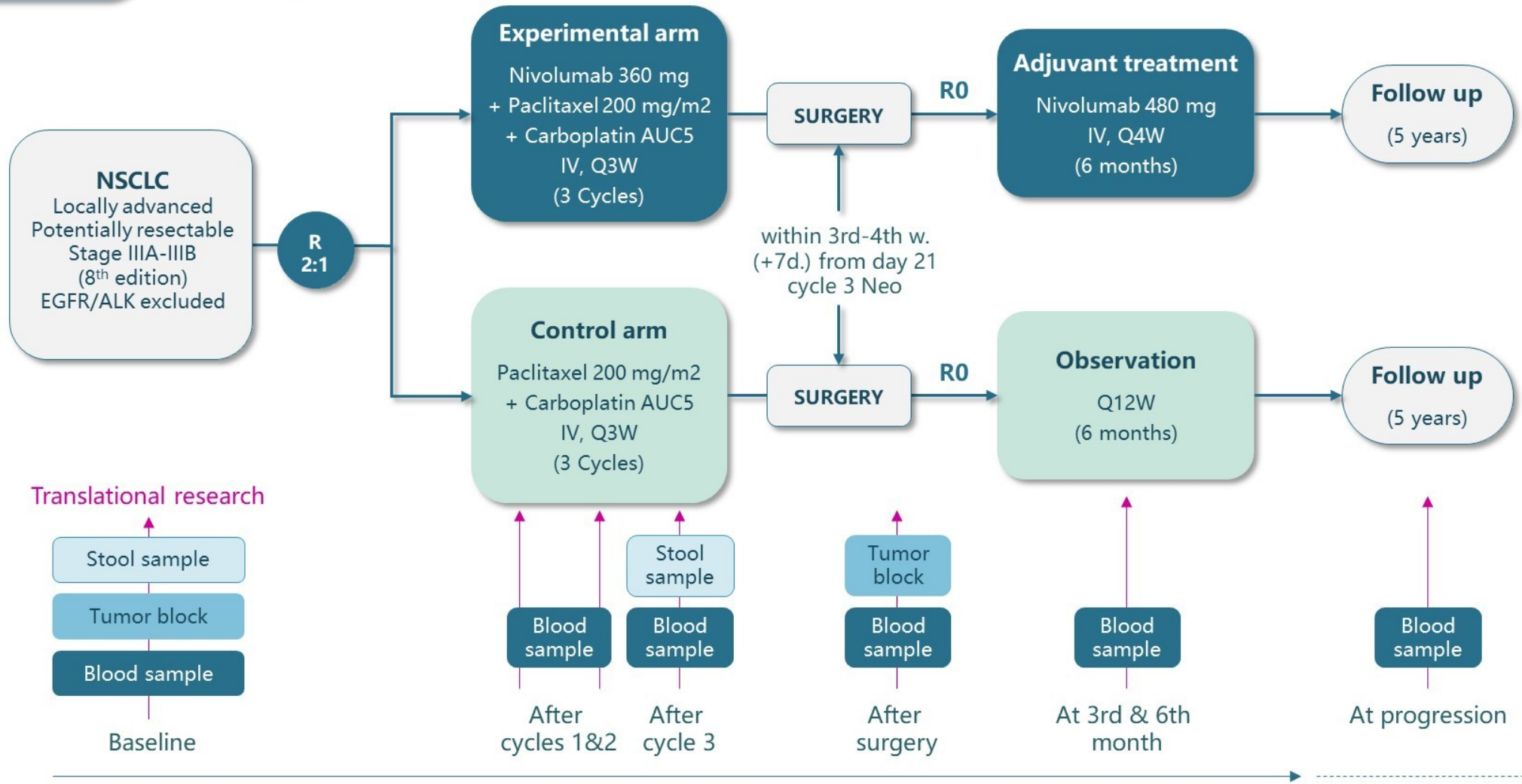
NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

2022 ASCO ANNUAL MEETING

#ASCO22

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

NADIM II Study design



NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

Endpoints

Primary endpoint

- Pathological complete response in the intention-to-treat population (ITT)

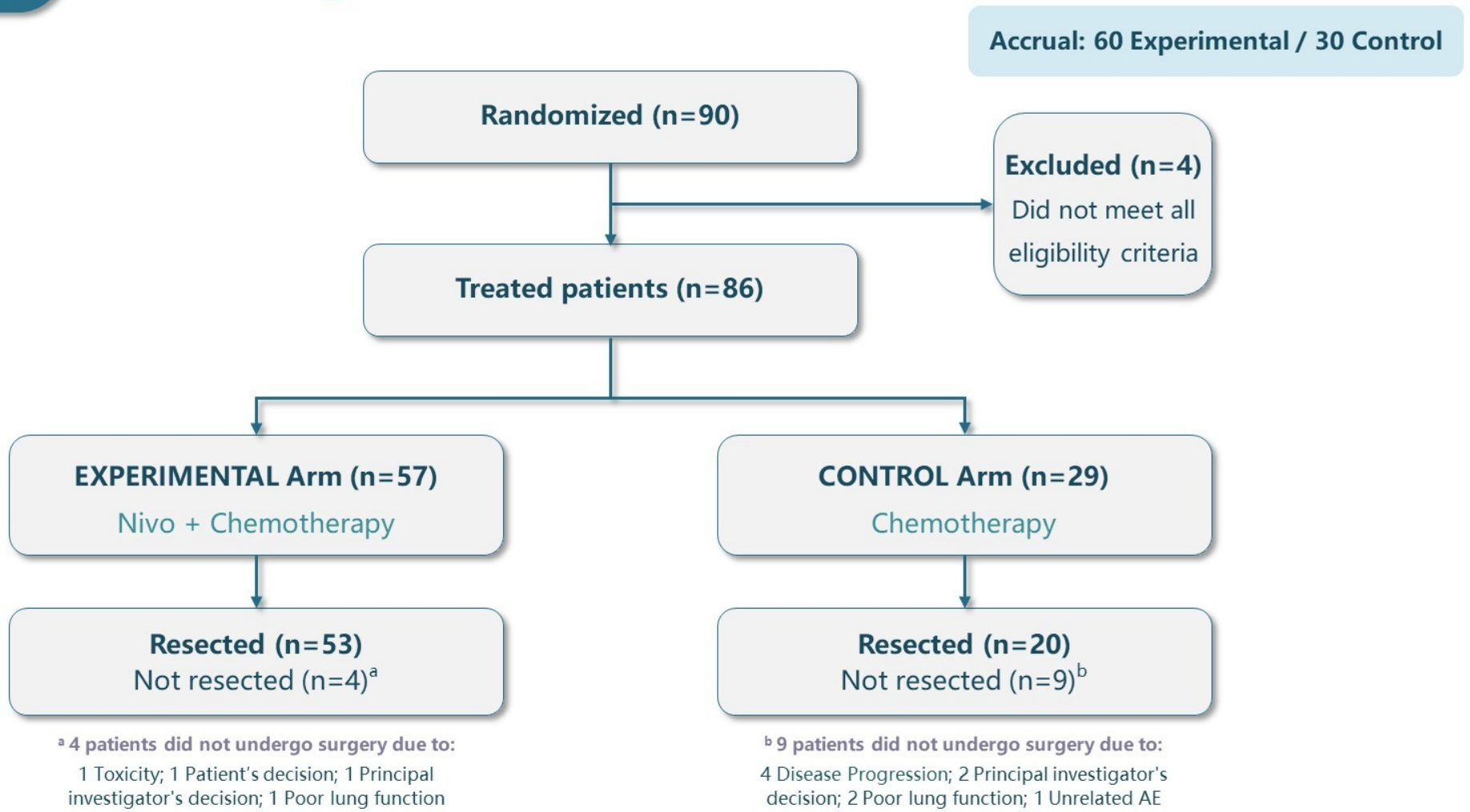
Secondary endpoints

- Major pathological response (MPR)
- Portion of delayed/canceled surgeries, length of hospital stays, surgical approach, incidence of AE/SAE related to surgery
- Safety and tolerability: Adverse events graded according to CTCAE v5.0
- Potential predictive biomarkers (ctDNA, TCR)
- Other: (i) OS at 12, 18 and 24 months; (ii) PFS at 12, 18 and 24 months; (iii) Down-staging; (iv) Mortality at 90 days after surgery; (v) Association between clinical baseline characteristics and ORR, pathological response, AEs, PFS and OS; (vi) Association between pathological response and PFS or OS; (vii) Association between MPR and histology; (viii) Association between histology and PFS at 18 months

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DFS, disease-free survival; EFS, event-free survival; ITT, intention-to-treat; MRP, major pathological response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SAE, serious adverse event

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

NADIM II Flow diagram



NADIM II (NCT03838159) is a randomized, phase 2, open-label, multicentre study evaluating nivolumab + chemotherapy vs chemotherapy as neoadjuvant treatment for potentially resectable NSCLC

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

Baseline characteristics (I)

Baseline characteristics - ITT population		
Characteristic	**NIVO + Chemo (n = 57)**	**Chemo (n = 29)**
Age – median (range), years	63 (58-70)	62 (57-66)
Female – No. (%)	21 (36.8)	13 (44.8)
History of tobacco use – No. (%)		
Never smoker	5 (8.7)	0 (0.0)
Former smoker	23 (40.4)	10 (34.5)
Current smoker	29 (50.9)	19 (65.5)
ECOG PS – No. (%)		
0	31 (54.4)	16 (55.2)
1	26 (45.6)	13 (44.8)
Histology – No. (%)		
Adenocarcinoma	25 (43.9)	11 (37.9)
Adenosquamous	1 (1.8)	0 (0.0)
Squamous	21 (36.8)	14 (48.3)
Large Cell Carcinoma	2 (3.5)	1 (3.5)
NOS / Undifferentiated	7 (12.3)	2 (6.9)
Other	1 (1.8)	1 (3.5)

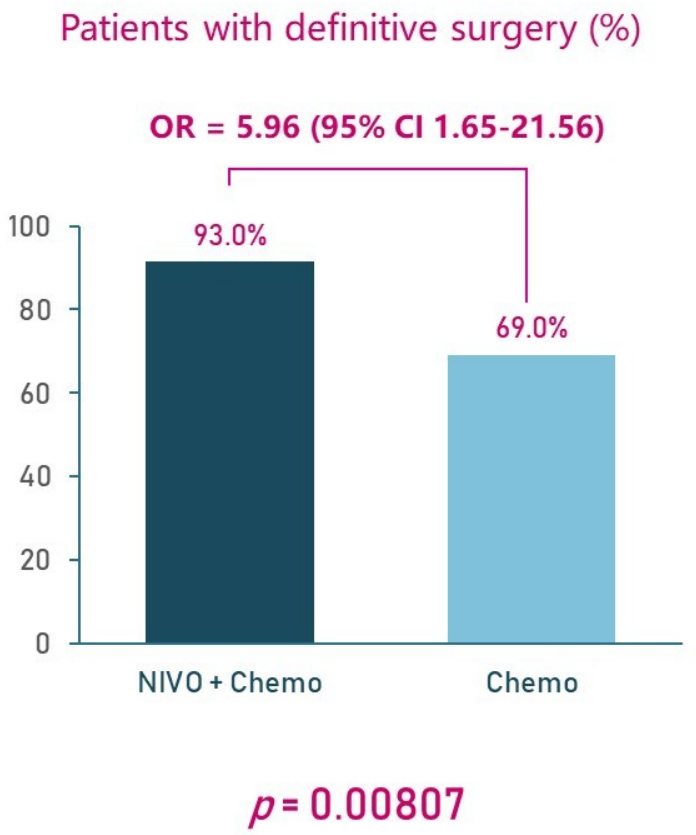
Baseline characteristics - ITT population		
Characteristic	**NIVO + Chemo (n = 57)**	**Chemo (n = 29)**
TNM classification (AJCC 8th edition)		
T1N2M0	12 (21.1)	4 (13.8)
T2N2M0	16 (28.1)	7 (24.1)
T3N1M0	2 (3.5)	1 (3.5)
T3N2M0	13(22.8)	5 (19.3)
T4N0M0	6 (10.5)	9 (31.0)
T4N1M0	8 (14.0)	3 (10.3)
Tumor size – Median (range), mm	43 (29-54)	52 (39-75)
Nodal stage – No. (%)		
N0	6 (10.5)	9 (31.0)
N1	10 (17.5)	4 (13.8)
N2	41 (71.9)	16 (55.2)
N2 multiple station	21(36.8)	10 (34.5)

Chemo, Chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention-to-treat; Nivo, Nivolumab; NOS, not otherwise specified

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

Surgery summary

Surgery summary			
Patients, No. (%)	**NIVO + chemo (n = 57)**	**Chemo (n = 29)**	**Total**
Patients with definitive surgery	53 (93.0)	20 (69.0)	73
Patients with cancelled definitive surgery	4 (7.0)	9 (31.0)	13
Due to adverse events	1 (1.7)	0 (0.0)	1
Due to disease progression	0 (0.0)	4 (13.7)	4
Not suitable for surgery	3 (5.2)	5 (17.2)	8



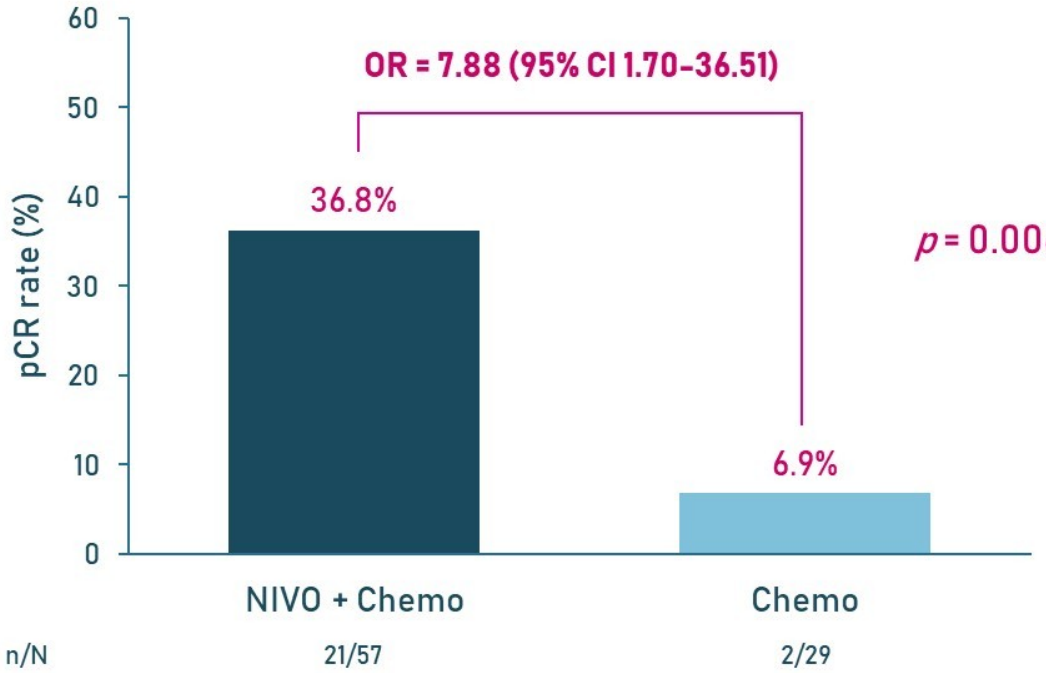
Nivo, nivolumab; Chemo, chemotherapy

PRESENTED BY: Mariano Provencio MD, PhD.
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

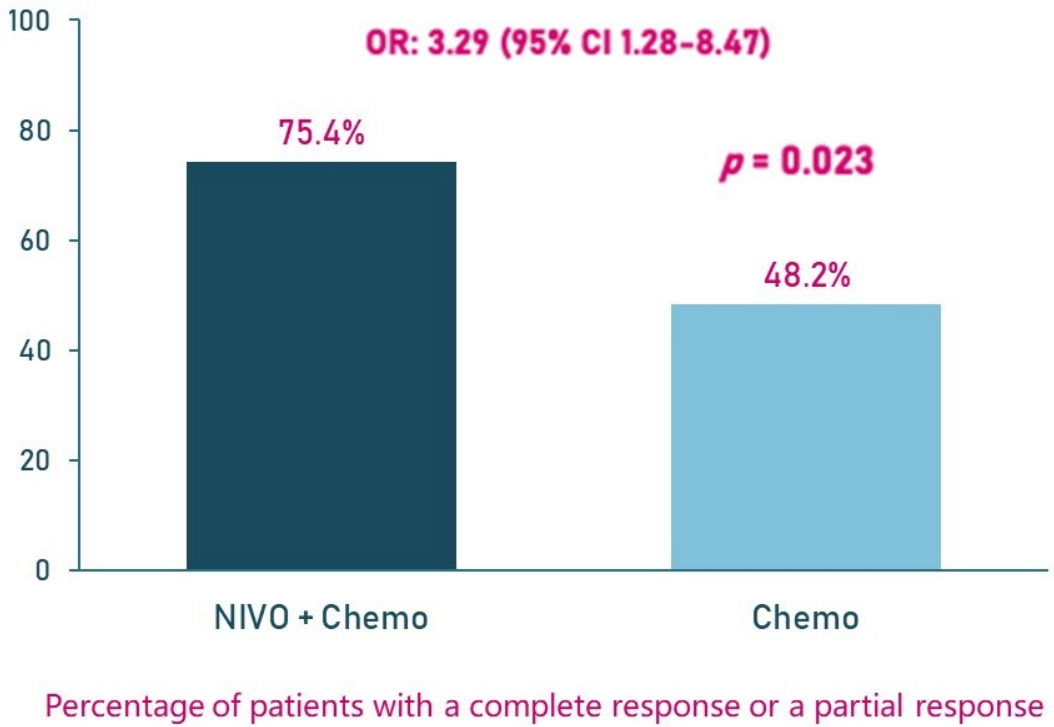
Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Primary endpoint - pCR

pCR[a] and Overall Response rate with neoadjuvant NIVO + CT vs CT in the ITT population[b]



$p = 0.0068$



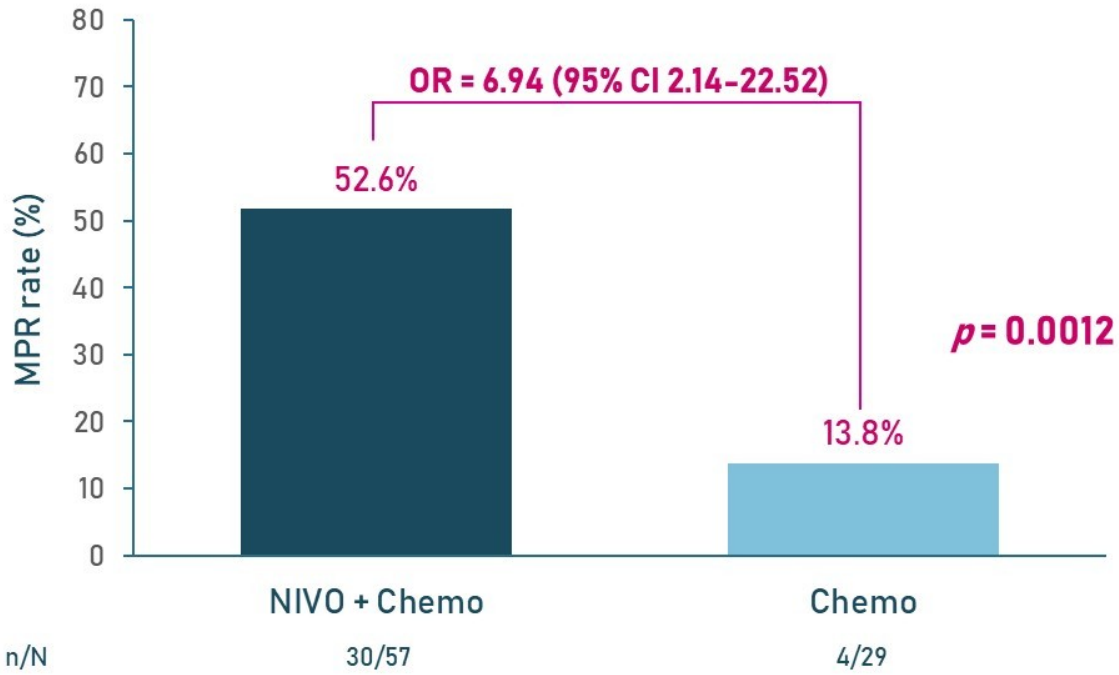
[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders
Chemo, chemotherapy; ITT, intention-to-treat; Nivo, nivolumab; pCR, pathological complete response; OR, risk ratio

PRESENTED BY: Mariano Provencio MD, PhD.
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Secondary endpoints - MPR

MPR[a] rate with neoadjuvant NIVO + CT vs CT in the ITT population [b]



Percentage of patients with a complete response or a major response

NNT: 2.57 (1.76-4.81)

[a]MPR was defined as ≤10% residual viable tumor cells in both the primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders

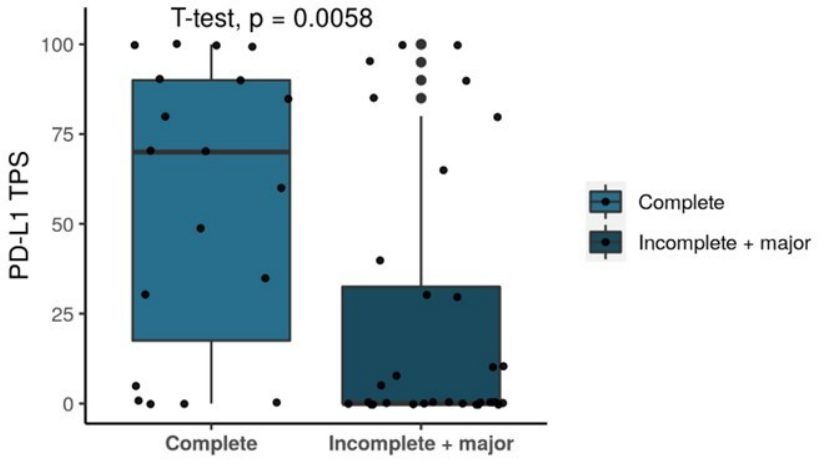
Chemo, chemotherapy; ITT, intention-to-treat; MPR, major pathological response; Nivo, nivolumab; RR, risk ratio

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

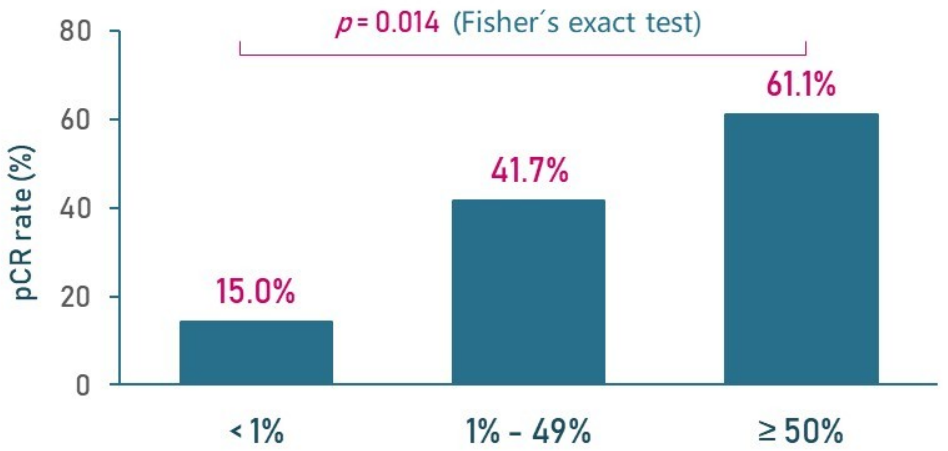
Secondary endpoints – Predictive biomarkers

Predictive biomarkers of response (pCR)[a] to neoadjuvant NIVO + CT (ITT population)[b]

- Patients who achieved pCR had higher PD-L1 expression than patients who did not
- pCR rate raised across increasing categories of PD-L1 TPS
- Predictive value of PD-L1 TPS for pCR was AUC 0.728 (95% CI 0.58-0.87; $p = 0.001$)
- **OR** for pCR in the PD-L1 positive group (**≥1%**): **16.0 (**95% CI 1.86-137.61; ***p* = 0.007)**



Pathological response



PD-L1 Tumor Proportion Score

[a]pCR was defined as 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes; [b]Patients who did not undergo surgery were considered as non-responders
IQR, interquartile range; ITT, intention-to-treat; pCR, pathological complete response; TPS, tumor proportion score, RR, risk ratio; PD-L1 positive group defined as ≥1% TPS.

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

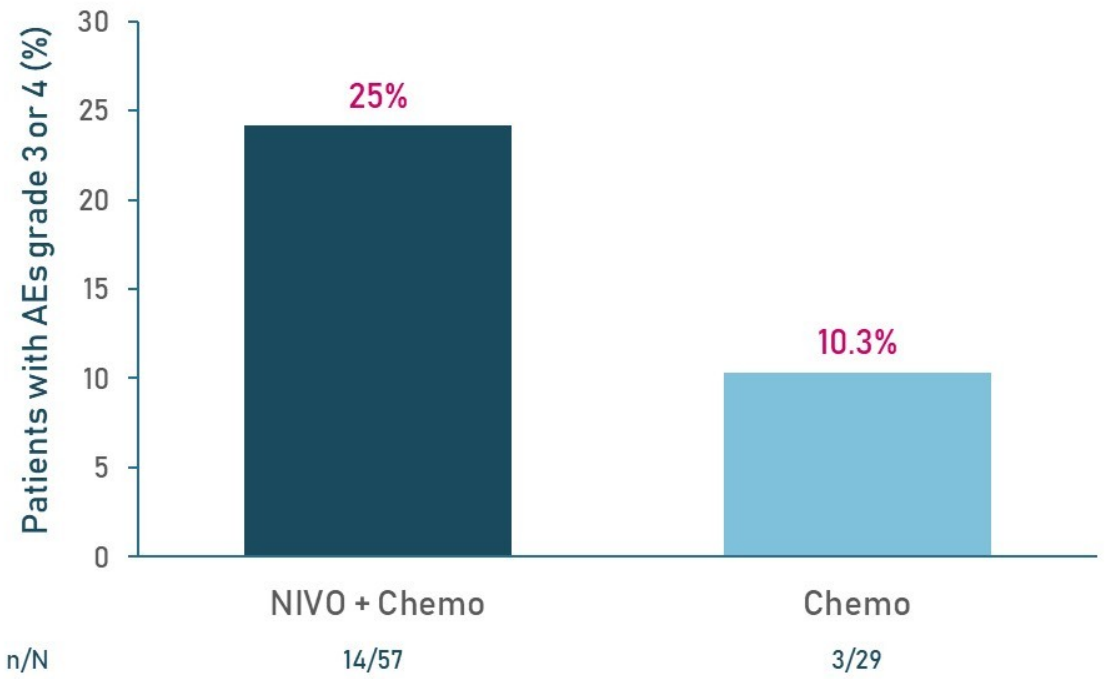
CheckMate 816 and NADIM II

	CheckMate 816		Nadim II	
AJCC	7th Edition		8th Edition.	
Stage Included	IB (>4 cm) to IIIA (resectable)		IIIA, IIIB (resectable)	
Phase	Phase III		Randomized Phase II	
	Nivolumab/Histology based Chemotherapy	Histology based Chemotherapy	Nivolumab/Carboplatin/ Paclitaxel	Carboplatin/Paclitaxel
Stage III (N)	114	114	57	29
Squamous	49%	53%	36.8%	48.3%
pCR Rate for Stage III	23%	1%	36.8%	6.9%

PRESENTED BY:
George R. Simon, MD
Professor; Medical Oncology.

Secondary endpoints – Safety (I)

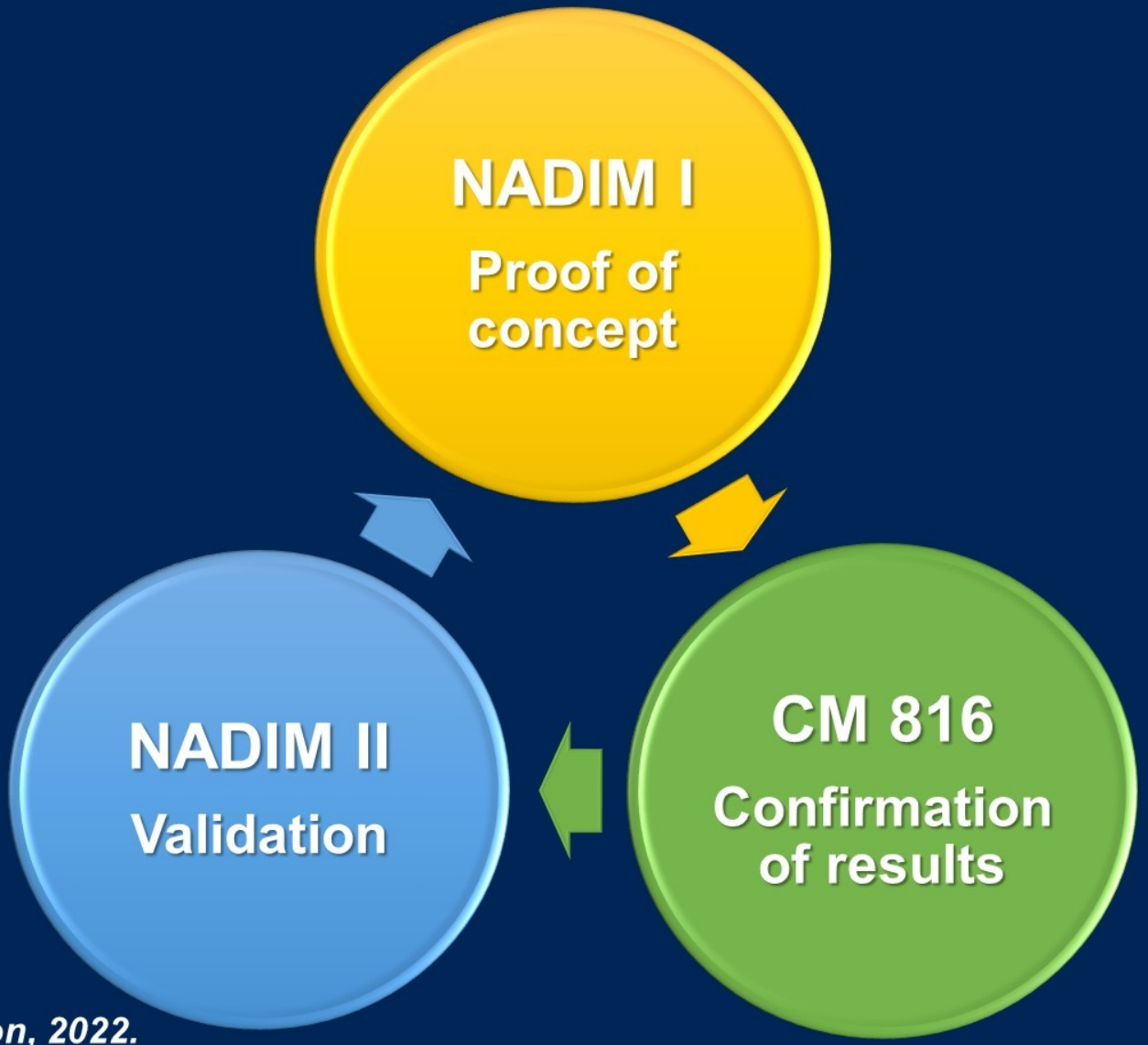
Adverse events G 3-4 summary (ITT population)



No grade 5 treatment-related adverse events were observed

AE, adverse event; Chemo, chemotherapy; Nivo, nivolumab; ITT, intention-to-treat

PRESENTED BY: Mariano Provencio MD, PhD.
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

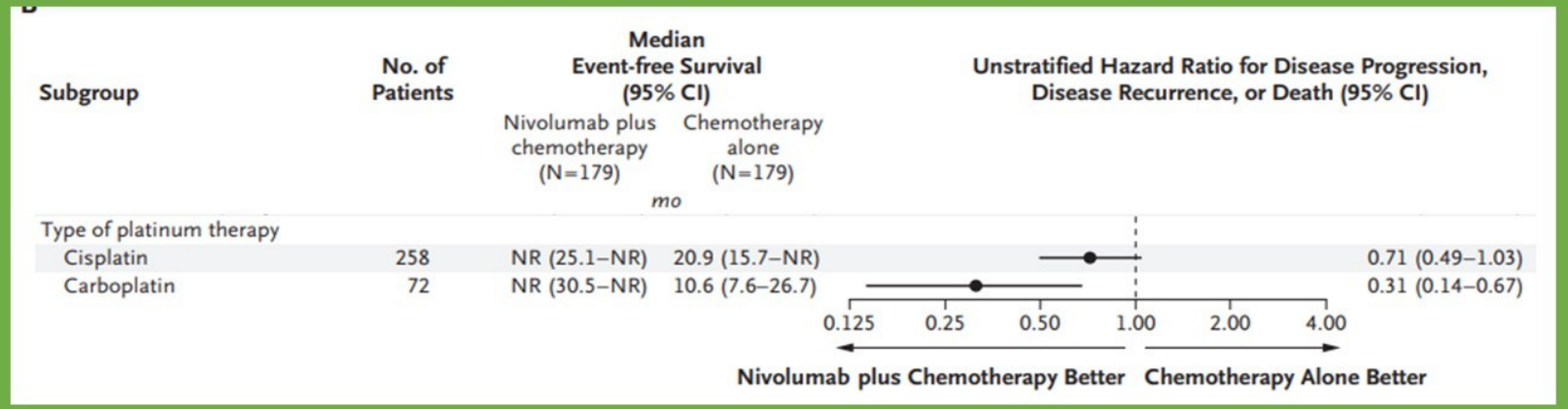


Provencio M, Communication, 2022.

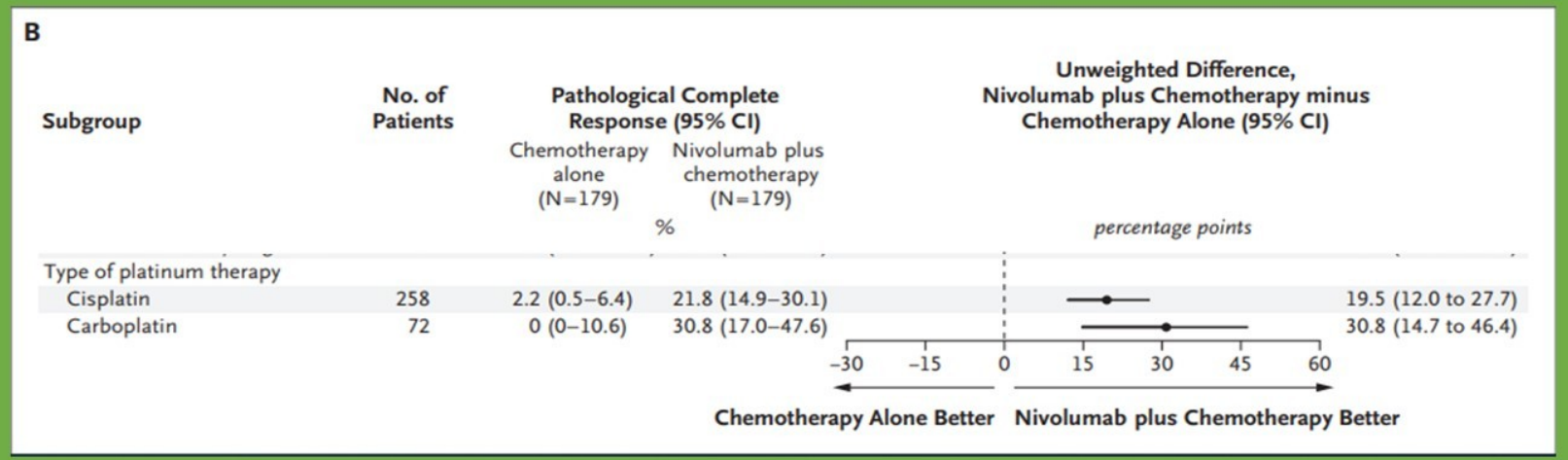
PRESENTED BY:
Jessica Donington, Thoracic Surgery University of Chicago

Is carboplatin better choice for induction I/O?

EFS



pCR



Forde PM, N Engl J Med 2022

PRESENTED BY:
Jessica Donington, Thoracic Surgery University of Chicago

Ongoing Phase III Trials of Neoadjuvant CT + Anti–PD-(L)1 Antibody Therapy in Early-Stage NSCLC

Study Title (Planned Accrual)	Status*	Disease Stage (TNM Edition)	CT Backbone	Neoadjuvant Intervention	Adjuvant IO Treatment	Primary Endpoint(s)
CheckMate 816 (N = 358)[1,2]	Reported FDA approved 03/04/22	IB-IIIA (7th)	3 cycles of cis/pemetrexed, carbo/pac, cis/gem, carbo/pac (nivolumab arm) ***or*** cis/pemetrexed, cis/vin, cis/doc, cis/gem, carbo/pac (CT arm)	± Nivolumab†	No	pCR, EFS
KEYNOTE-671 (N = 786)[3]	Accrual ongoing	II-IIIB (8th)	≥4 cycles of cis/(gem or pemetrexed)	Pembrolizumab or placebo	13 x 3-wk cycles of pembrolizumab or placebo	EFS, OS
IMpower030 (N = 450)[4]	Accrual ongoing	II-IIIB (8th)	4 cycles of carbo/pemetrexed, carbo/nab-pac, cis/pemetrexed, or cis/gem	Atezolizumab or placebo	16 x 3-wk cycles of atezolizumab or BSC	EFS
AEGEAN (N = 800)[5,6]	Accrual ongoing	IIA-IIIB (8th)	4 cycles of carbo/pac, carbo/pemetrexed, cis/gem, or cis/pemetrexed	Durvalumab or placebo	12 x 4-wk cycles of durvalumab or placebo	pCR, EFS
CheckMate 77T (N = 452)[7,8]	Accrual ongoing	IIA-IIIB (8th)	≥4 cycles carbo/pac, cis/doc, carbo/pemetrexed, cis/pemetrexed, or carbo/pac	Nivolumab or placebo	Nivolumab or placebo for 1 yr	EFS

1. NCT02998528. 2. Spicer. ASCO 2021. Abstr 8503. 3. NCT03425643. 4. NCT03456063.
5. NCT03800134. 6. Heymach. WCLC 2019. Abstr P1.18-02. 7. Cascone. ASCO 2020. Abstr TPS9076. 8. NCT04025879.

Slide credit: clinicaloptions.com

PRESENTED BY:
George R. Simon, MD
Professor; Medical Oncology.

Conclusions

- NADIM II confirms superiority of neoadjuvant nivolumab plus chemotherapy combination in patients with resectable stage IIIA-B NSCLC
- The addition of neoadjuvant nivolumab to chemotherapy:
  - → Significantly improved pCR (OR = 7.88 [95% CI 1.70-36.5]) (Chi-squared test: p = 0.0068)
  - → Maintained a tolerable safety profile, with a moderate increase in grade 3-4 toxicity
  - → Did not impede the feasibility of surgery
- PD-L1 TPS has a predictive value for pCR (AUC 0.728 [95% CI 0.59-0.87]); (Chi-squared test: p = 0.002)

AUC, area under the ROC curve; pCR, pathological complete response; RR, risk ratio; TPS, tumor proportion score

PRESENTED BY: **Mariano Provencio MD, PhD.**
Hospital Puerta de Hierro Majadahonda-Madrid, SPAIN
Spanish Lung Cancer Group

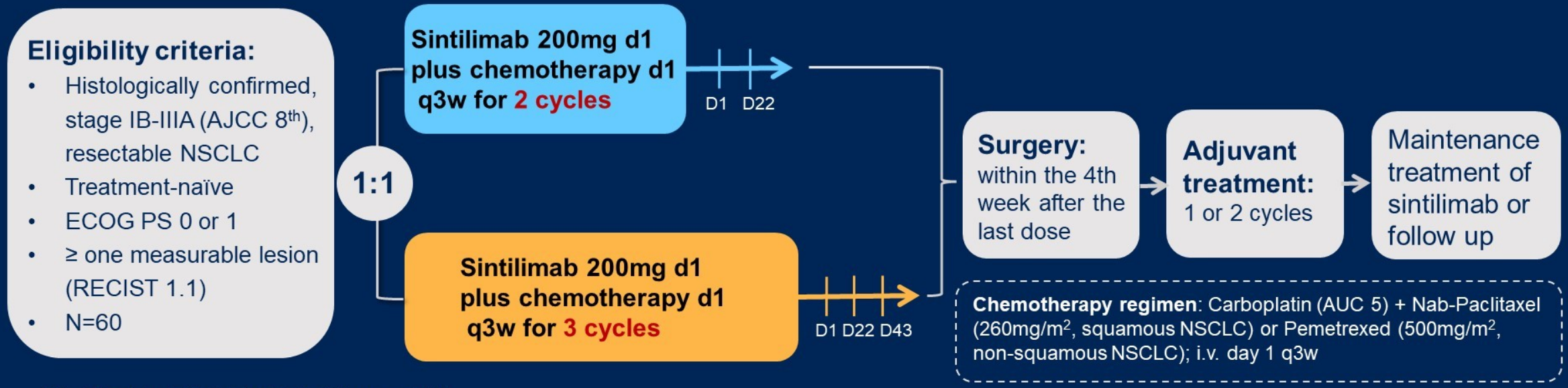
Neoadjuvant immuno-chemotherapy clinical trials

Trial	Phase	Enrollment	Stage	Neoadjuvant treatment	MPR	pCR
NCT02716038	II	30	IB-IIIA*	Atezolizumab + platinum doublet × 4 cycles	57%	33%
NADIM	II	46	IIIA*	Nivolumab + platinum doublet × 3 cycles	83%	63%
NCT04304248	II	33	IIIA, T3-4N2 IIIB**	Toripalimab + platinum doublet × 3 cycles	67%	50%
SAKK16/14	II	68	T1-3N2M0, IIIA(N2)*	Platinum doublet × 3 cycles, followed by durvalumab × 2 cycles	62%	18%
CheckMate816	III	358	IB-IIIA*	Nivolumab + platinum doublet vs platinum doublet × 3 cycles	36.9% vs 8.9%	24% vs 2.2%

*, per American Joint Committee on Cancer 7th edition
**, per American Joint Committee on Cancer 8th edition
pCR, complete pathology response.

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Trial design



Stratified by PD-L1 TPS (≥1% vs < 1%)

- **Primary endpoint:** MPR rate
- **Secondary endpoints:** pCR rate, ORR, 2-year DFS rate, 2-year OS rate, safety
- **Exploratory endpoints:** novel immune biomarkers and the impact of sintilimab maintenance on 2-year DFS and OS

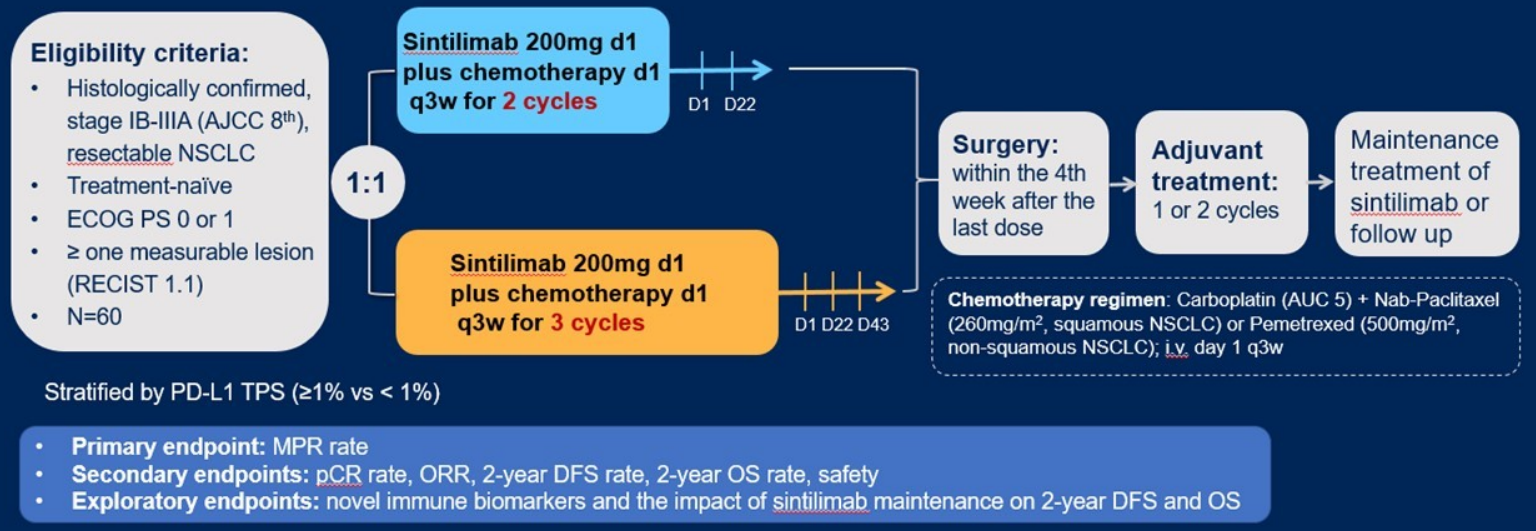
AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, Response Evaluation Criteria in Solid Tumors; PD-L1, programmed cell death ligand-1; TPS, tumor proportion score; i.v., intravenously; q3w, every 3 weeks; AUC, area under curve; ORR, objective response rate; DFS, disease-free survival; OS, overall survival.

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

neoSCORE: 2 vs. 3 cycles neoadjuvant chemo + I/O

- 2-4 cycles of neoadjuvant immuno-chemotherapy used in trials
- No consensus on optimal period
- Sintilimab, a monoclonal AB against PD-1, favorable MPR rate in single-agent neoadjuvant setting

Trial design



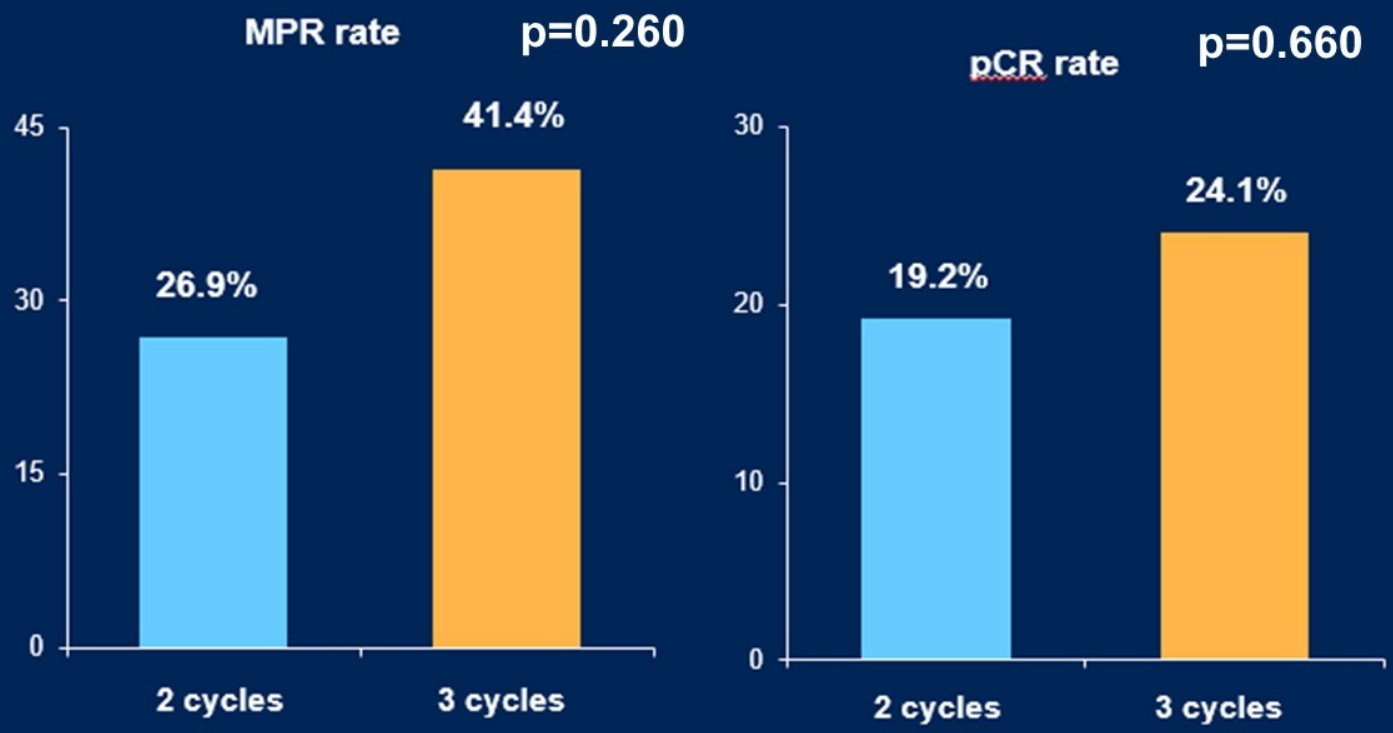
Qui F, ASCO 2022

PRESENTED BY:
Jessica Donington, Thoracic Surgery, University of Chicago

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

neoSCORE: Pathologic Response

- **Planned sample size:**
  102 patients
- **An unplanned interim analysis:**
  Enrollment：60 patients
  Date: Dec 3, 2021



Qui F, ASCO 2022

PRESENTED BY:
Jessica Donington, Thoracic Surgery, University of Chicago

neoSCORE: Toxicity

- No increase in TRAE in 2 vs. 3 cycles

TRAE, n (%)	2 cycles (n=29)		3 cycles (n=31)	
	Any grade	≥grade 3	Any grade	≥grade 3
Hematological toxicities				
Anemia	15 (51.7)	0	19 (61.3)	2 (6.5)
Decreased white blood cell count	8 (27.6)	2 (6.9)	6 (19.4)	2 (6.5)
Neutropenia	5 (17.2)	4 (13.8)	6 (19.4)	3 (9.7)
Thrombocytopenia	4 (13.8)	2 (6.9)	6 (19.4)	1 (3.2)
Non-hematological toxicities				
Alopecia	20 (69.0)	0	19 (61.3)	0
Paresthesia	8 (27.6)	0	11 (35.5)	0
Fatigue	11 (37.9)	0	10 (32.3)	0
Nausea	4 (13.8)	0	7 (22.6)	0
Vomiting	4 (13.8)	0	5 (12.9)	0
Rash	6 (20.7)	0	6 (19.4)	0
Constipation	2 (6.9)	0	5 (16.1)	0
Diarrhea	2 (6.9)	2 (6.9)	1 (3.2)	0
Increased alanine aminotransferase	12 (41.4)	1 (3.4)	14 (45.2)	2 (6.5)
Increased aspartate aminotransferase	5 (17.2)	0	7 (22.6)	1 (3.2)
Increased blood lactate dehydrogenase	8 (27.6)	0	5 (16.1)	0
Blood creatinine increased	3 (10.3)	0	2 (6.5)	0
Increased lipase	12 (41.4)	0	9 (29.0)	0
Immune-related colitis	0	0	1 (3.2)	1 (3.2)
Immune-related pneumonia	1 (3.4)	1 (3.4)	1 (3.2)	1 (3.2)

Qui F, ASCO 2022

neoSCORE: Surgical Details

Surgical parameters		Overall (n=55)	2 cycles (n=26)	3 cycles (n=29)	*P* value
Type of resection, n (%)	Segmentectomy	1 (1.8)	0	1 (3.4)	0.281
	Lobectomy	43 (78.2)	20 (76.9)	23 (79.3)	
	Bilobectomy	9 (16.4)	6 (23.1)	3 (10.3)	
	Pneumonectomy	2 (3.6)	0	2 (6.9)	
Surgical approach, n (%)	Thoracotomy	1 (1.8)	0	1 (3.4)	1.0
	Thoracoscopy	54 (98.2)	26 (100.0)	28 (96.6)	
Timing of operation (minute)		110 (50-345)	120 (50-260)	110 (50-345)	0.946
Intraoperative blood loss (mL)		20 (10-300)	20 (10-100)	25 (10-300)	0.704
Intraoperative blood transfusion (mL)		0 (0-400)	0 (0-0)	0 (0-400)	0.095
Hospitalization time (day)		4 (2-12)	4 (2-12)	4 (2-12)	0.574

Impressive for cohort
50% stage IIIa

Qui F, ASCO 2022

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Conclusion

- Three cycles neoadjuvant treatment achieved a numerically higher MPR rate (26.9% vs 41.4%) compared with two cycles, and was consistent across most subgroups.
- The neoadjuvant regimen with an extra cycle was well tolerated.

My Conclusions

- **Additional prospective evidence supporting neoadjuvant chemo + I/O w/ pCR rate ≥ 20%**
- **Exceptional surgical results following chemo I/O**

Qui F, ASCO 2022

PRESENTED BY:
Jessica Donington, Thoracic Surgery University of Chicago

2022 ASCO® ANNUAL MEETING

Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy for patients with stage III-N2M0 non-small cell lung cancer (NSCLC): A population-based study

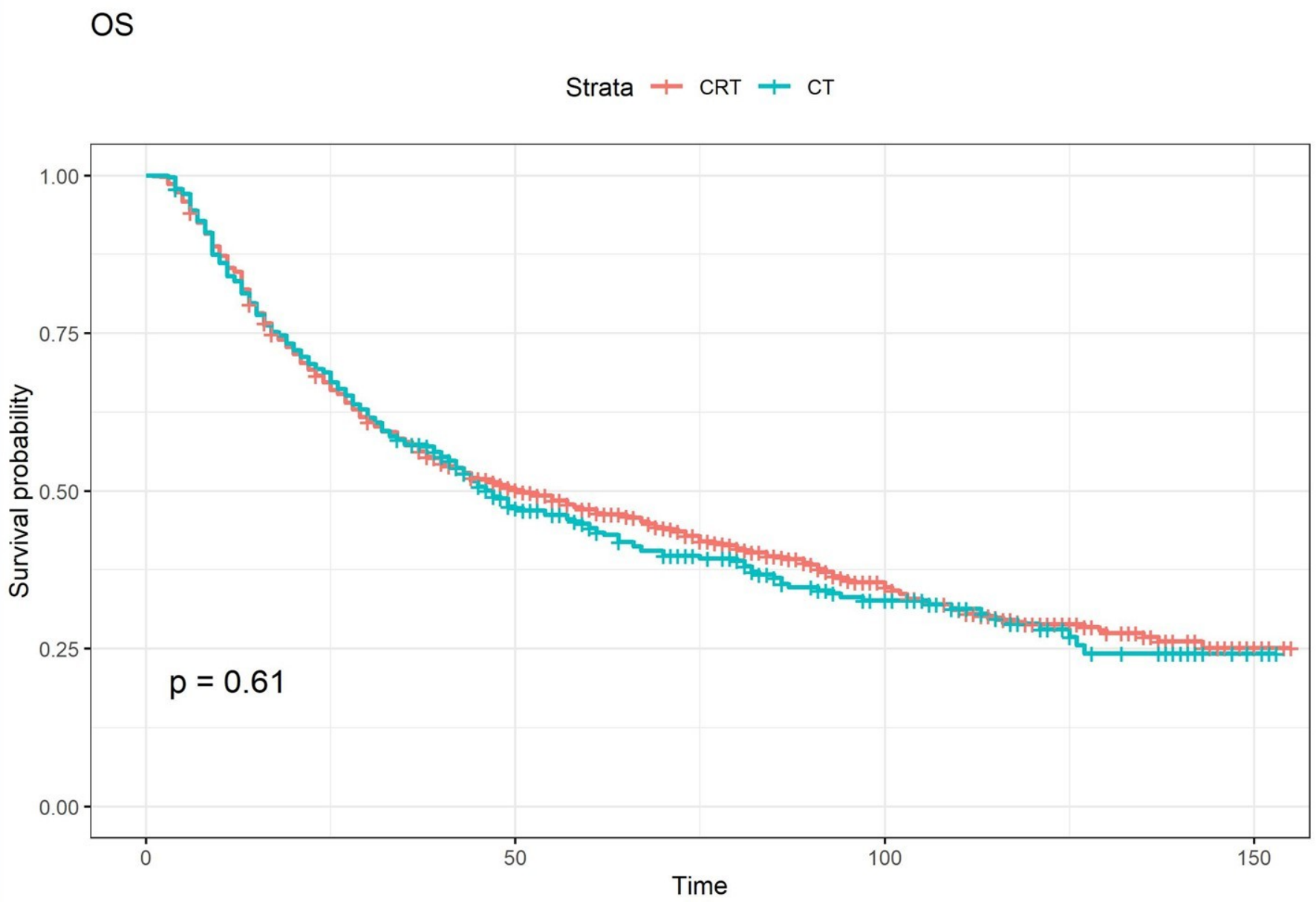
Marah Akhdar[1], **Sebawe Syaj**[1], Osaid Alser, MD, MSc(Oxon)[2], Mohamedraed Elshami, MD, MMSc, [3] and Shadi Hamouri[1] MD, MRCSI, FCCP, FEBTS, FACS

1 Department of General Surgery and Urology, Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan

2 Department of General Surgery, Texas Tech University Health Sciences Center, Lubbock, TX, USA

3 Division of Surgical Oncology, Department of Surgery, University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Results – OS



PRESENTED BY:
Sebawe Syaj

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

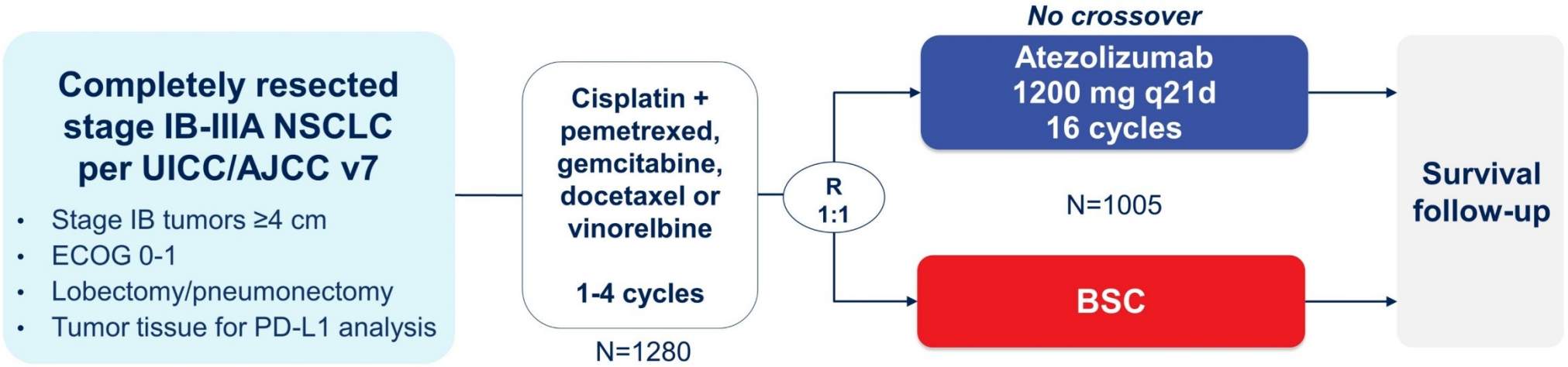
Fazit

- Neoadjuvante Chemoimmuntherapie in NSCLC wird in der Zukunft unsere aktuelle Praxis ändern
- 3 Zyklen Chemoimmuntherapie ist besser als 2
- Eine Verbesserung der pCR hat bisher noch keine Verbessung des OS gezeigt
- Carboplatin könnte eine gute Option für dieses Setting sein
- RCT hat keinen Stellenwert in einem neoadjuvanten Setting

Was ist neu?

- Neoadjuvante Therapie in NSCLC
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT
- **Adjuvante Therapie in NSCLC**
  - Impower 010
- Fortgeschrittenes Stadium NSCLC
  - Immunchemotherapie
  - TKI
  - Post Immuntherapie
  - Leptomeningeale Metastasen
- SCLC

IMpower010: study design



Stratification factors

- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

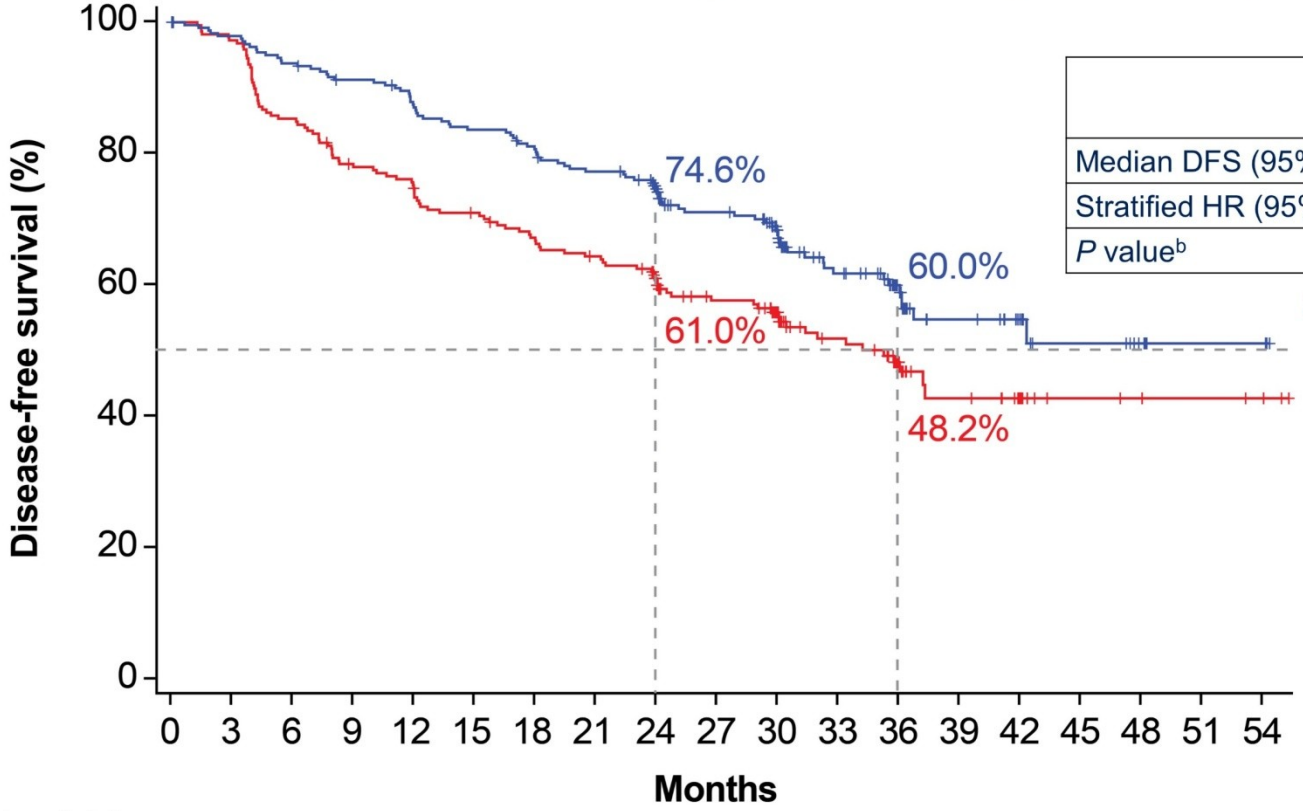
Key secondary endpoints

- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

Presented By: Dr. Heather A. Wakelee
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint)



	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

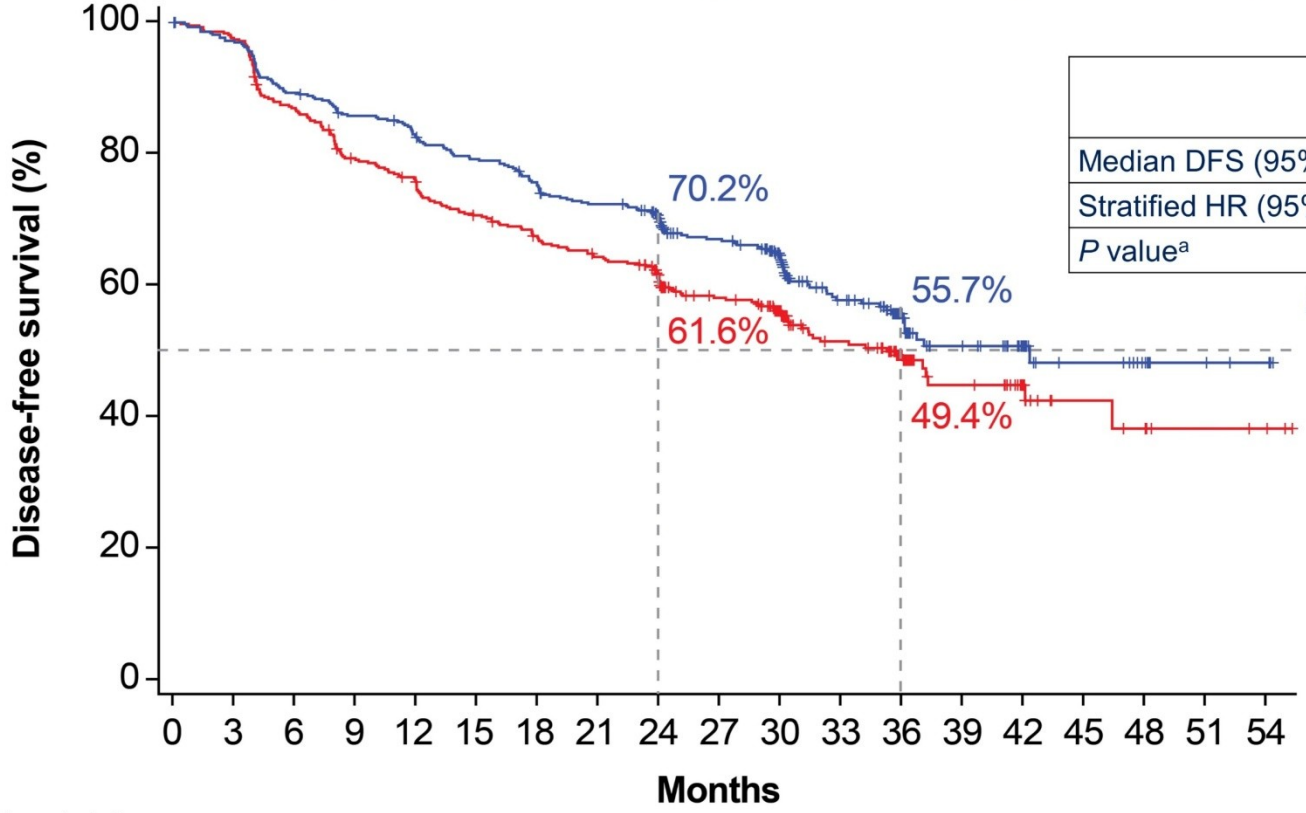
Median follow-up: 32.8 mo (range, 0.1-57.5)

No. at risk

Atezolizumab	248	235	225	217	206	198	190	181	159	134	111	76	54	31	22	12	8	3	3
BSC	228	212	186	169	160	151	142	135	117	97	80	59	38	21	14	7	6	4	3

Clinical cutoff: January 21, 2021. CI, confidence interval; HR, hazard ratio; NE, not evaluable. [a] Per SP263 assay. [b] Stratified log-rank. [c] Crossed the significance boundary for DFS.

IMpower010: DFS in the all-randomized stage II-IIIA population (primary endpoint)



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Median follow-up: 32.2 mo (range, 0-57.5)

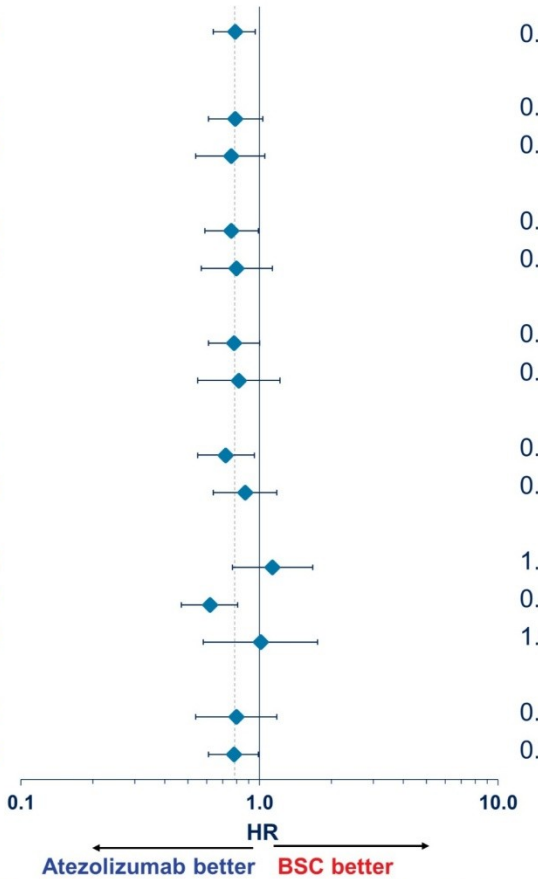
No. at risk

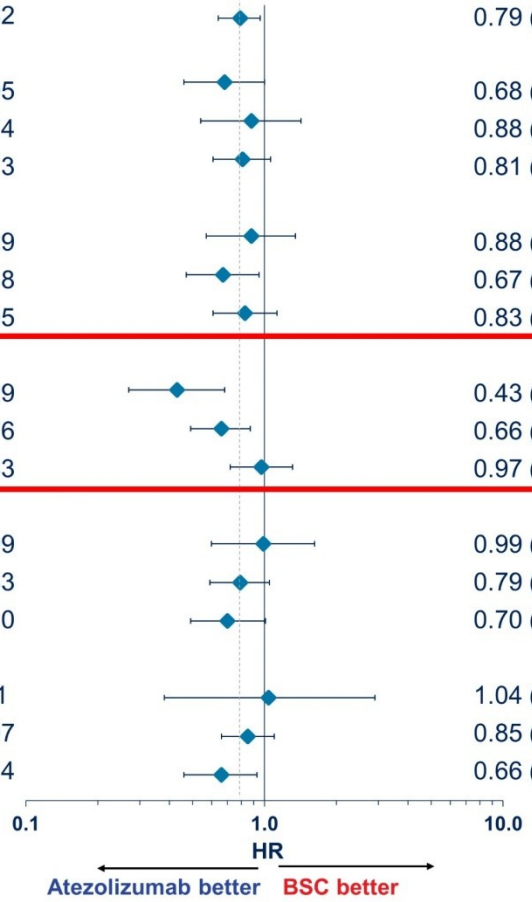
Atezolizumab	442	418	384	367	352	337	319	305	269	225	185	120	84	48	34	16	11	5	3
BSC	440	412	366	331	314	292	277	263	230	182	146	102	71	35	22	10	8	4	3

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population

Subgroup	N	HR (95% CI)[a]
All patients	882	0.79 (0.64, 0.96)
Age		
<65 y	544	0.79 (0.61, 1.03)
≥65 y	338	0.76 (0.54, 1.05)
Sex		
Male	589	0.76 (0.59, 0.99)
Female	293	0.80 (0.57, 1.13)
Race		
White	631	0.78 (0.61, 1.00)
Asian	227	0.82 (0.55, 1.22)
ECOG PS		
0	491	0.72 (0.55, 0.95)
1	388	0.87 (0.64, 1.18)
Tobacco use history		
Never	196	1.13 (0.77, 1.67)
Previous	547	0.62 (0.47, 0.81)
Current	139	1.01 (0.58, 1.75)
Histology		
Squamous	294	0.80 (0.54, 1.18)
Non-squamous	588	0.78 (0.61, 0.99)
Stage		
IIA	295	0.68 (0.46, 1.00)
IIB	174	0.88 (0.54, 1.42)
IIIA	413	0.81 (0.61, 1.06)
Regional lymph node stage (pN)		
N0	229	0.88 (0.57, 1.35)
N1	348	0.67 (0.47, 0.95)
N2	305	0.83 (0.61, 1.13)
SP263 PD-L1 status		
TC≥50%	229	0.43 (0.27, 0.68)
TC≥1%	476	0.66 (0.49, 0.87)
TC<1%	383	0.97 (0.72, 1.31)
***EGFR* mutation status**		
Yes	109	0.99 (0.60, 1.62)
No	463	0.79 (0.59, 1.05)
Unknown	310	0.70 (0.49, 1.01)
***ALK* rearrangement status**		
Yes	31	1.04 (0.38, 2.90)
No	507	0.85 (0.66, 1.10)
Unknown	344	0.66 (0.46, 0.93)





Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

Presented By: Dr. Heather A. Wakelee
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

#ASCO21

2021 ASCO ANNUAL MEETING

Adjuvante Therapie heute

- **Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥ 50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC**

Fazit

- Adjuvante Chemotherapie ist bereits zugelassen
- In NSCLC Frühstadien, müssen EGFR, ALK und PD-L1 Status bestimmt werden
- Alle Patienten sollten eine adjuvante Chemotherapie und 3-4 Wochen danach eine adjuvante Immuntherapie erhalten

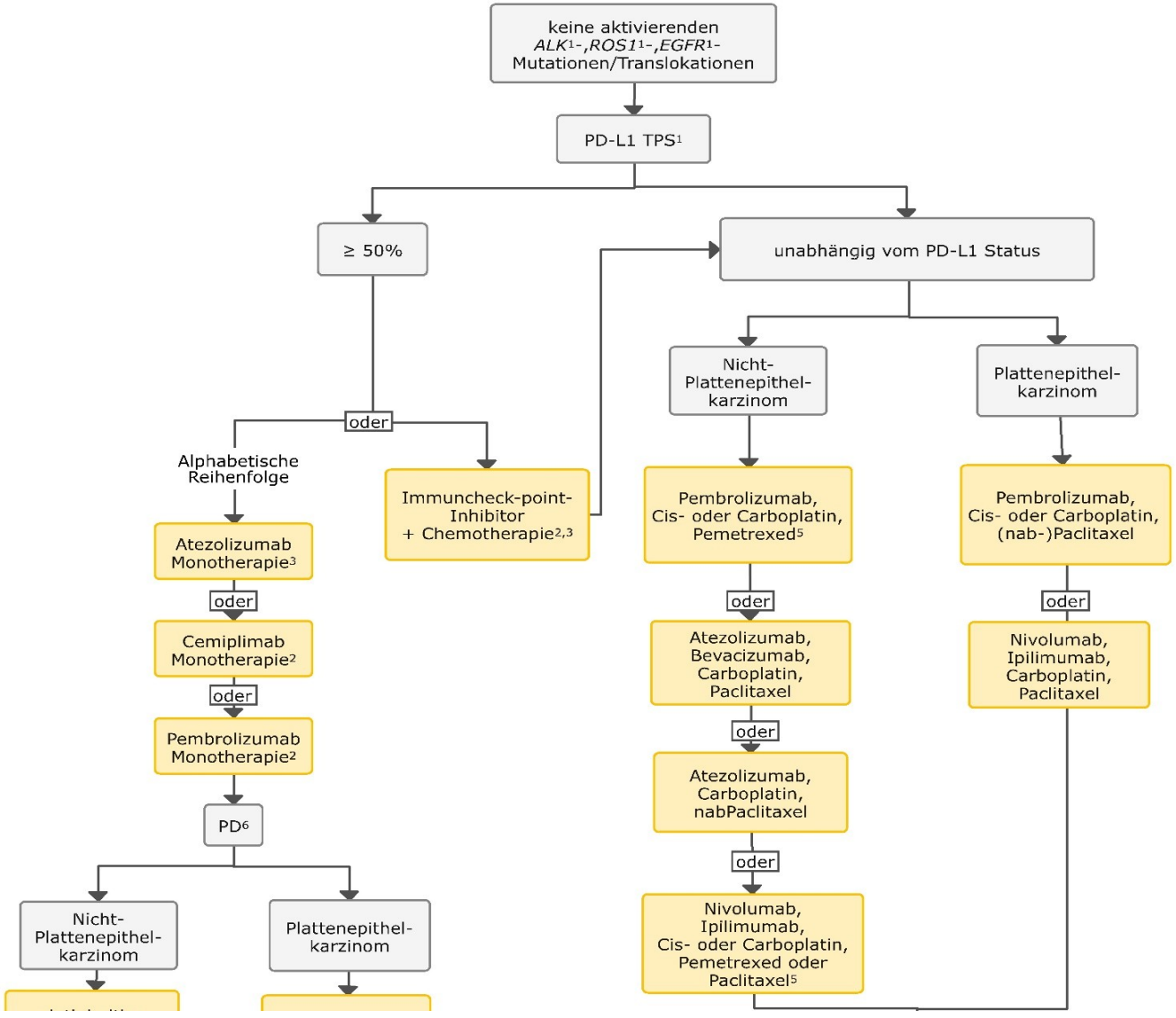
Was ist neu?

- Neoadjuvante Therapie in NSCLC
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT
- Adjuvante Therapie in NSCLC
  - Impower 010
- **Fortgeschrittene Stadium NSCLC**
  - Immunchemotherapie
  - Post Immuntherapie
  - TKI
  - Leptomeningeale Metastasen
- SCLC

Was ist neu?

- Fortgeschrittene Stadium NSCLC
  - **Immunchemotherapie**
  - Post Immuntherapie
  - TKI
  - Leptomeningeale Metastasen

Fortgeschrittenes Stadium NSCLC



2022 ASCO® ANNUAL MEETING

FDA

Outcomes of anti-PD-(L)1 therapy with or without chemotherapy (chemo) for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score ≥50%: FDA Pooled Analysis

Oladimeji Akinboro[1], Jonathon Vallejo[1], Erica Nakajima[1], Yi Ren[1], Pallavi Mishra-Kalyani[1], Erin Larkins[1], Paz Vellanki[1], Nicole Drezner[1], Mathieu Luckson[1], Shenghui Tang[1], Martha Donoghue[1,2], Richard Pazdur[1,2], Julia A. Beaver[1,2], Harpreet Singh[1,2]

[1]Center for Drug Evaluation and Research, U.S. Food and Drug Administration

[2]Oncology Center of Excellence, U.S. Food and Drug Administration

Oladimeji Akinboro, MD, MPH

FDA-approved regimens for advanced/metastatic NSCLC not harboring tumor genomic alterations

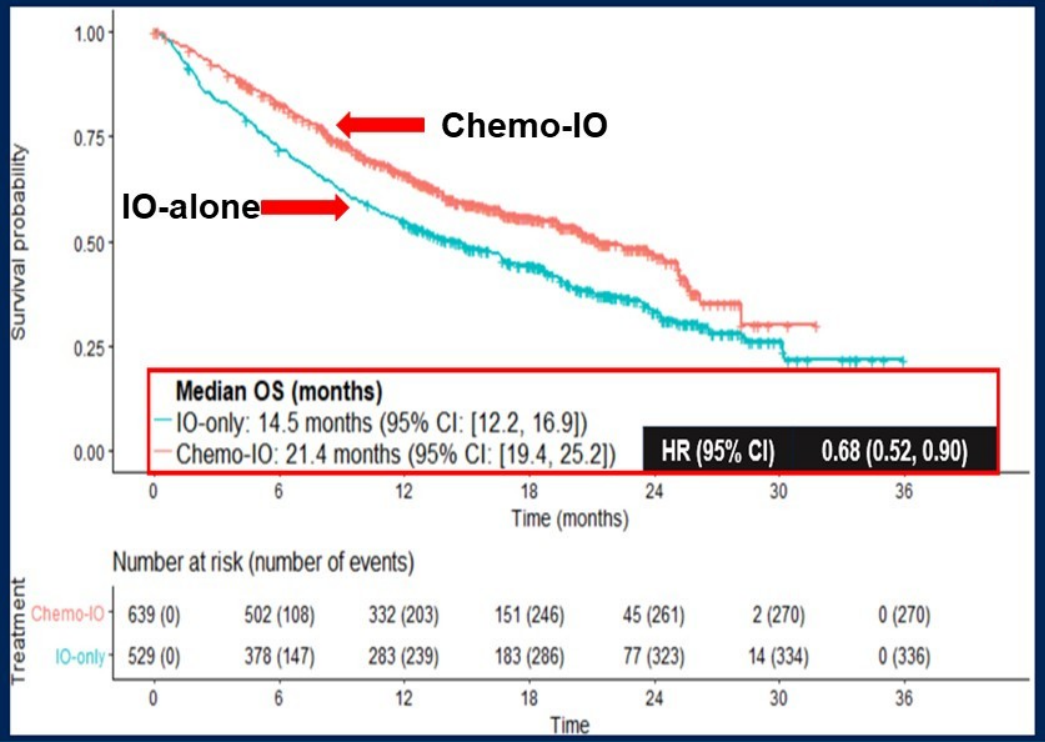
PD-L1 level	Regimen	Histology	Approval endpoint
≥ 50%	**Pembrolizumab**	NSCLC	**OS** & PFS
	Atezolizumab [a]	NSCLC	**OS**
	Cemiplimab	NSCLC	**OS** & PFS
≥ 1%	**Pembrolizumab**	NSCLC	**OS**
	Nivolumab + Ipilimumab	NSCLC	**OS**
None	**Pembrolizumab** + Platinum + Pemetrexed [b]	NSq-NSCLC	**OS** & PFS
	Pembrolizumab + Carboplatin + Paclitaxel	Sq-NSCLC	**OS** & PFS
	Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel	NSq-NSCLC	**OS** & PFS
	Atezolizumab + Carboplatin + Nab-paclitaxel	NSq-NSCLC	**OS** & PFS
	Nivolumab + Ipilimumab + Platinum doublet	NSCLC	**OS**

Abbreviations: NSCLC=non-small cell lung cancer; Nsq=non-squamous; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival; Sq=squamous.
[a] PD-L1 high population for atezolizumab defined as PD-L1 staining ≥ 50% of tumor cells or tumor-infiltrating immune cells covering ≥ 10% of the tumor area.
[b] Initial Accelerated approval in 2017 based on PFS.

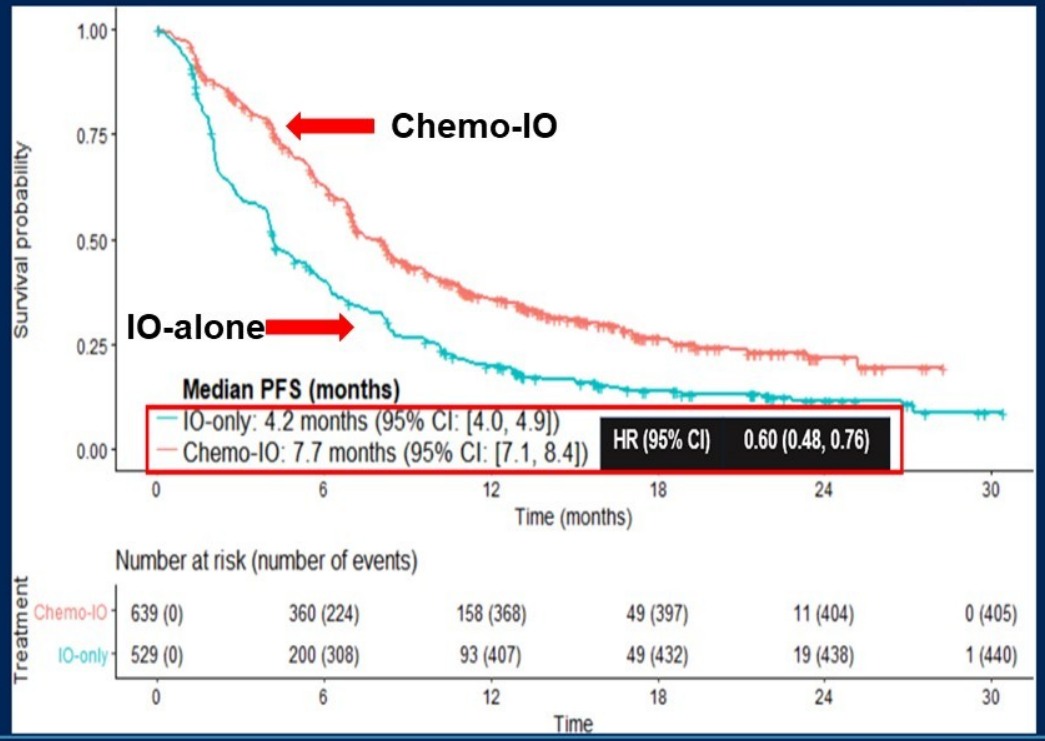
PRESENTED BY:
Oladimeji Akinboro, MD, MPH

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Exploratory OS: NSCLC PDL1 1-49%



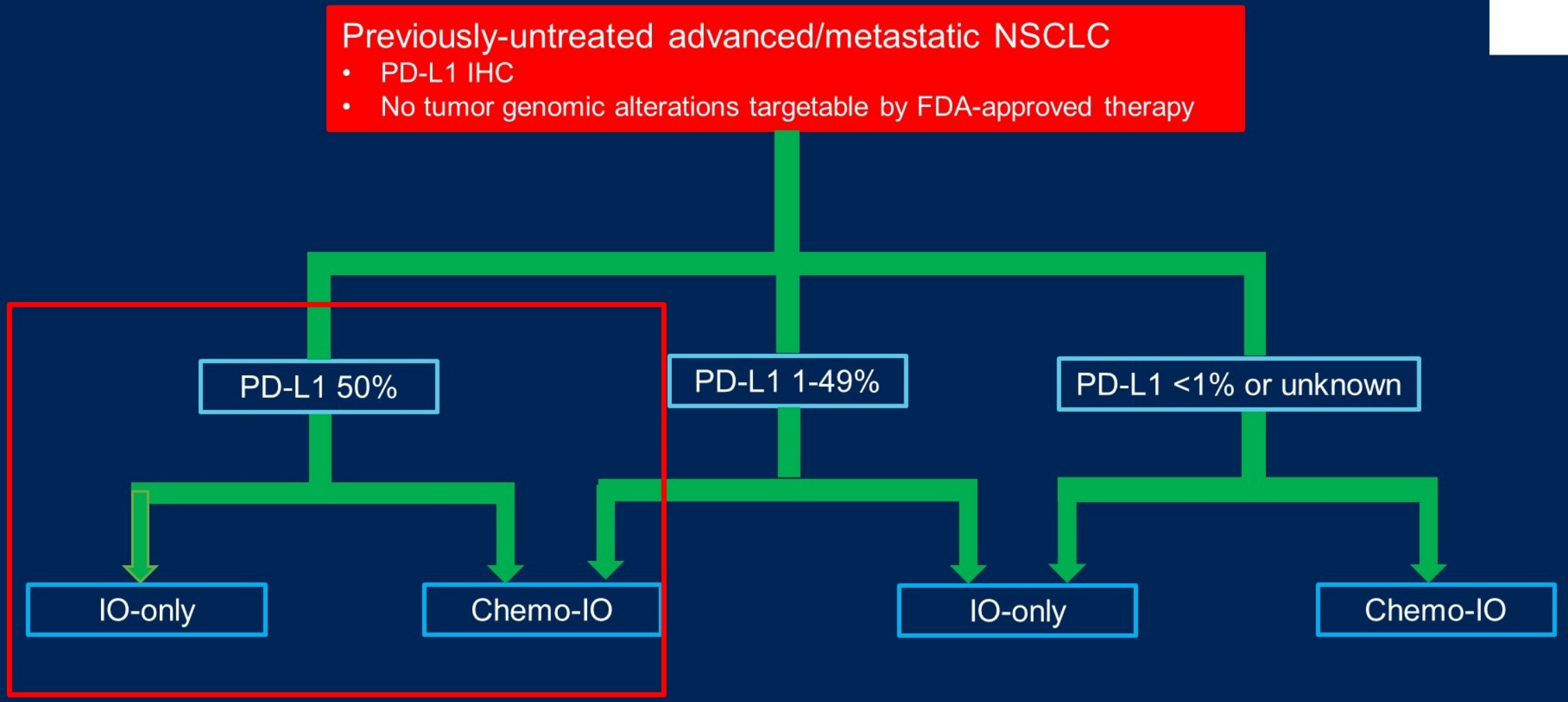
Exploratory PFS: NSCLC PDL1 1-49%



Presented By:
Oladimeji Akinboro; June 4, 2021

#ASCO21 | Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

2021 ASCO ANNUAL MEETING



Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; IO=immunotherapy; NSCLC=non-small-cell lung cancer; PD-L1=programmed death ligand-1.

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Study Design

Pooled Analysis Population

- Advanced NSCLC
- PD-L1 TPS ≥50%
  - Excluded staining by tumor-infiltrating immune cells
- No sensitizing *EGFR* mutations or *ALK* alterations
- Clinical trial supported FDA approval of IO-based regimen

Chemo-IO

IO-only

Exploratory Primary Outcome measure

- OS

Other exploratory outcome measures

- PFS
- ORR

Sub-group analyses

- Age (yrs): *<65 vs 65-75 vs ≥75*
- ECOG PS: *0 vs. ≥ 1*
- Smoking history: *Never vs. Ever*

Abbreviations: *ALK*=anaplastic lymphoma kinase gene; Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; ECOG PS=Eastern Cooperative Oncology Group Performance Status; *EGFR*=epidermal growth factor receptor gene; FDA=U.S. Food and Drug Administration; IO=immunotherapy; NSCLC=non-small-cell lung cancer; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival; TPS=tumor proportion score; yrs=years.

Statistical analysis

- OS and PFS:
  - Medians estimated with Kaplan-Meier methods
  - Hazard ratios estimated with Cox proportional hazards model stratified by trial
- ORR:
  - Odds ratios estimated with a logistic regression model with trial as a covariate
- All analyses were covariate-adjusted for:
  - Age, sex, race, ECOG PS, histology and smoking history

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Clinical trials of first-line Chemo-IO and IO regimens included in FDA pooled analysis

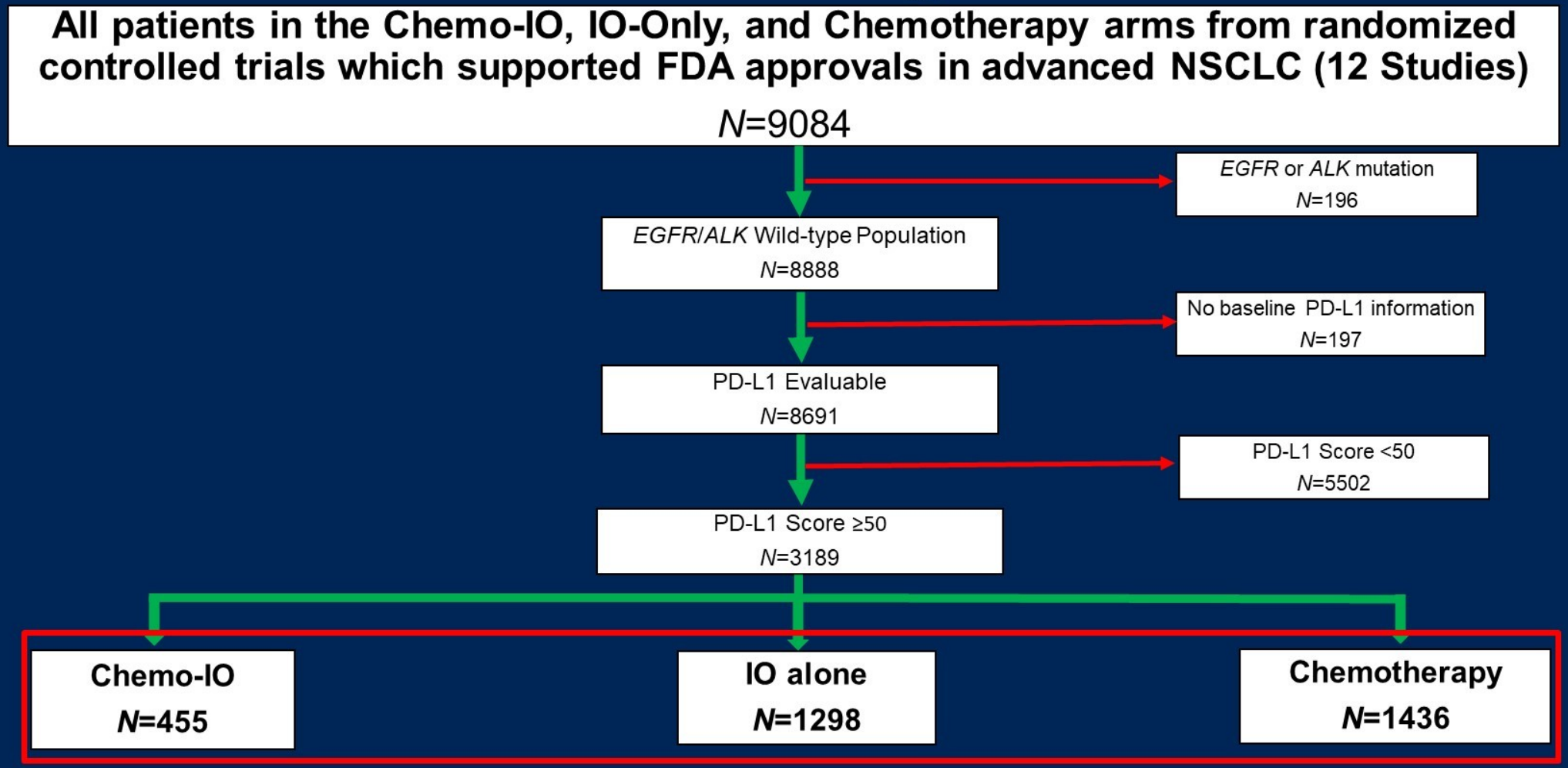
Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy immunotherapy; IO=immunotherapy.
* Cohort G
** Control arms: Platinum-based doublet chemotherapy
*** Control arm in IMpower150: Bevacizumab plus platinum-based doublet chemotherapy

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Consort Diagram



Abbreviations: *ALK*=anaplastic lymphoma kinase gene; Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; *EGFR*=epidermal growth factor receptor gene; FDA=U.S. Food and Drug Administration; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; PD-L1=programmed death ligand-1.

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

Demographic and baseline characteristics

		Chemo-IO (*N*=455)	IO alone (*N*=1,298)	Chemo (*N*=1,436)	Overall (*N*=3,189)
Age	Median, years	65	64	64	64
	<65 years, %	49	53	50	51
	65-74 years, %	41	36	39	38
	≥75 years, %	10	11	11	11
Sex	Female	37	29	31	31
Race	White, %	91	77	80	80
	Black, %	1	1	2	1
	Asian, %	8	20	16	16
Smoking history	Ever smoked, %	87	89	88	89
ECOG PS	≥1, %	59	68	67	66
Histology	Non-squamous, %	78	69	68	70

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IO=immunotherapy; *N*=number.

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

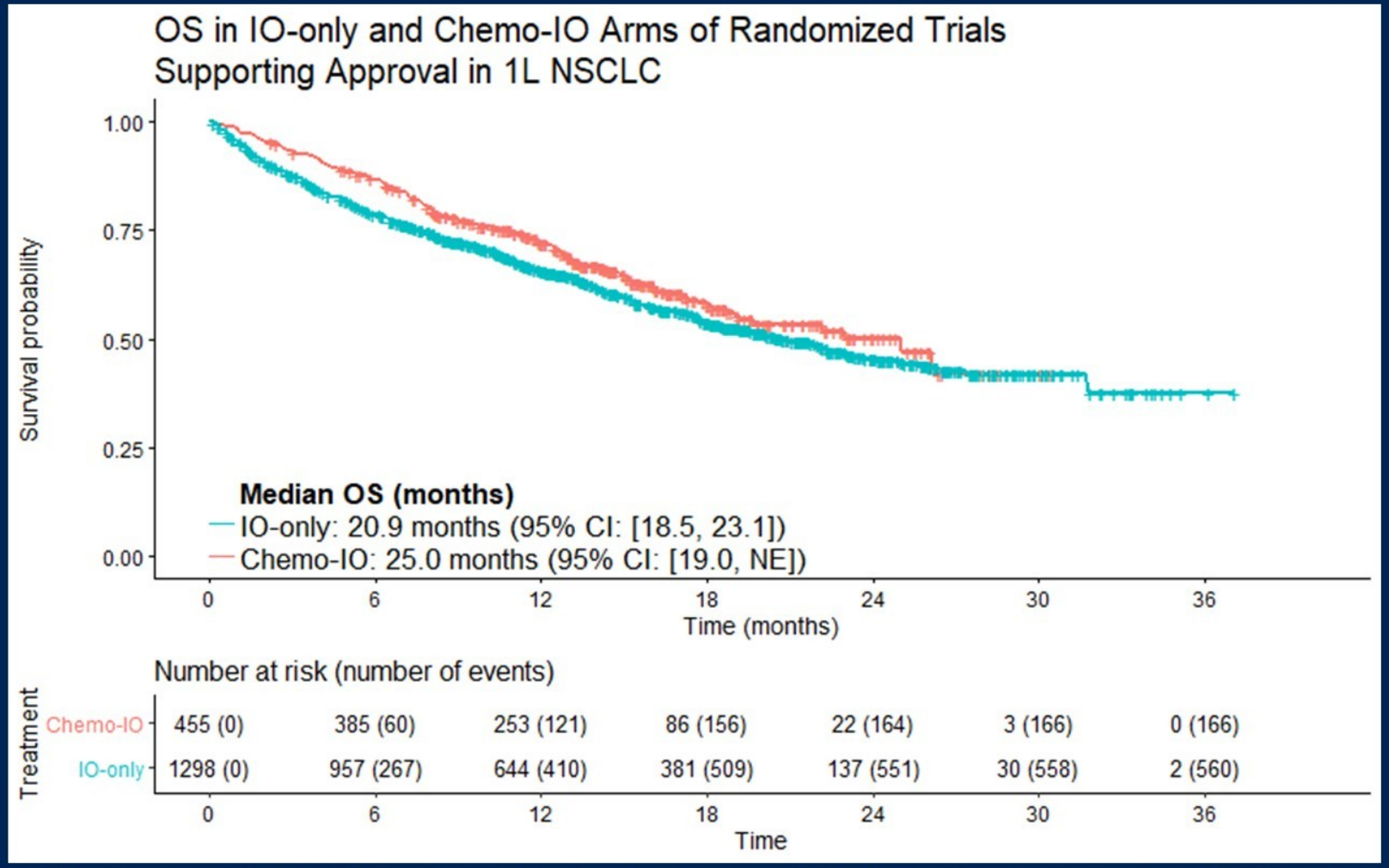
Exploratory OS, PFS, and ORR: NSCLC PD-L1 ≥50%

	Chemo-IO (*N*=455)	IO-alone (*N*=1,298)
OS		
Median, months (95% CI)	25.0 (19.0, NE)	20.9 (18.5, 23.1)
HR (95% CI)	0.82 (0.62, 1.08)	
PFS		
Median, months (95% CI)	9.6 (8.4, 11.1)	7.1 (6.3, 8.3)
HR (95% CI)	0.69 (0.55, 0.87)	
ORR		
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio	1.2 (1.1, 1.3)	

Abbreviations: Chemo-IO=platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR-hazards ratio; IO=immunotherapy; *N*=number; NSCLC=non-small-cell lung cancer; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

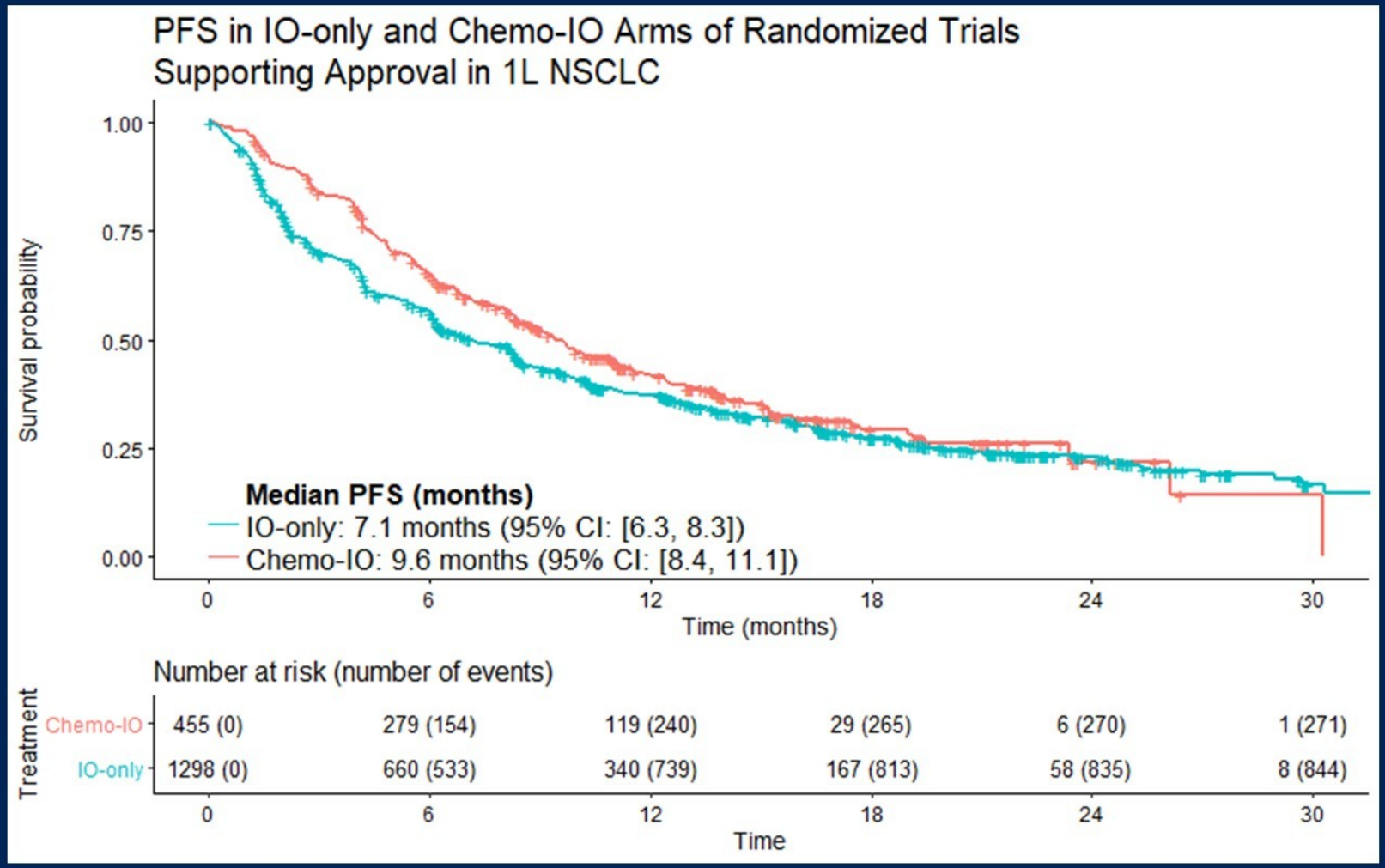
Exploratory OS: Chemo-IO vs IO in NSCLC PD-L1 ≥50%



Abbreviations: Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; CI=confidence interval; HR=hazard ratio; 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

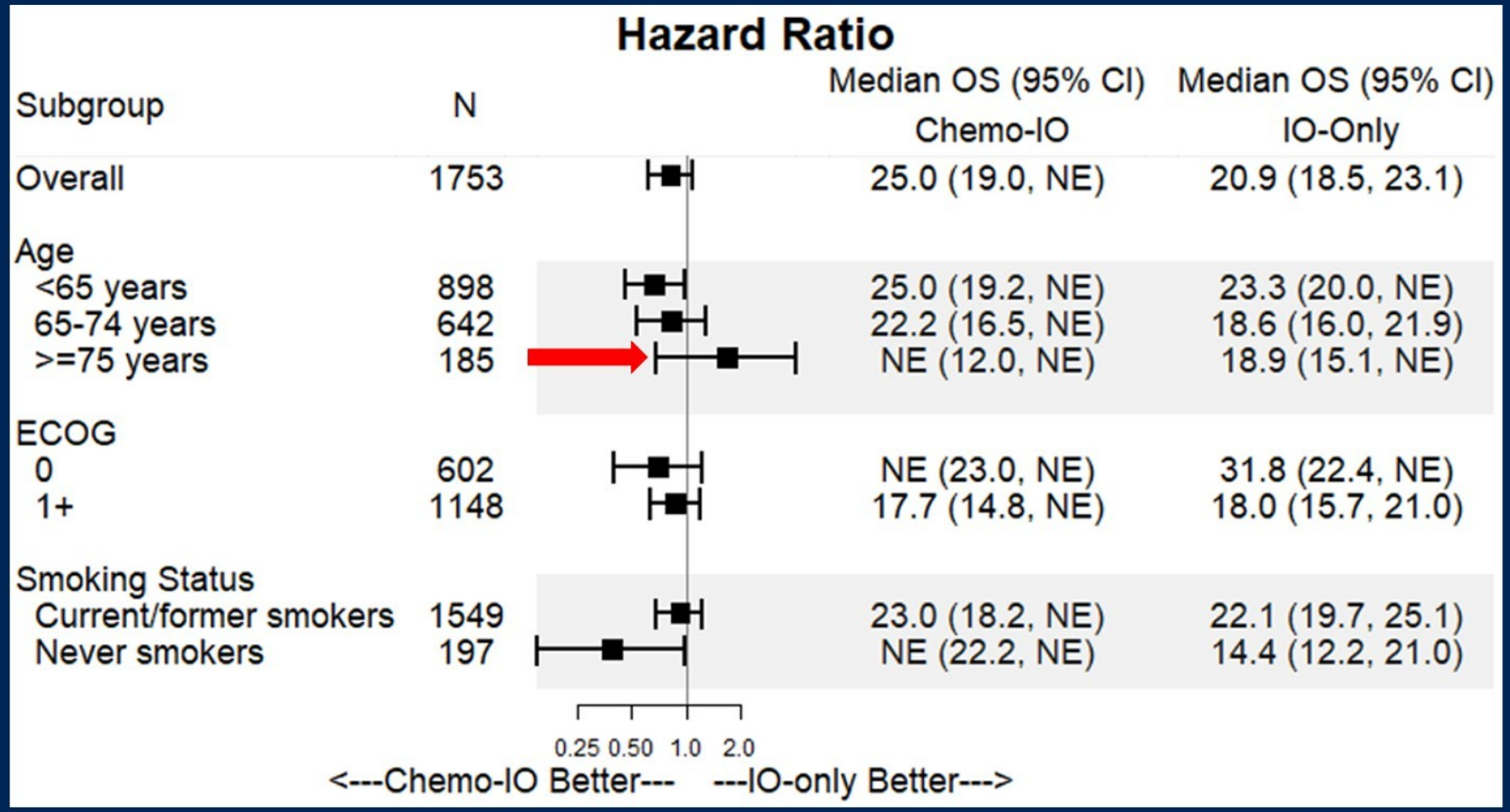
Exploratory PFS: Chemo-IO vs IO in NSCLC PD-L1 ≥50%



Abbreviations: Chemo-IO= platinum-based doublet chemotherapy plus immunotherapy; CI-confidence interval; HR=hazard ratio; IO=immunotherapy; NSCLC=non-small-cell lung cancer; PD-L1=programmed death ligand-1; PFS=progression-free survival.

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

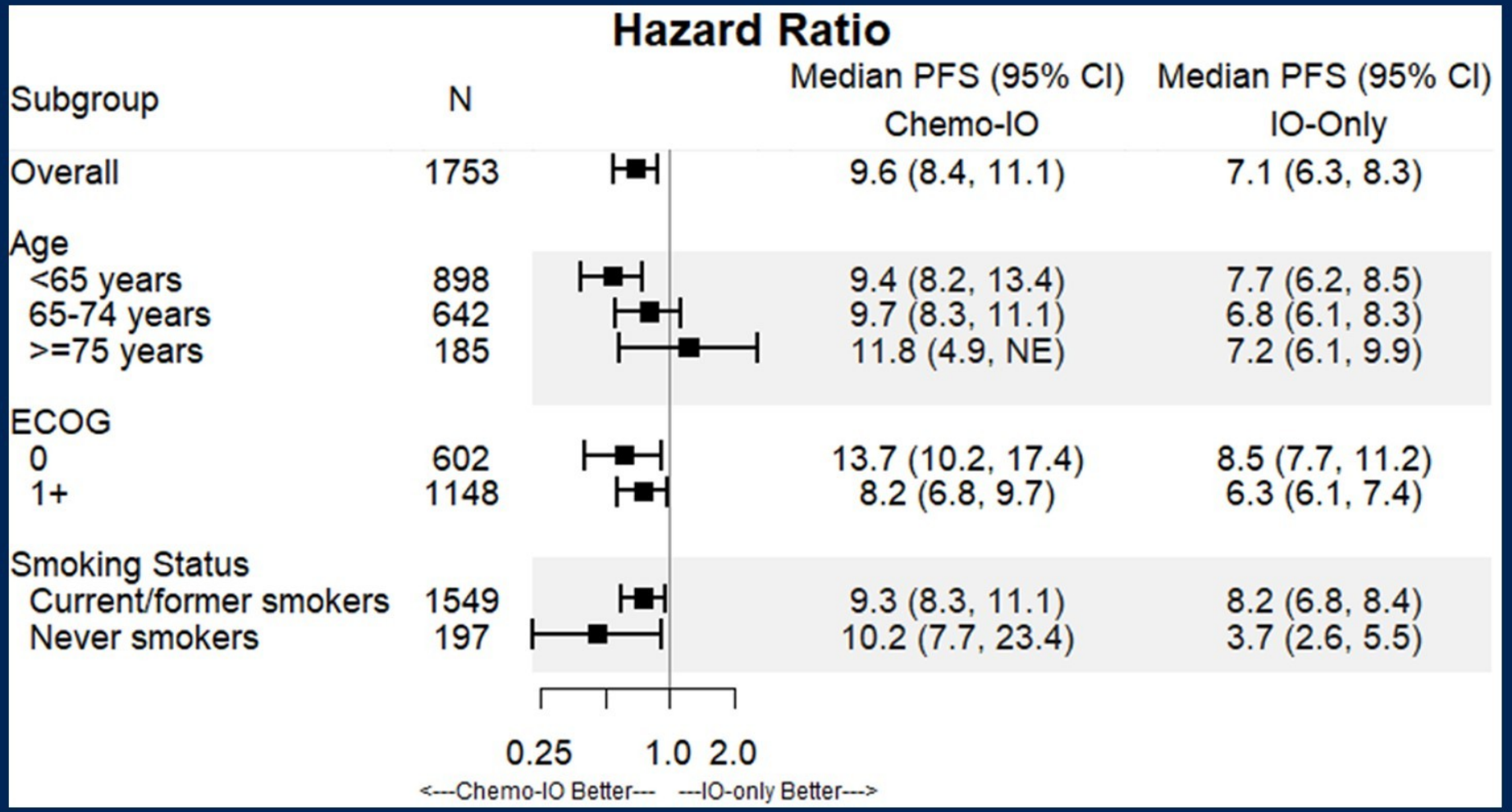
OS in NSCLC PD-L1 ≥50% in selected subgroups



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

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



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; PD-L1=programmed death ligand-1; PFS=progression-free survival.

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

Limitations

- Retrospective exploratory pooled analyses
  - Results only hypothesis-generating
- Analyses do not explain the lack of concordance between OS and PFS/ORR results
  - Subsequent therapies in the IO-only arm
  - Deaths and treatment-discontinuation due to toxicity
- Potential heterogeneity across trials
  - Differences in PD-L1 assays
- Notable differences between clinical trial populations and real-world patients

Abbreviations: Chemo-IO=chemoimmunotherapy; IO=immunotherapy; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand-1; PFS=progression-free survival.

PRESENTED BY:
Oladimeji Akinboro, MD, MPH

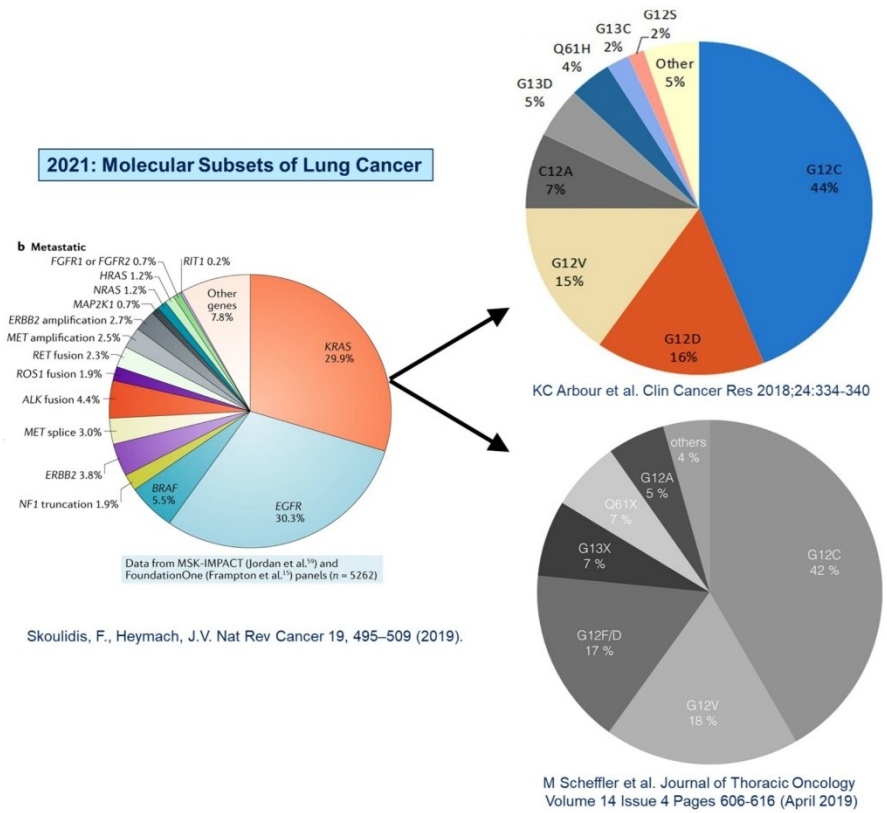
Fazit

- Überlegenheit der Immunmonotherapie im fortgeschrittenen Stadium wurde nicht nachgewiesen
- Immunchemotherapie für Patienten ≥ 75 und Nichtraucher Vorteilhaft
- Abhängig von Komorbidität und Tumorlast könnte Immunchemotherapie auch für Patienten mit erhöhter PD-L1 Expression eingesetzt werden

Was ist neu?

- Neoadjuvante Therapie in NSCLC
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT
- Adjuvante Therapie in NSCLC
  - Impower 010
- Advanced stage NSCLC
  - Immunchemotherapie
  - **TKI**
  - Post Immuntherapie
  - Leptomeningeale Metastasen
- SCLC

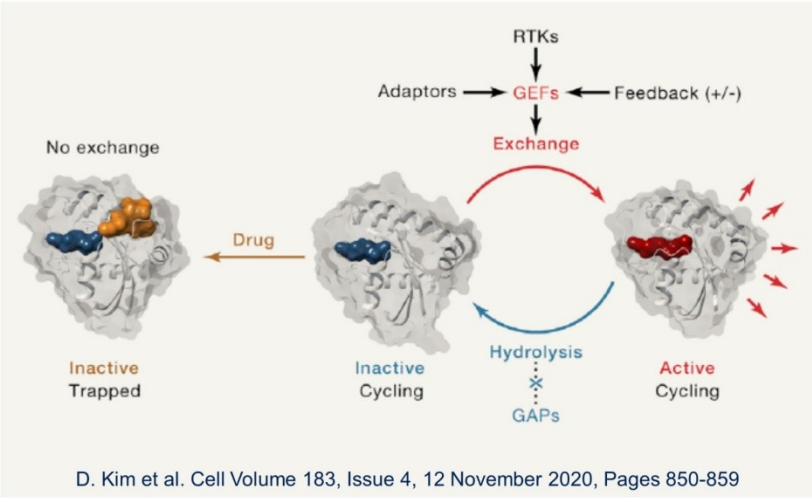
Focus on KRAS mutations in Non-Small Cell Lung Cancer



- KRAS G12C most common KRAS variant
- 13% (1 in 8) or all lung adenocarcinomas
- Multiple KRAS G12C inhibitors being developed

KRAS G12C Inhibitors - Mechanism of Action

- Novel class of drugs → these are targeted therapies but they are not TKIs
- Allele-specific inhibitors targeting the Cysteine (C) residue.
- The inhibitors bind covalently to the mutant cysteine residue and occupy a pocket in the switch II region (SIIP) when KRAS G12C is in its inactive GDP-bound state (inactive-state selective drugs).



D. Kim et al. Cell Volume 183, Issue 4, 12 November 2020, Pages 850-859

2022 ASCO® ANNUAL MEETING

KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients with Advanced/Metastatic Non-Small Cell Lung Cancer Harboring a $KRAS^{G12C}$ Mutation

Alexander I. Spira[1], Gregory J. Riely[2], Shirish M. Gadgeel[3], Rebecca S. Heist[4], Sai-Hong Ignatius Ou[5], Jose M. Pacheco[6], Melissa L. Johnson[7], Joshua K. Sabari[8], Konstantinos Leventakos[9], Edwin Yau[10], Lyudmila Bazhenova[11], Marcelo V. Negrao[12], Nathan A. Pennell[13], Jun Zhang[14], Karen Velastegui[15], James G. Christensen[15], Xiaohong Yan[15], Kenna Anderes[15], Richard C. Chao[15], Pasi A. Jänne[16]

[1]Virginia Cancer Specialists, Fairfax, VA; US Oncology Research, The Woodlands, TX; NEXT Oncology Virginia, Fairfax, VA; [2]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY; [3]Henry Ford Cancer Institute, Detroit, MI; [4]Massachusetts General Hospital, Boston, MA; [5]University of California, Irvine, Chao Family Comprehensive Cancer Center, Orange, CA; [6]University of Colorado Anschutz Medical Campus, Aurora, CO; [7]Sarah Cannon Research Institute Tennessee Oncology, Nashville, TN; [8]Perlmutter Cancer Center, New York University Langone Health, New York, NY; [9]Mayo Clinic, Rochester, MN; [10]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [11]UC San Diego Moores Cancer Center, La Jolla, CA; [12]MD Anderson Cancer Center, Houston, TX; [13]Cleveland Clinic, Cleveland, OH; [14]University of Kansas Medical Center, Kansas City, KS; [15]Mirati Therapeutics, Inc., San Diego, CA; [16]Dana-Farber Cancer Institute, Boston, MA

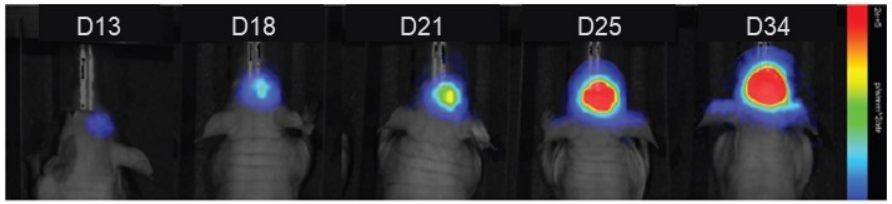
PRESENTED BY:
Dr Alexander I. Spira

Adagrasib (MRTX849) is a Differentiated KRAS^{G12C} Inhibitor

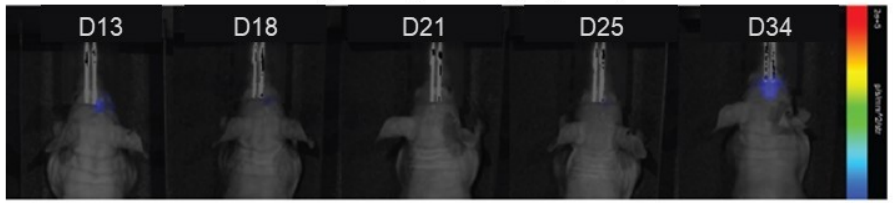
- KRAS^{G12C} mutations act as oncogenic drivers and occur in ~14% of patients with NSCLC (adenocarcinoma)[1]
  - Approximately 27–42% of patients with KRAS^{G12C}-mutated NSCLC have CNS metastases at diagnosis[2,3]
- Adagrasib, a covalent inhibitor of KRAS^{G12C}, was optimized for desired properties of a KRAS^{G12C} inhibitor, including a long half-life (23 hours), dose-dependent PK and CNS penetration[4,5]
- In the FIH Phase 1/1b trial of adagrasib in patients with KRAS^{G12C}-mutated NSCLC (n=15), the ORR was 53.3%, median DOR was 16.4 months, and median PFS was 11.1 months[6]
- Adagrasib demonstrated CNS penetration and CNS tumor regressions in preclinical models.[7] In a preliminary analysis in a Phase 1b cohort evaluating adagrasib in patients with NSCLC and active, untreated CNS metastases (n=2):[7]
  - Mean $K_{p,uu}$ value was 0.47
  - Regression of CNS metastases was observed in both patients

LU99Luc KRAS^{G12C} Brain Metastases Model[7]

Vehicle



Adagrasib (100 mg/kg BID)



- Clinical activity with adagrasib has been shown in patients with various KRAS^{G12C}-mutated solid tumors, including NSCLC, CRC, PDAC, ovarian and endometrial cancers, and other GI cancers[5,8–10]

KRYSTAL-1 (849-001) Phase 2 Cohort A Study Design

Phase 2
NSCLC Monotherapy Treatment

Key Eligibility Criteria

- NSCLC with KRAS^{G12C} mutation[a]
- Unresectable or metastatic disease
- Prior treatment with a PD-1/L1 inhibitor in combination or in sequence with chemotherapy
- Treated, stable CNS metastases were allowed

Adagrasib 600 mg BID (Capsule, Fasted)

Study Objectives

- Primary endpoint: ORR (RECIST 1.1) per BICR
- Secondary endpoints: DOR, PFS, OS, safety

Here we report data from a registrational Phase 2 cohort evaluating adagrasib 600 mg BID in previously treated patients with NSCLC harboring a KRAS^{G12C} mutation (N=116)

Enrollment period, January 2020 to December 2020

[a]KRAS^{G12C} mutation detected in tumor tissue by sponsor-approved local laboratory testing
ClinicalTrials.gov. NCT03785249

Demographics and Baseline Characteristics

	Adagrasib Monotherapy (N=116)[a]
Median age (range), years	64 (25–89)
Female sex, n (%)	65 (56%)
Race, n (%)	
White	97 (84%)
Black or African American	9 (8%)
Asian / Other	5 (4%) / 5 (4%)
ECOG PS, n (%)[b]	
0 / 1	18 (16%) / 97 (84%)
Smoking history, n (%)	
Never smoker	5 (4%)
Current smoker / former smoker	11 (10%) / 100 (86%)
Prior lines of systemic therapy, n (%)	
1	50 (43%)
2	40 (35%)
3+	26 (22%)
Prior platinum-based therapy and/or checkpoint inhibitor therapy, n (%)[c]	
Received prior platinum-based therapy only	2 (2%)
Received both	114 (98%)
Baseline metastases, n (%)	
Bone	46 (40%)
CNS	24 (21%)
Adrenal	22 (19%)
Liver	19 (16%)

[a]Among the enrolled patients, 113 (97%) had adenocarcinoma and 3 (3%) had squamous histology; 103 patients (89%) had metastatic disease and 13 (11%) had locally advanced disease; [b]Missing, n=1; [c]78 patients (67%) had received checkpoint inhibitor therapy as their immediate prior line of therapy

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Tumor Response by BICR

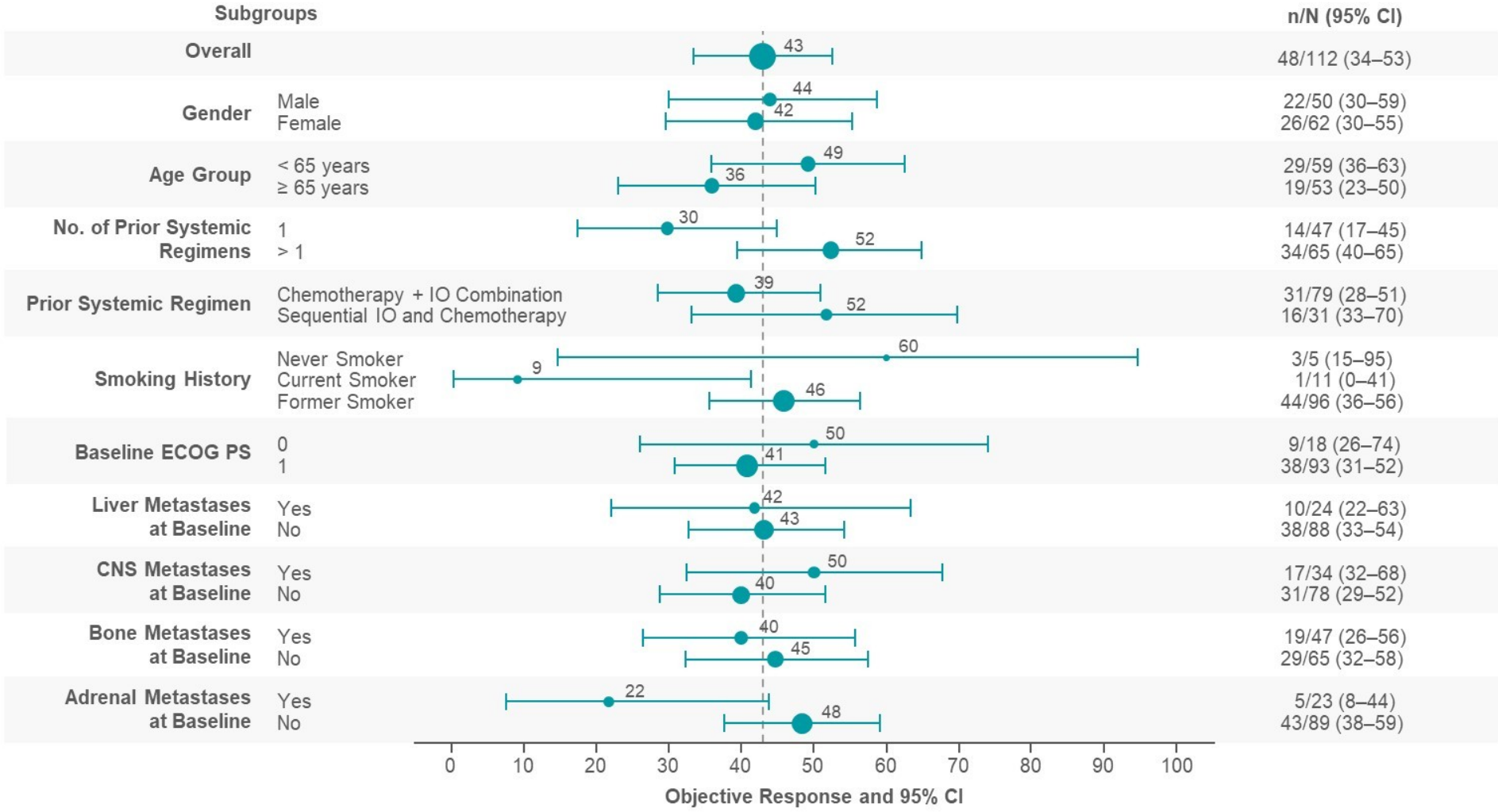
Efficacy Outcome	Adagrasib Monotherapy (n=112)[a]
Objective response rate, n (%)	48 (43%)
Best overall response, n (%)	
Complete response	1 (1%)
Partial response	47 (42%)
Stable disease	41 (37%)
Progressive disease	6 (5%)
Not evaluable	17 (15%)
Disease control rate, n (%)	89 (80%)

- 17 patients were not evaluable due to having received post-baseline scans too early (n=3) or study withdrawal prior to first scheduled assessment (n=14)[b]
- For evaluable patients (on treatment and who had a scan at ~6 weeks[c]), ORR was 51% (48/95)

[a]Full analysis set as per BICR excludes 4 patients who did not have measurable disease at baseline; [b]Due to reasons of: withdrawal by patient (n=5), AEs (n=3; 2 patients experienced AEs not related to treatment, 1 patient experienced a TRAE), global deterioration of health (n=3), death (n=2), non-compliance (n=1); [c]6 weeks ± 10 days

Data as of October 15, 2021 (median follow-up: 12.9 months)

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Exploratory Subgroup Analyses

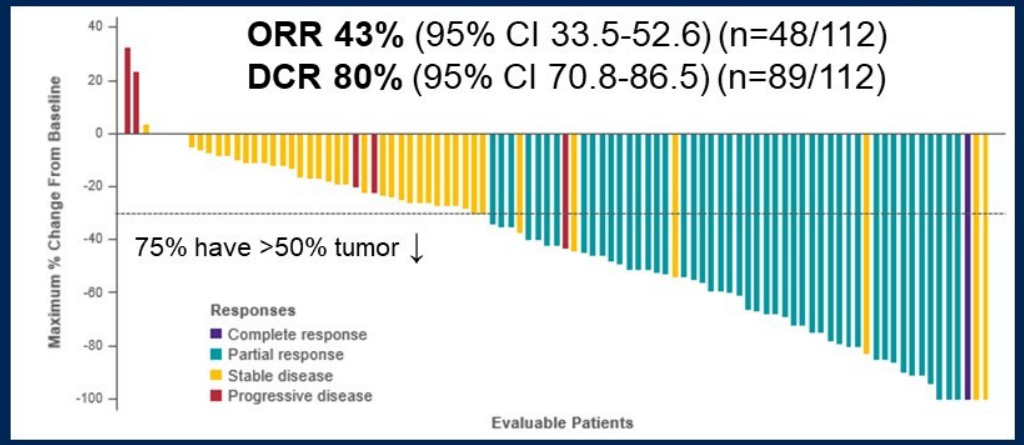


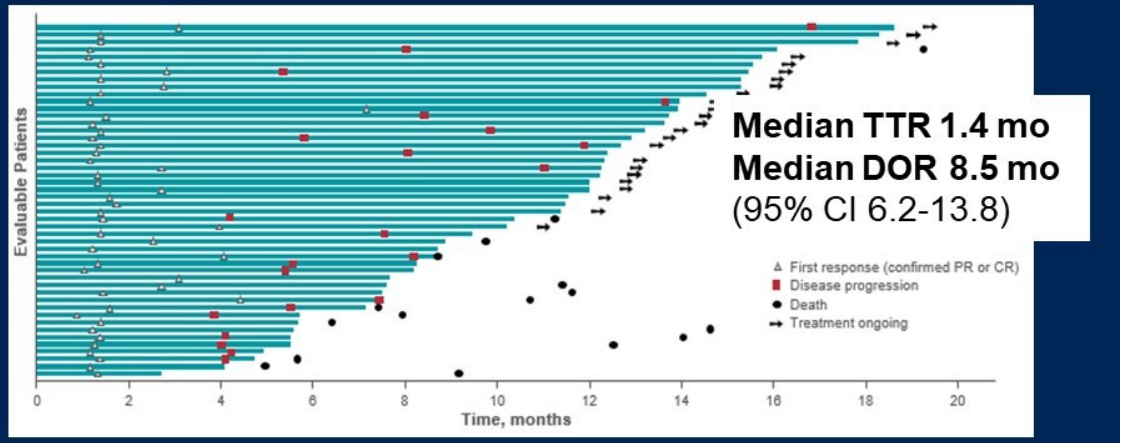
All results are based on BICR. Dot size indicates sample size. Note that for the 3 patients with squamous NSCLC: 1 patient had a BOR of PR, 2 patients had a BOR of SD

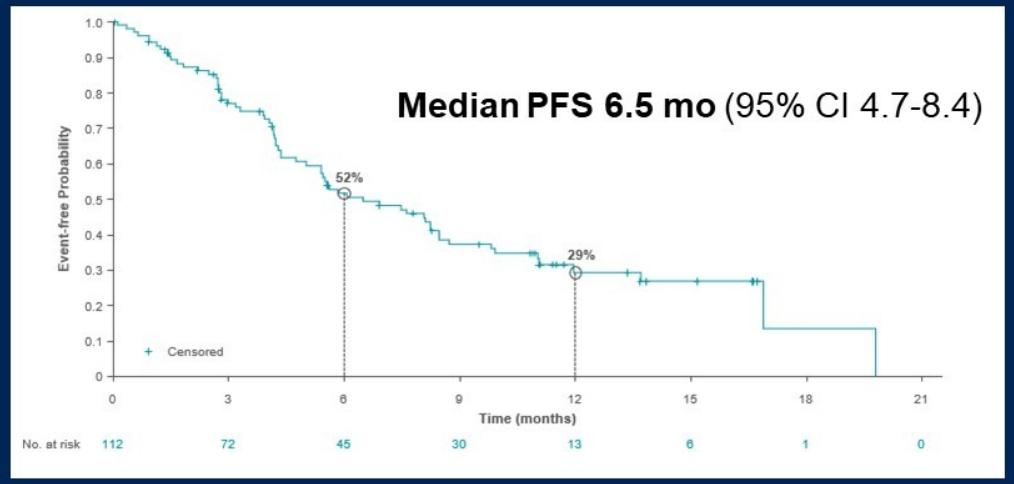
Data as of October 15, 2021 (median follow-up: 12.9 months)

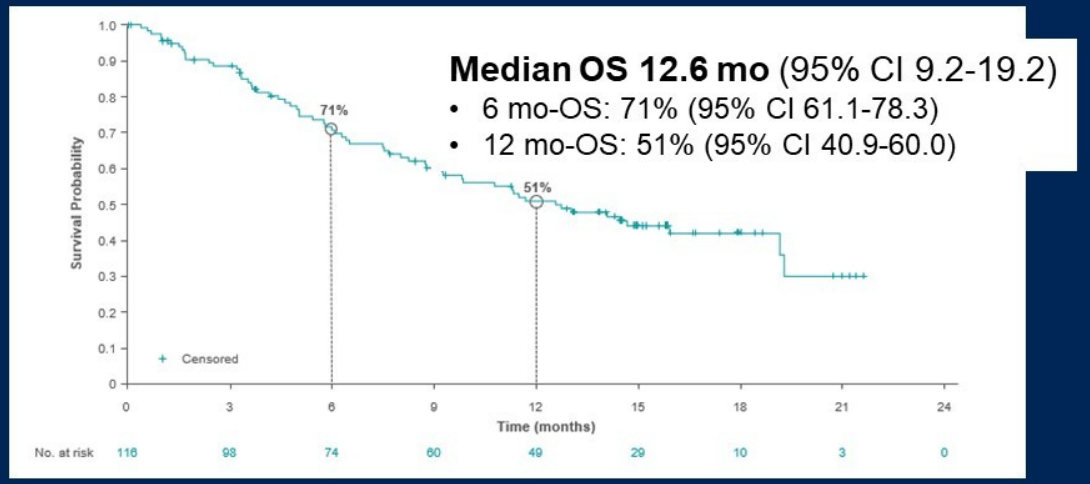
#9002 (Spira): *In pts with KRAS G12C advanced NSCLC, is adagrasib an optimal second line treatment option?*

KRYSTAL-1 Ph 2 Cohort A: 112 had measurable disease (15% (n=17) not evaluable)









PRESENTED BY:
Sukhmani K. Padda MD
Cedars-Sinai Medical Center/Samuel Oschin Cancer Center

Efficacy KRAS G12C inhibitor: Adagrasib vs. Sotorasib

Parameter	Adagrasib (KRYSTAL-1)	Sotorasib (CodeBreaK100)[1]
N=	116 (112 for efficacy)	126 (124 for efficacy)
Prior Platinum Chemo + IO	**98%**	**81%**
ORR	**43%** (95% CI 33.5-52.6)	**37.1%** (95% CI 28.6-46.2)
DCR	**80%** (95% CI 70.8-86.5)	**80.6%** (95% CI 72.6-87.2)
TTR, median (range)	**1.4 mo** (0.9-7.2)	**1.4 mo** (1.2-10.1)
DOR, median	**8.5 mo** (95% CI 6.2-13.8)	**11.1 mo** (95% CI 6.9-NE)
PFS, median	**6.5 mo** (95% CI 4.7-8.4)	**6.8 mo** (95% CI 5.1-8.2)
OS, median	**12.6 mo** (95% CI 9.2-19.2)	**12.5 mo**[2] (95% CI 10.0-NE)
Follow-up, median	12.9 mo	15.3 mo[2]

1= Skoulidis et al. N Engl J Med. 2021 Jun 24;384(25):2371-2381; 2=Pooled phase 1/2 of 174 pts with median f/u 24.9 mo, median OS 12.5 mo (95% CI 10.0-17.8), 1-year OS 50.8%, 2-year OS 32.5% (Dy G et al. AACR 2022)

PRESENTED BY:
Sukhmani K. Padda MD
Cedars-Sinai Medical Center/Samuel Oschin Cancer Center

Treatment-Related Adverse Event (TRAE)

ADAGRASIB

	Adagrasib (N=116)[1]	
TRAEs, n (%)	**Any Grade**	**Grades 3–4[2]**
Any TRAEs	113 (97%)	50 (43%)
Most frequent TRAEs, n (%)		
**Diarrhea*	73 (63%)	1 (<1%)
**Nausea*	72 (62%)	5 (4%)
**Vomiting*	55 (47%)	1 (<1%)
**Fatigue*	47 (41%)	5 (4%)
**ALT increase*	32 (28%)	5 (4%)
Blood creatinine increase	30 (26%)	1 (<1%)
**AST increase*	29 (25%)	4 (3%)
Decreased appetite	28 (24%)	4 (3%)
Anemia	21 (18%)	6 (5%)
Amylase increase	20 (17%)	1 (0.9%)
QT prolongation	19 (16%)	5 (4%)

1=Capsule, Fasted
2=3 Grade 4 TRAEs. 2 Grade 5 TRAE (1 Cardiac Failure, 1 Pulmonary Hemorrhage)

SOTORASIB

	Sotorasib (N=126)	
TRAEs, n (%)	**Any Grade**	**Grades 3–4[1]**
Any TRAEs	88 (70%)	26 (21%)
Most frequent TRAEs, n (%)		
Diarrhea	40 (32%)	5 (4%)
Nausea	24 (19%)	0
ALT increase[2]	19 (15%)	8 (6%)
AST increase[2]	19 (15%)	7 (6%)
Fatigue	14 (11%)	0
Vomiting	10 (8%)	0

1= Only 1 patient with Grade 4 TRAE of dyspnea & pneumonitis. No Grade 5 TRAE.
2=TRAE (Any Grade/G3): Blood alk phos increase 9 (7%)/1 (<1%); Drug-induced liver injury 3 (2.4%)/ 2 (1.6%); Gamma-GGT increase 3 (2.4%)/3 (2.4%); Abnl hepatic function 2 (1.6%)/1 (<1%); 1 G3 event each of Hepatotoxic Event, Increase liver function level, Abnormal aminotransferase level

- **Dose Reduction/Interruption**
- Adagrasib: **52%** Dose Reduction, 61% Dose Interruption
  - 33% 400 mg bid, 11% 600 mg qd, 14% (200 mg bid or 400 mg qd)
- Sotorasib (both interruption/reduction): 22.2%
- **TRAEs led to dose discontinuation**: Adagrasib 7%, Sotorasib 7.1%

Skoulidis F et al. N Engl J Med. 2021 Jun 24;384(25):2371-2381.

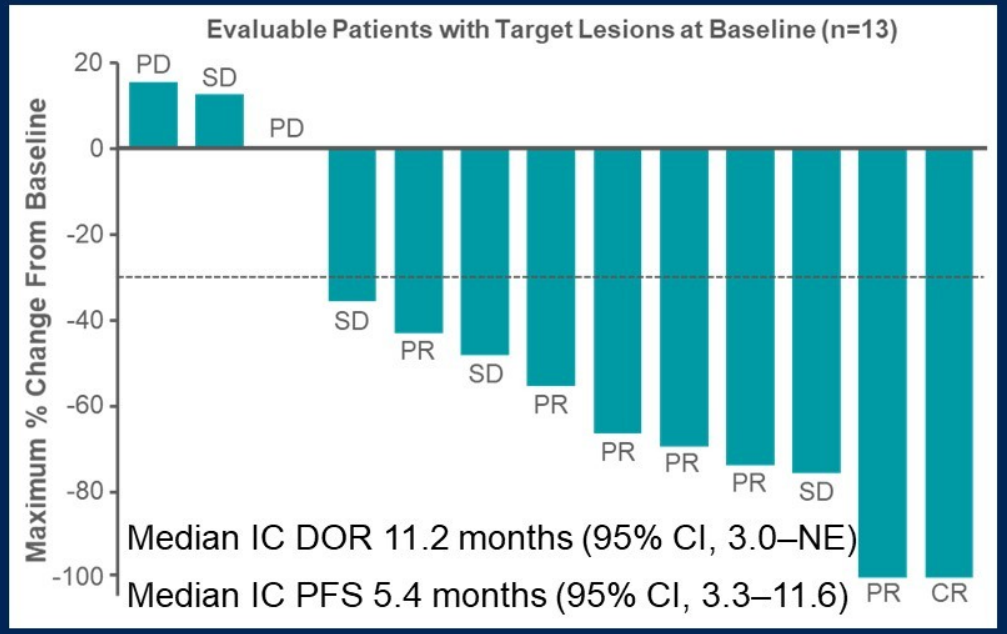
PRESENTED BY:
Sukhmani K. Padda MD
Cedars-Sinai Medical Center/Samuel Oschin Cancer Center

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Adagrasib intracranial response – treated stable brain metastases[1]

Caveat: 82% (27/33) received prior radiation[2]; 59% < 3 mo and 37% ≥ 6 mo before study entry

Best Overall Response (RANO-BM)[3]	Overall (n=33)	Patients with Non-target Lesions Only (n=19)	Patients with Target Lesions (n=13)
IC ORR, n (%)	**11 (33%)**	**4 (21%)**	**7 (54%)**
Complete response	5 (15%)	4 (21%)	1 (8%)
Partial response	6 (18%)	-	6 (46%)
Stable disease	17 (52%)	13 (68%)	4 (31%)
IC DCR, n (%)	**28 (85%)**	**17 (89%)**	**11 (85%)**



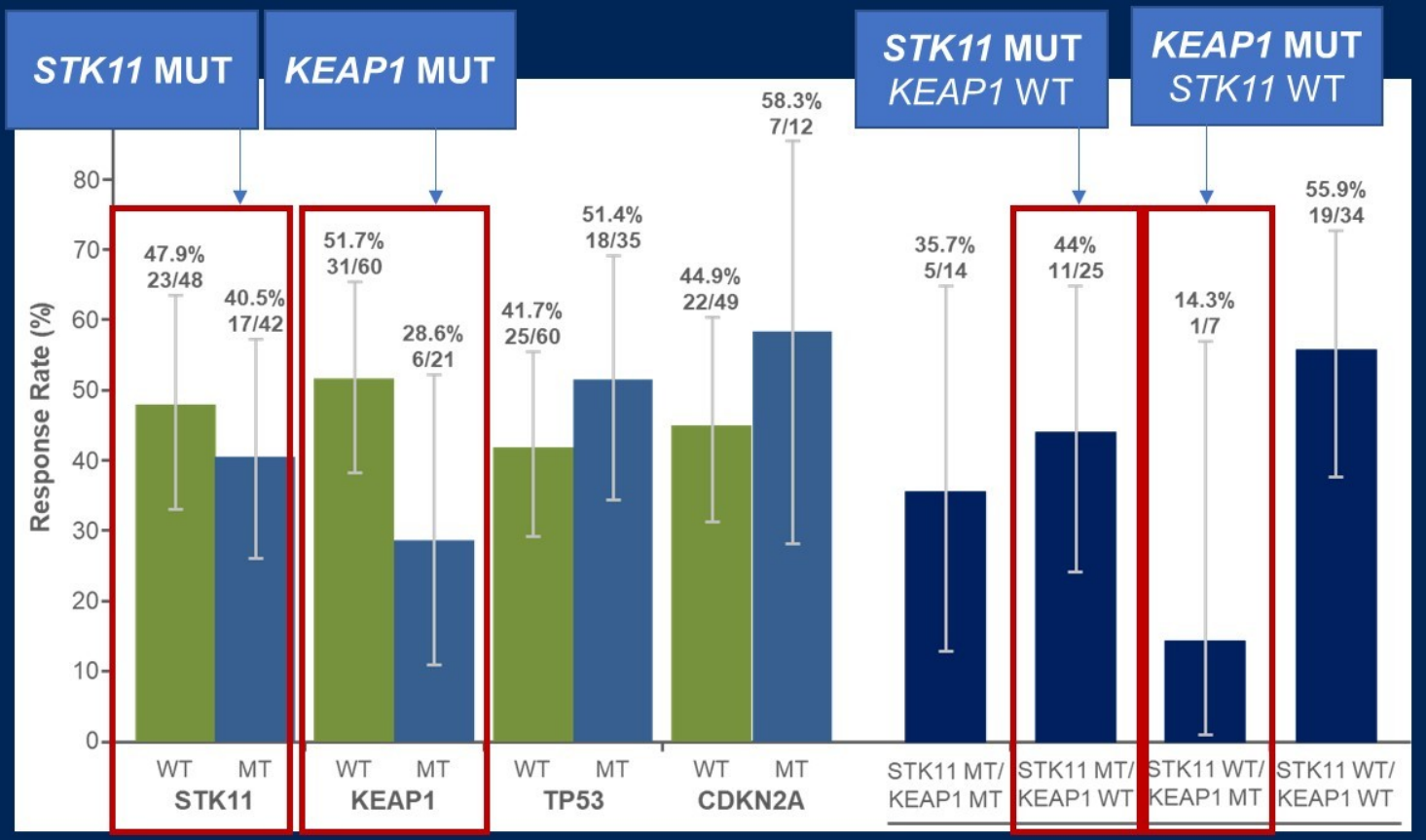
- **Sotorasib[4]: IC DCR 88% (14/16); 2 CRs, 12 SD**
  - Exclude active untreated brain mets, 75% had prior surgery or RT
  - Only 3 with target lesions

1=Exclude active brain metastases (mets). Patients are eligible if brain mets are adequately treated and patients are neurologically stable (except for residual signs or symptoms related to the central nervous system (CNS) treatment) for at least 2 weeks prior to enrollment without the use of corticosteroids or are on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent). 2=Prior RT preceded baseline assessment.;3=For know or suspected brain mets, baseline MRI brain w/ and w/o gadolinium (or CT brain with contrast) every 6 weeks.; 4=Ramalingam S et al. WCLC 2021.

PRESENTED BY:
Sukhmani K. Padda MD
Cedars-Sinai Medical Center/Samuel Oschin Cancer Center

Adagrasib across co-mutation subsets & PD-L1 expression

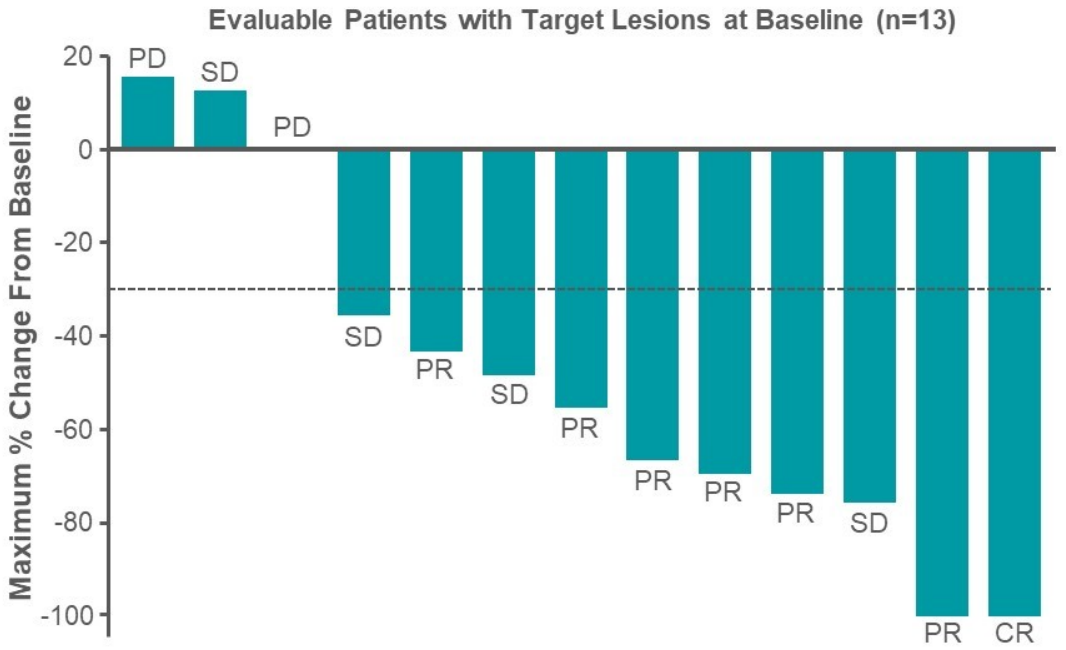
- ORR similar across PD-L1 expression (86 evaluable)
  - PD-L1 <1%, 1-49% and ≥50% had similar ORR: 46.8% (22/47), 44.4% (12/27) and 41.7% (5/12)



PRESENTED BY:
Sukhmani K. Padda MD
Cedars-Sinai Medical Center/Samuel Oschin Cancer Center

Adagrasib in Previously Treated Patients with KRAS^{G12C}-mutated NSCLC: Intracranial Response in Patients with Treated, Stable CNS Metastases[a]

Best Overall Response	Overall (n=33)[b]	Patients with Non-target Lesions Only (n=19)	Patients with Target Lesions (n=13)[c]
IC ORR, n (%)	**11 (33%)**	**4 (21%)**	**7 (54%)**
Complete response	5 (15%)	4 (21%)	1 (8%)
Partial response	6 (18%)	-	6 (46%)
Stable disease	17 (52%)	13 (68%)	4 (31%)
IC DCR, n (%)	**28 (85%)**	**17 (89%)**	**11 (85%)**



- IC ORR by modified RANO-BM was 33% (95% CI, 18–52); median IC DOR was 11.2 months (95% CI, 3.0–NE)
- IC DCR was 85% (95% CI, 68–95); median IC PFS was 5.4 months (95% CI, 3.3–11.6)

Target lesions: all measurable lesions (size ≥5 mm) with ≤5 lesions in total, and representative of all involved organs; non-target lesions: all non-measurable lesions and measurable lesions not identified as target lesions
[a]Among patients with adequately treated, stable CNS metastases, 33 patients were radiographically evaluable (i.e., had a baseline and on-treatment brain scan for evaluation), of whom 27 (82%) received radiation prior to adagrasib treatment (59% <3 months before study entry and 37% ≥6 months before study entry); [b]One patient with tumor shrinkage of 8% was deemed to be 'not evaluable' as the post-baseline scan was performed too early for evaluation; [c]Patients with target lesions may have also had non-target lesions
Data as of December 31, 2021 (median follow-up: 15.4 months)

Conclusions and Future Directions

- In this registrational Phase 2 cohort, adagrasib demonstrated promising clinical activity (ORR, 43%; DCR, 80%; 1-year OS, 51%) as well as a manageable safety profile, in patients with previously treated NSCLC harboring a KRAS^{G12C} mutation
- Based on these data, the NDA for adagrasib has been accepted and under review for accelerated approval in the US and the MAA has been recently submitted to the European Medicines Agency
- A confirmatory Phase 3 study is evaluating adagrasib versus docetaxel in previously treated patients with KRAS^{G12C}-mutant NSCLC (KRYSTAL-12; NCT04685135)
- Adagrasib has demonstrated responses across 9 tumor types (NSCLC, CRC, PDAC, ovarian and endometrial cancers, and other GI cancers), across NSCLC-relevant molecular subsets, and patients with NSCLC with either stable/treated or untreated CNS metastases[5,8–10]

For further data describing the efficacy of adagrasib in patients with active, untreated CNS metastases, please see Sabari et al, ASCO 2022 abstract LBA9009

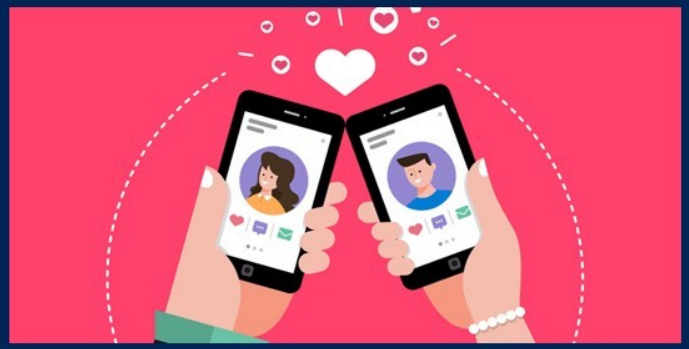
Monday, June 6, 2022, 4:30 PM–6:00 PM CDT

Session: Clinical Science Symposium/Including the Excluded: Advancing Care for All Patients With Lung Cancer

Was ist neu?

- Neoadjuvante Therapie in NSCLC
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT
- Adjuvante Therapie in NSCLC
  - Impower 010
- Fortgeschrittenes Stadium NSCLC
  - Immunchemotherapie
  - TKI
  - **Post Immuntherapie**
  - Leptomeningeale Metastasen
- SCLC

Outline: "Plus One"



PRETREATED

- Lung-MAP S1800A: Phase II Randomized Study Ramucirumab (VEGFR-2 antibody) plus Pembrolizumab vs SOC
- COSMIC-021: Cabozantinib (multi-target receptor TKI) Plus Atezolizumab or Cabozantinib Alone

TREATMENT NAIVE

- TACTI-002: Phase II Study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab

https://www.thedrum.com/news/2021/06/15/dating-after-lockdown-top-matchmaking-trends-singles-brands

Shared Questions: Lung-MAP S1800A and COSMIC-021

- How do we improve on current second line therapies?
- Can IO be efficacious after progression on immunotherapy?
- How do we overcome resistance to immunotherapy?

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

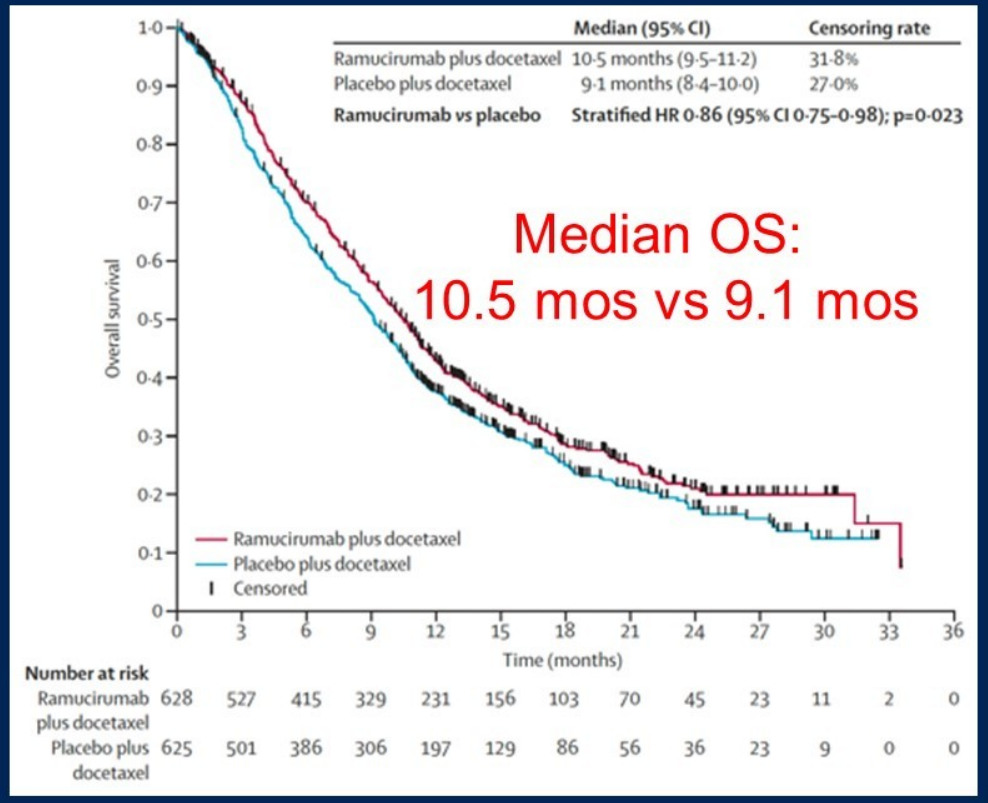
2+ Line: How do we do better?

- Docetaxel + Ramucirumab: PFS 4.5 months, OS 10.5 months
- Docetaxel + Nintedanib: PFS 3.4 months, OS 10.1 months
- Docetaxel: PFS 3.0 months, OS 9.1 months
- Gemcitabine: OS 5.7 months, same as best supportive care
- Pemetrexed: PFS 2.9 months, OS 8.3 months

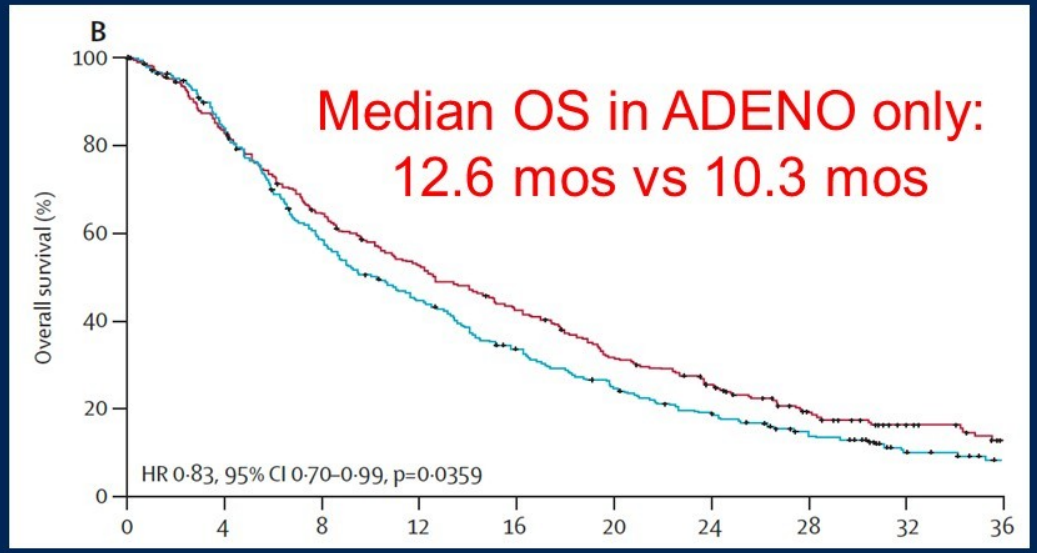
Garon Lancet 2014
Reck Lancet Onc 2014
Hanna JCO 2004
Anderson BJC 2000

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Doce + Ram vs. Doce



Doce + Nintedinib vs. Doce



Garon Lancet 2014
Reck Lancet Onc 2014

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

WJOG @Be Study: A Phase II Study of Atezolizumab with Bevacizumab

WJOG10718L; A single arm, open label, multi-institutional study

Advanced Non-Sq NSCLC

- PD-L1 TPS ≥ 50% (Dako 22C3)
- w/o EGFR/ALK/ROS1 alterations
- ECOG PS=0-1
- No prior therapy
- Fit to anti-angiogenesis therapy

→

Atezolizumab 1200mg
+
Bevacizumab 15mg/kg

Every 3 weeks
Up to 2years

→

Until PD
or intolerable toxicity

JapicCTI-184038

Sample size: 38
Threshold-Expected ORR: 40-62%.
One side α = 0.05 1-β = 0.8

Primary endpoint : ORR (IRC)
Secondary endpoints: PFS (IRC), DoR (IRC), OS, Safety

Summary of Results

@Be study met the primary endpoint of ORR

ORR: 64.1% (90% CI: 49.69-76.83, 95% CI: 47.18-78.80)

Showed investigational clinical activities

PFS median: 15.9 months (95% CI: 5.7-15.9)

1 year PFS rate: 54.9% (95% CI: 35.7-70.6)

DoR median: 10.4 months (95% CI: 4.6-NR)

1 year survival rate 70.6% (95% CI: 50.5-83.4)

Half of patients still ongoing study treatment at the cut off date

KEYNOTE 024:
ORR 45%
PFS 10.3 months

No unexpected adverse event was observed

SAEs: 23 in 12 patients (no grade 4/5)

2 patients discontinued due to toxicities

*: immune-related adverse events (sclerosing cholangitis and encephalopathy)

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

"Real-World" Control Arm; "Messy" Control Arm

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

Randomization

R (1:1)
N= 130

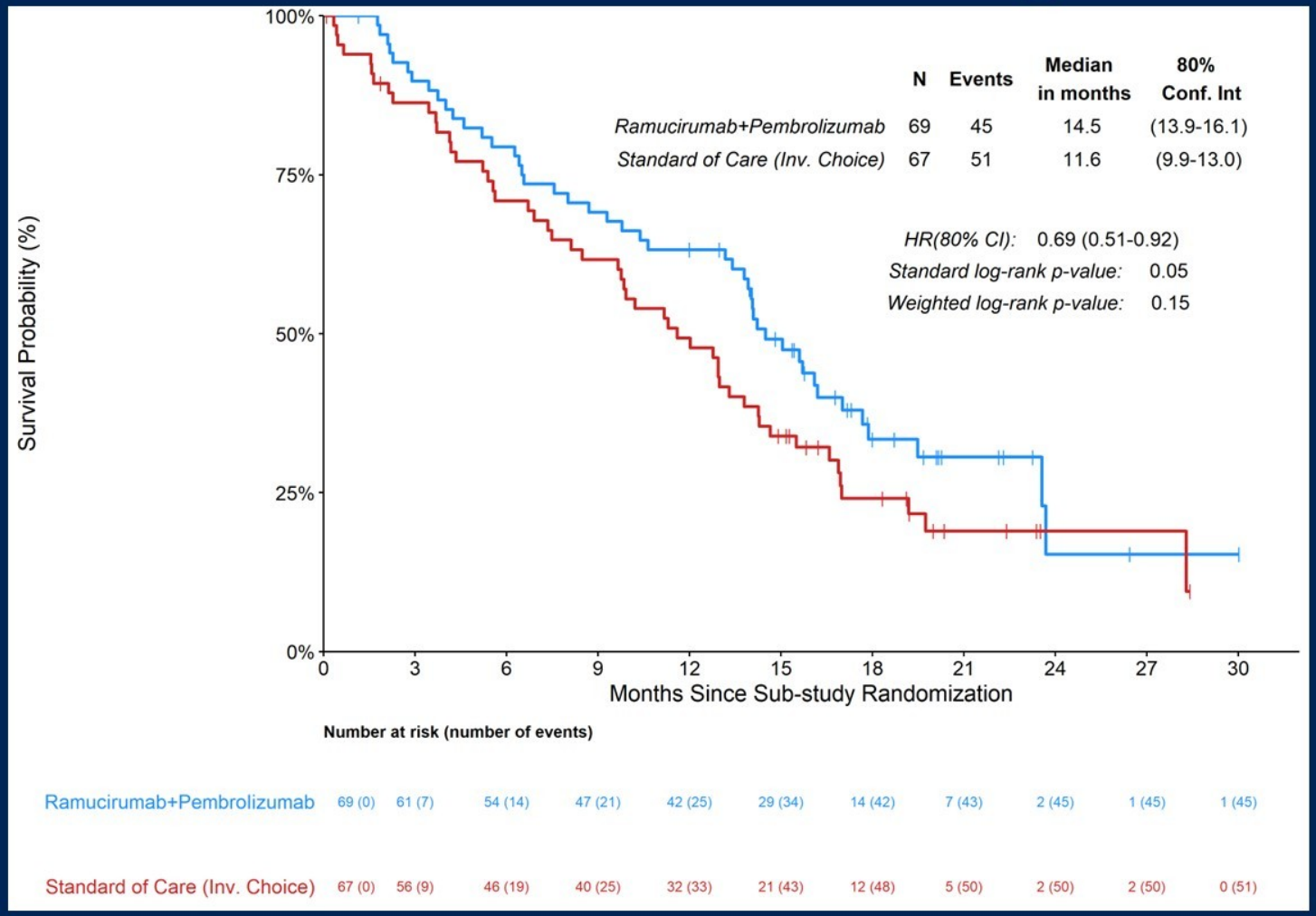
ARM B
Pembrolizumab
200 mg Q3W for up to 35 cycles
+
Ramucirumab
10 mg/kg Q3W

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

PRESENTED BY:
Karen L. Reckamp, MD, MS

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Overall survival: The Right Primary Endpoint



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

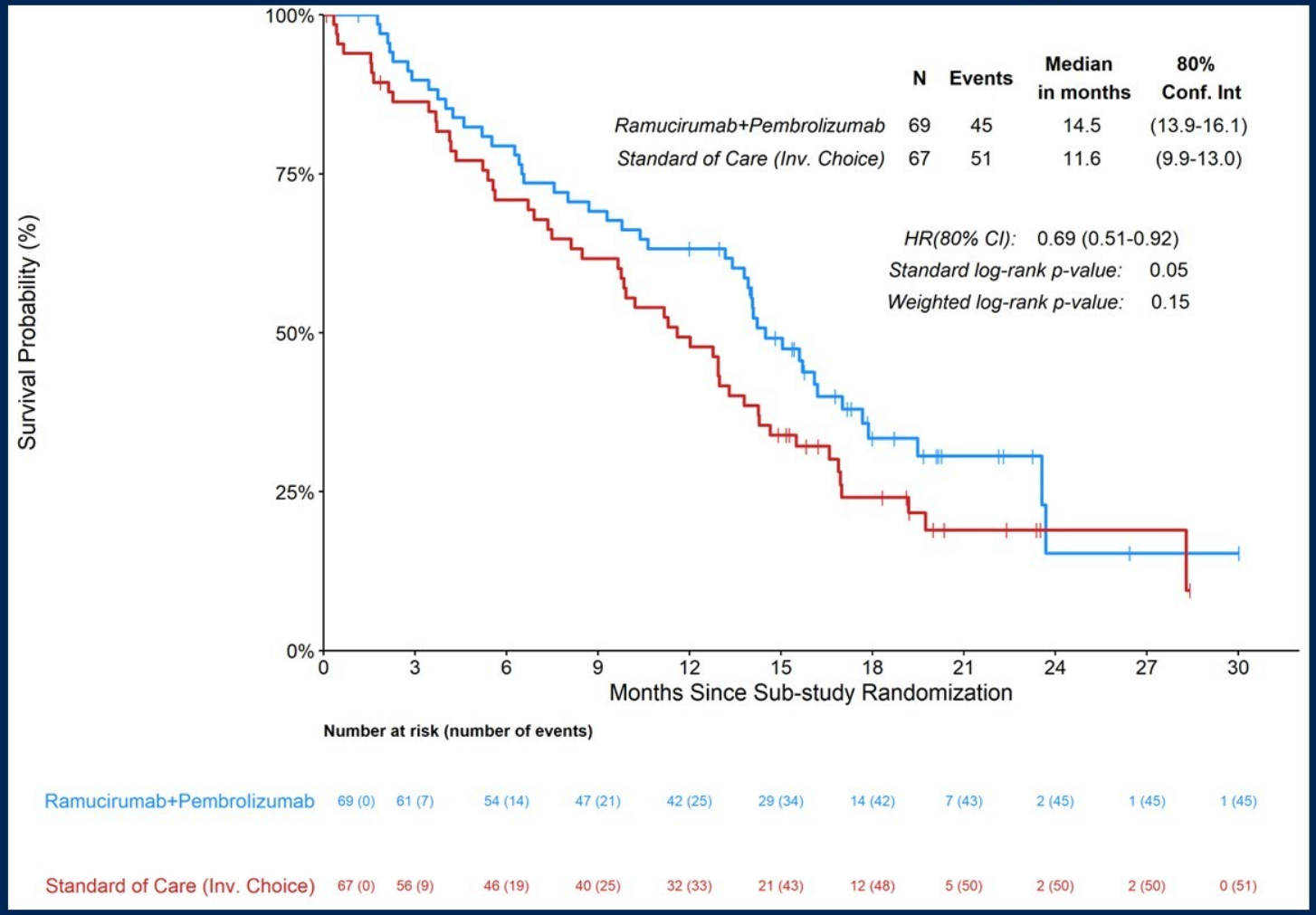
Standard of care therapy received:

- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

PRESENTED BY:
Karen L. Reckamp, MD, MS

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Overall survival: The Right Primary Endpoint



45/67 Received Ramucirumab:

Benefit observed is not just Ram, but the synergistic benefit of IO+Ram

Standard of care therapy received:

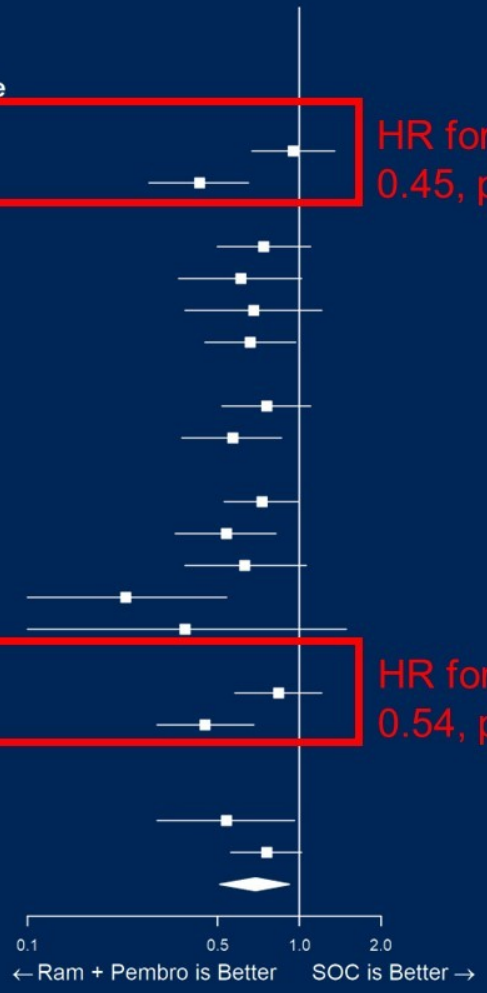
- Docetaxel + Ramucirumab (n = 45)
- Docetaxel (n = 3)
- Gemcitabine (n = 12)
- Pemetrexed (n = 1)
- No treatment (n = 6)

PRESENTED BY:
Karen L. Reckamp, MD, MS

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Overall survival—subgroup analysis

	Ram+ Pembro Events/N	SOC Events/N	HR (80% CI)	P-value
HISTOLOGY				
Non-Squamous	27/40	27/39	0.95 (0.67,1.35)	0.43
Squamous/Mixed	18/29	24/28	0.43 (0.28,0.65)	0.005
PD-L1				
PD-L1 0	21/29	21/26	0.74 (0.50,1.10)	0.16
PD-L1 1-49	11/21	15/22	0.61 (0.36,1.02)	0.11
PD-L1 50+	8/12	12/16	0.68 (0.38,1.21)	0.20
PD-L1 1+	19/33	27/38	0.66 (0.45,0.97)	0.08
TMB				
TMB <10	23/32	28/38	0.76 (0.52,1.10)	0.17
TMB 10+	18/33	20/25	0.57 (0.37,0.86)	0.04
BIOMARKER				
TP53	31/48	35/48	0.73 (0.53,1.00)	0.10
CDKN2A	18/27	21/24	0.54 (0.35,0.82)	0.03
KRAS	12/21	13/16	0.63 (0.38,1.06)	0.13
STK11	4/7	10/10	0.23 (0.10,0.54)	0.01
KEAP1	1/3	7/10	0.38 (0.10,1.49)	0.18
PRIOR TREATMENT				
IO+CHEMO COMBO	20/32	32/42	0.84 (0.58,1.21)	0.27
CHEMO->IO	25/36	18/23	0.45 (0.30,0.68)	0.006
PERFORMANCE STATUS				
PS 0	15/23	8/9	0.54 (0.30,0.96)	0.08
PS 1	30/46	43/58	0.76 (0.56,1.02)	0.12
OVERALL	**45/69**	**51/67**	**0.69 (0.51,0.92)**	**0.05**



HR for Interaction: 0.45, p=0.005

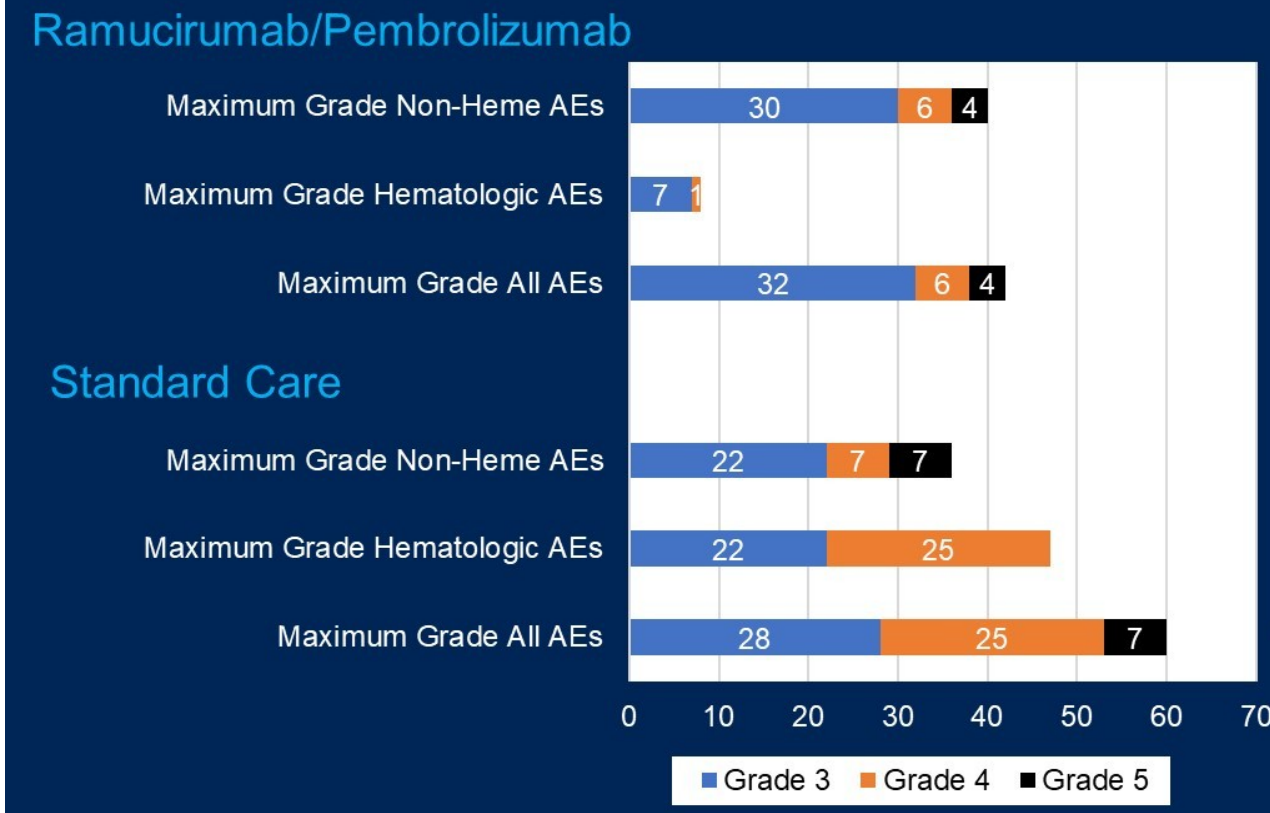
HR for Interaction: 0.54, p=0.026

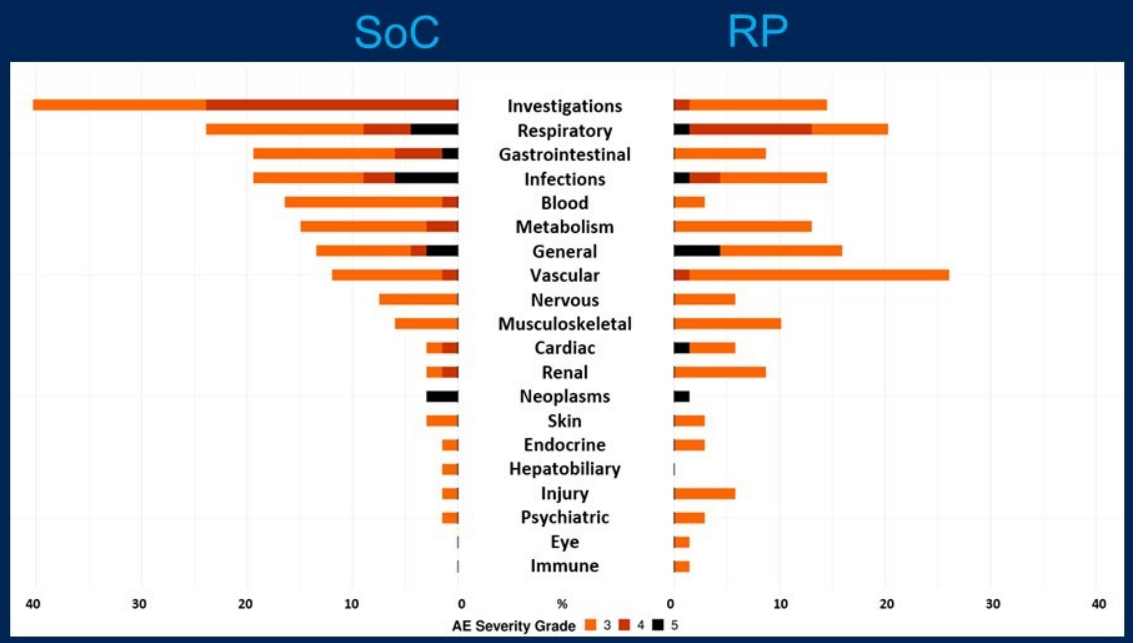
Future areas of Research:

- Histologic benefit
- IO+Chemo vs Chemo-->IO
- Biomarker

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Safety summary—Percentage of patients with Grade 3-5 Aes: Toxicity Less, SOC options vary widely in toxicity





- Grade ≥3 TRAEs: 42% on RP; 60% on SOC
- Nine (31%) Grade 3–5 irAEs on RP

PRESENTED BY:
Karen L. Reckamp, MD, MS

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Was ist neu?

- Post Immuntherapie
- Ramucirumab in Kombination mit Pembrolizumab ist eine Option bei Therapieresistenz mit Immuntherapie
- Phase III Studien sind notwendig um den Stellenwert dieser Therapie zu sichern

Was ist neu?

- Neoadjuvante Therapie in NSCLC
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT
- Adjuvante Therapie in NSCLC
  - Impower 010
- Fortgeschrittenes Stadium NSCLC
  - Immunchemotherapie
  - TKI
  - Post Immuntherapie
  - **Leptomeningeale Metastasen**
- SCLC

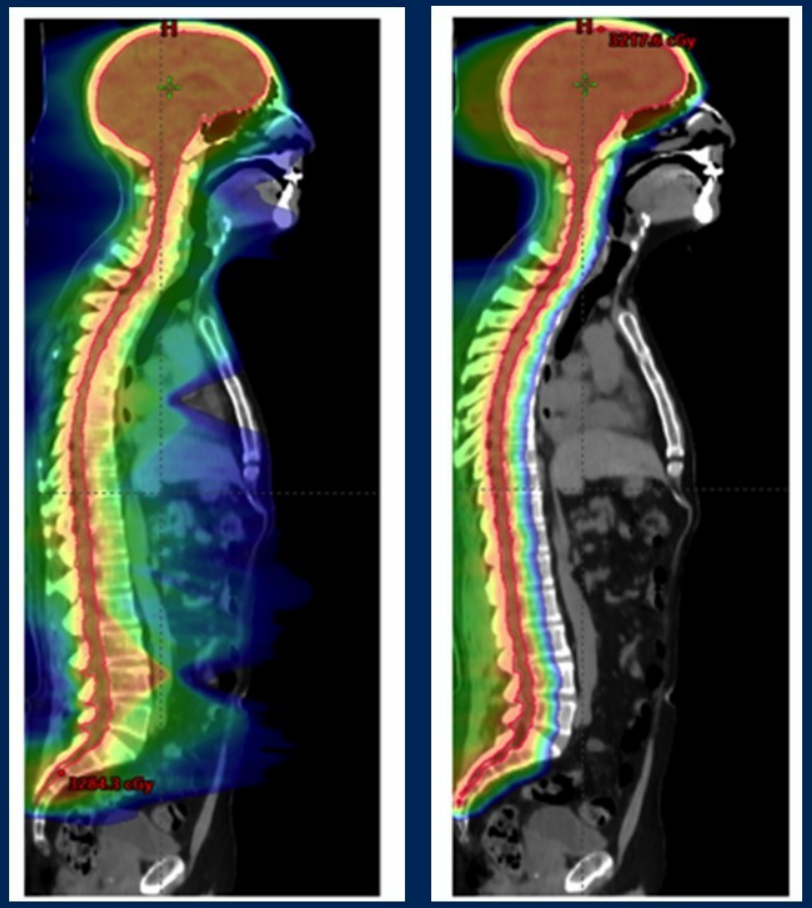
2022 ASCO® ANNUAL MEETING

Phase II Randomized Study Comparing Proton Craniospinal Irradiation with Photon Involved-Field Radiotherapy for Patients with Solid Tumor Leptomeningeal Metastasis

Jonathan T. Yang, N. Ari Wijetunga, Elena Pentsova, Suzanne Wolden, Robert Young, Denise Correa, Zhigang Zhang, Junting Zheng, Allison Betof Warner, Helena Yu, Mark Kris, Andrew Seidman, Rachna Malani, Andrew Lin, Lisa DeAngelis, Nancy Lee, Simon Powell, Adrienne Boire

Memorial Sloan Kettering Cancer Center

- Background
  - LMD a/w marked morbidity and mortality
    - Death within 4-6 weeks without treatment or 4-6 months with standard therapies
  - Standard-of-care: photon (IFRT)
    - WBRT and/or focal spine radiation
    - Palliation of symptoms without survival benefit
  - Data from prospective medulloblastoma studies: proton CSI significantly less toxic compared to photon CSI
- Question
  - Is pCSI, with its reduced side effects, safe and efficacious (e.g. OS) for patients with LMD?
    - **Phase I study published showing limited toxicity and promising OS and CNS PFS outcomes.**

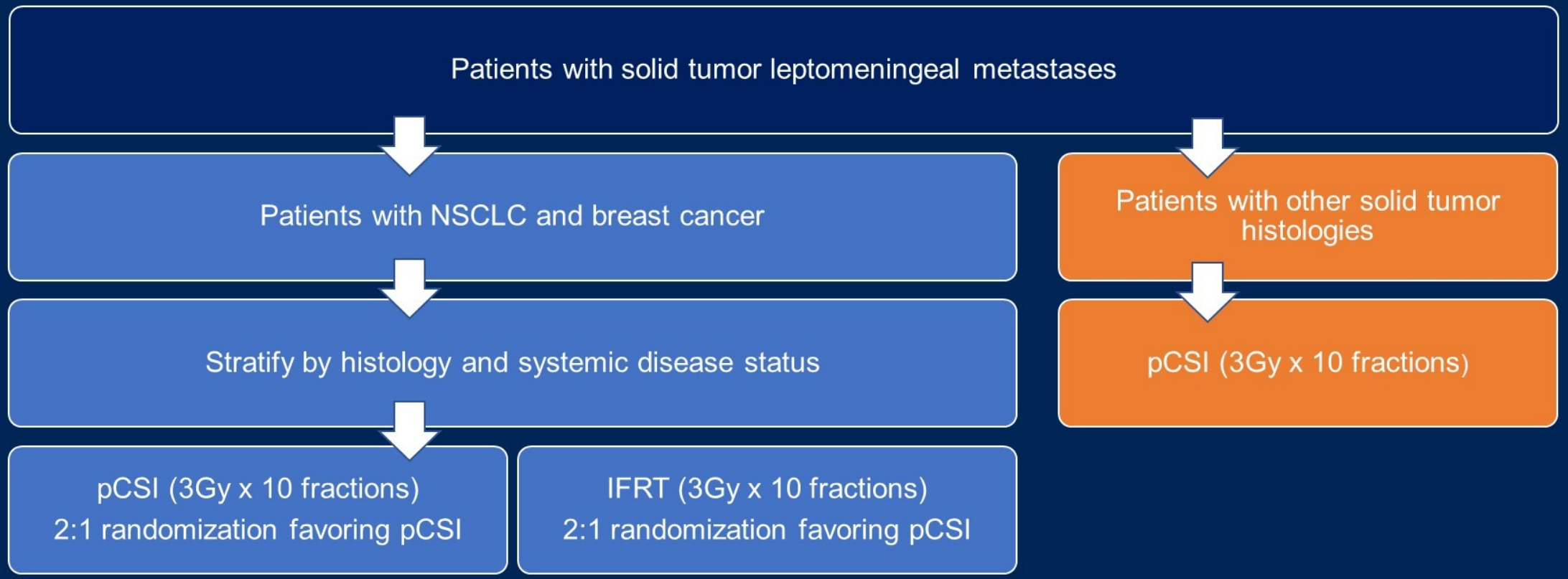


Photon CSI

Proton CSI

Brown et al. IJROBP 2013

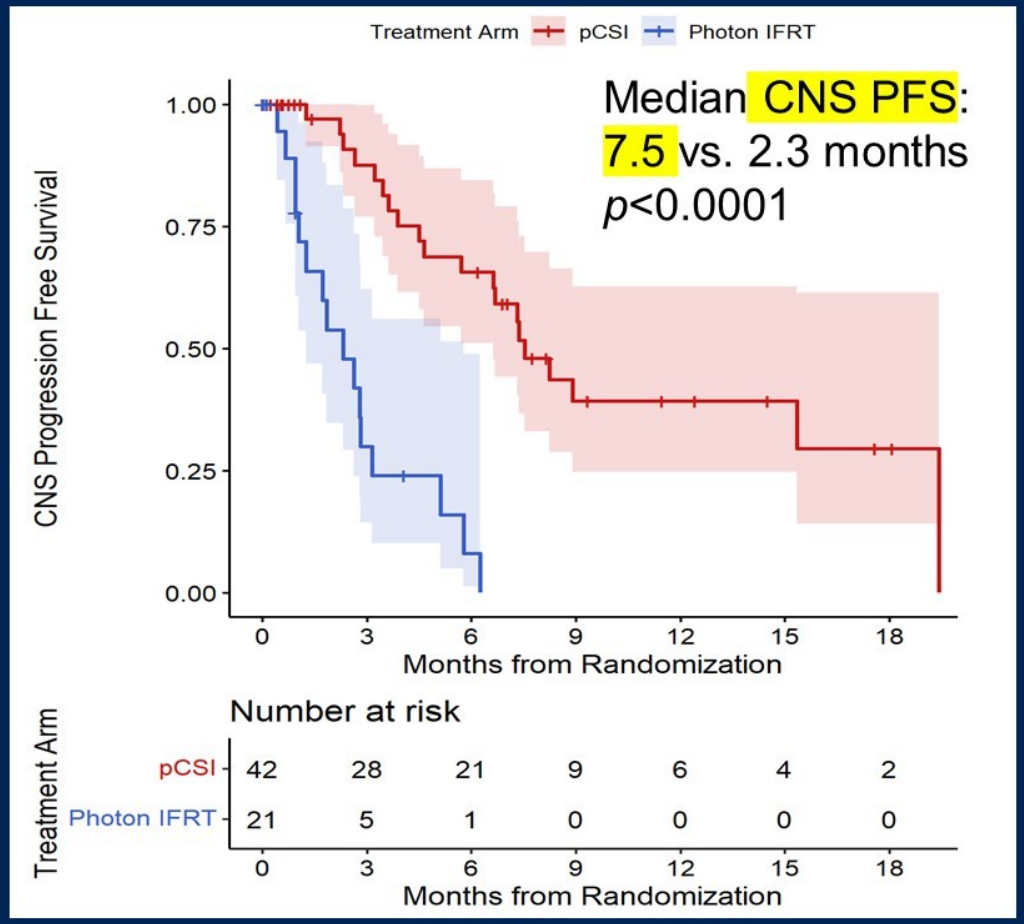
Phase II Trial Design

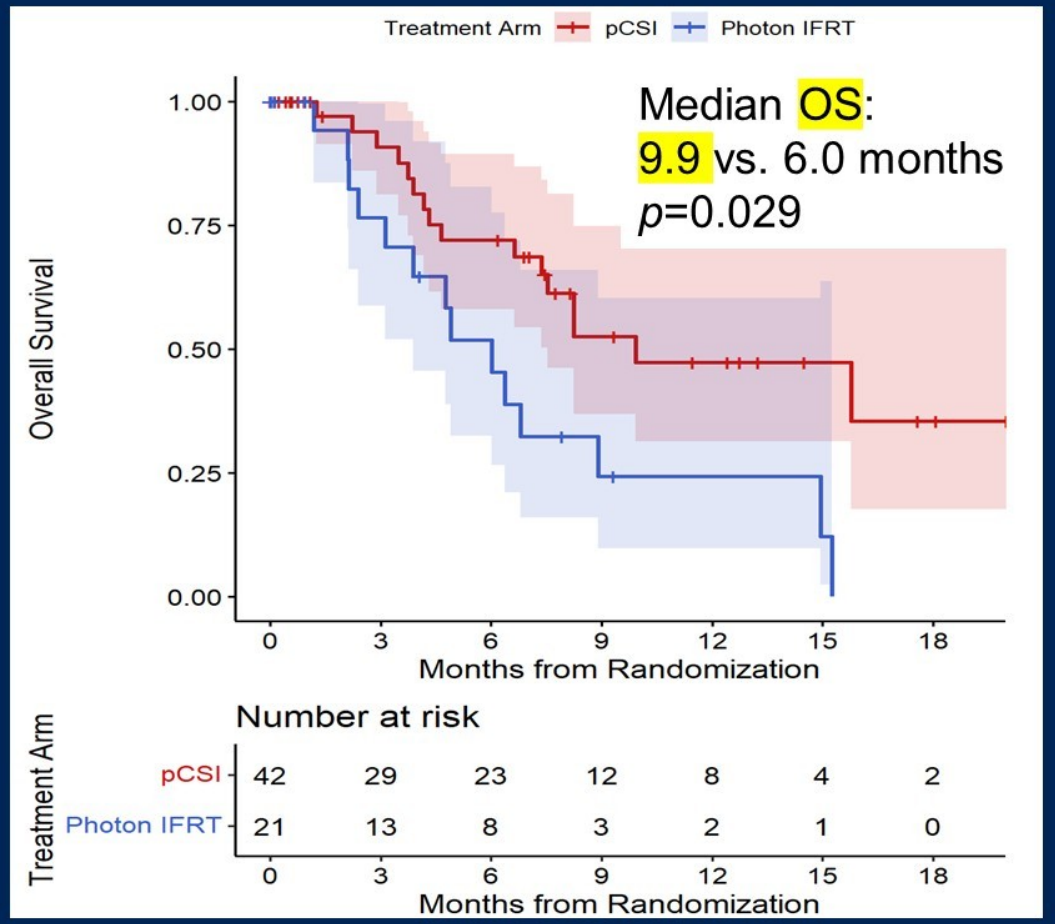


Primary endpoint: To compare CNS PFS for patients with NSCLC or breast cancer
Secondary endpoints: To compare OS and TAEs for patients with metastatic NSCLC
Exploratory endpoints: To evaluate CNS TTP, CNS PFS, OS, and TAEs in patients with other solid tumor histology

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Planned Interim Analysis - CNS PFS and OS





Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Was ist neu?

- Neoadjuvante Therapie in NSCLC
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT
- Adjuvante Therapie in NSCLC
  - Impower 010
- Fortgeschrittenes Stadium NSCLC
  - Immunchemotherapie
  - TKI
  - Post Immuntherapie
  - Leptomeningeale Metastasen
- **SCLC**

PROGRESS

Lung Cancer—Non-Small Cell Local-Regional/Small Cell/ Other Thoracic Cancers

8505 (375438)

Presentation Title: Serplulimab, a novel anti-PD-1 antibody, plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small-cell lung cancer: An internal randomized phase 3 study

LBA8507 (371224)

Presentation Title: SKYSCRAPER-02: Primary results of a phase III, randomized, double-blind, placebo-controlled study of atezolizumab (atezo) + carboplatin + etoposide (CE) with or without tiragolumab (tira) in patients (pts) with untreated extensive-stage small cell lung cancer (EL-SCLC).

PRESENTED BY:
Chandra P. Belani, MD

Chemo-immunotherapy for ES-SCLC

IMpower133	FDA approval March 2019

- Addition of anti–PD-L1 (atezolizumab) to 1L chemotherapy improves OS without significant toxicity

CASPIAN	FDA approval March 2020

- Addition of anti–PD-L1 (durvalumab) to 1L chemotherapy improves OS without significant toxicity

PRESENTED BY:
Chandra P. Belani, MD

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Chemo-immunotherapy for First-line ES-SCLC

STUDY	N	OS (mos.)	HR	P-value	Median F/U (mos)
IMPOWER 133 *ATEZO (PDL-1)*	403 *1:1*	12.3/10.3	0.76	0.0154	22.9
CASPIAN *DURVA (PDL-1)*	*805* *1:1*	12.9/10.5	0.71	0.003	39.4

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

ASTRUM-005: Study Design

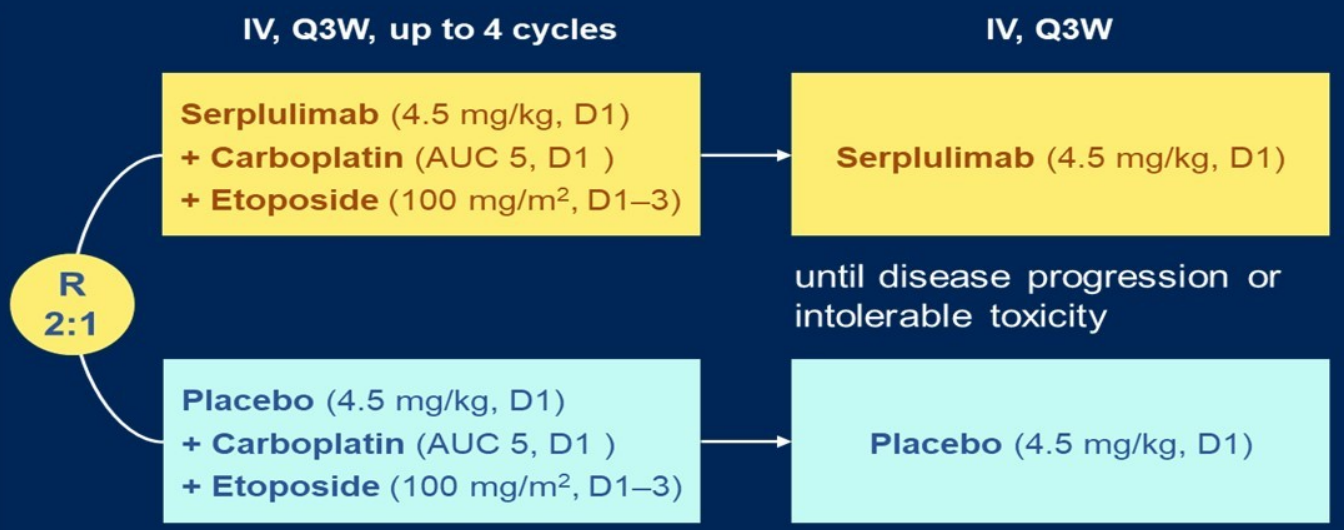
A randomized, double-blind, multicenter, placebo-controlled, phase 3 trial (NCT04063163)

Main inclusion criteria

- Histologically/cytologically diagnosed with ES-SCLC
- No prior systemic therapy for ES-SCLC
- At least one measurable lesion
- ECOG PS 0/1

Stratification factors

- PD-L1 expression levels (negative: TPS <1%, positive: TPS ≥1%, or NA)
- Brain metastases (Yes vs No)
- Age (<65 vs ≥65)



Primary endpoint: OS

Secondary endpoints: PFS, ORR, DOR, Safety and immunogenicity

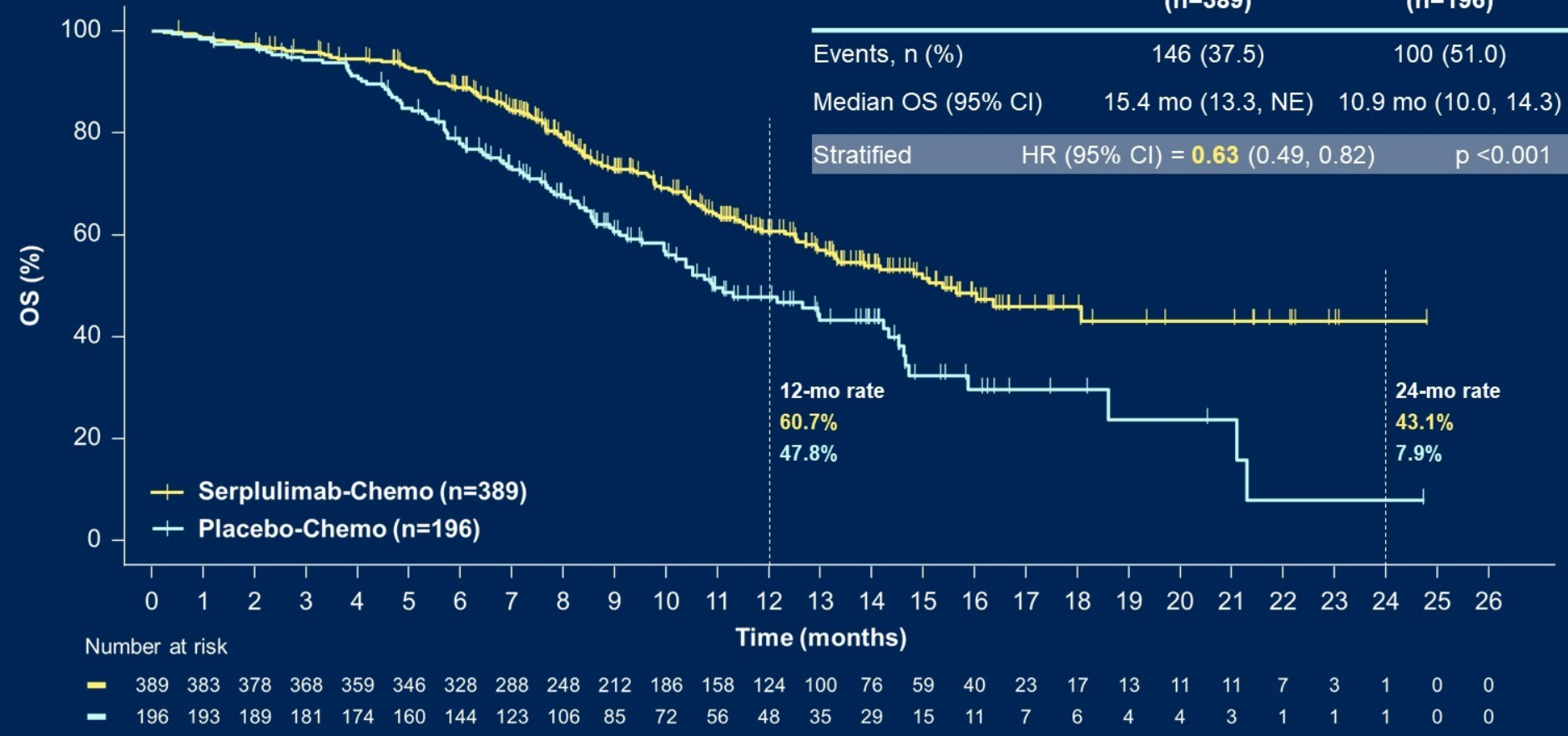
- 567 patients ; 342 OS events to provide 85% power to assess a HR of 0.7 at α=0.05 (two-sided)

AUC, area under curve; *DOR*, duration of response; *ECOG PS*, Eastern Cooperative Oncology Group performance status; *ES-SCLC*, extensive-stage small-cell lung cancer; *IV*, intravenous infusion; *NA*, not available; *ORR*, objective response rate; *OS*, overall survival; *PFS*, progression-free survival; *PD-L1*, programmed death ligand-1; Q3W, every 3 weeks; *TPS*, tumor proportion score;

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

ASTRUM-005: Overall Survival

	Serplulimab-Chemo (n=389)	Placebo-Chemo (n=196)
Events, n (%)	146 (37.5)	100 (51.0)
Median OS (95% CI)	15.4 mo (13.3, NE)	10.9 mo (10.0, 14.3)
Stratified	HR (95% CI) = **0.63** (0.49, 0.82)	p <0.001



CI, confidence interval; *HR*, hazard ratio; *mo*, month; *NE*, not evaluable; *OS*, overall survival;

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

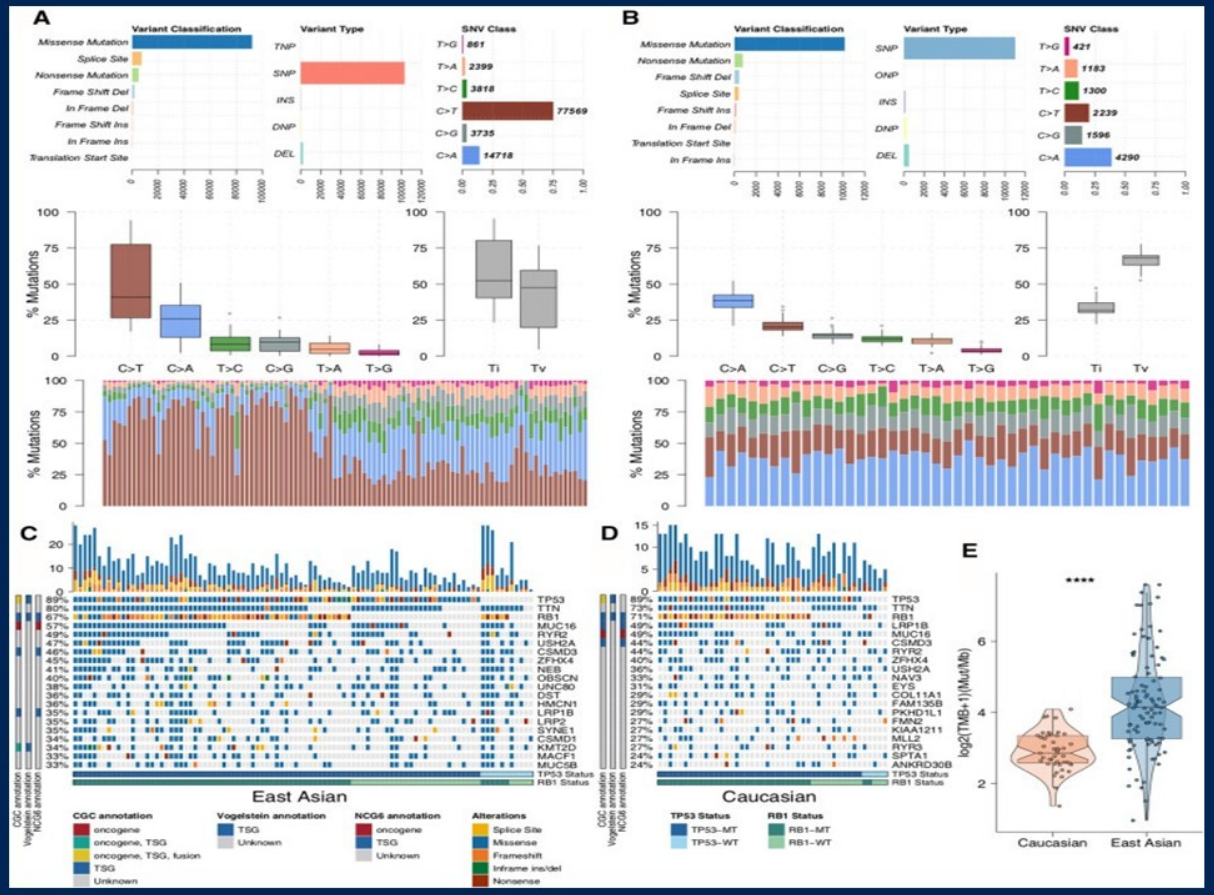
Chemo-immunotherapy for First-line ES-SCLC

STUDY	N	OS (mos.)	HR	P-value	Median F/U (mos)
IMPOWER 133 *ATEZO (PDL-1)*	403 *1:1*	12.3/10.3	0.76	0.0154	22.9
CASPIAN *DURVA (PDL-1)*	*805* *1:1*	12.9/10.5	0.71	0.003	39.4
ASTRUM-005 *SERP (PD-1)*	*585* *2:1*	15.4/10.9	0.63	<0.001	12.3

PRESENTED BY:
Chandra P. Belani, MD

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Genomic alterations in SCLC : EA *vs.* Caucasian

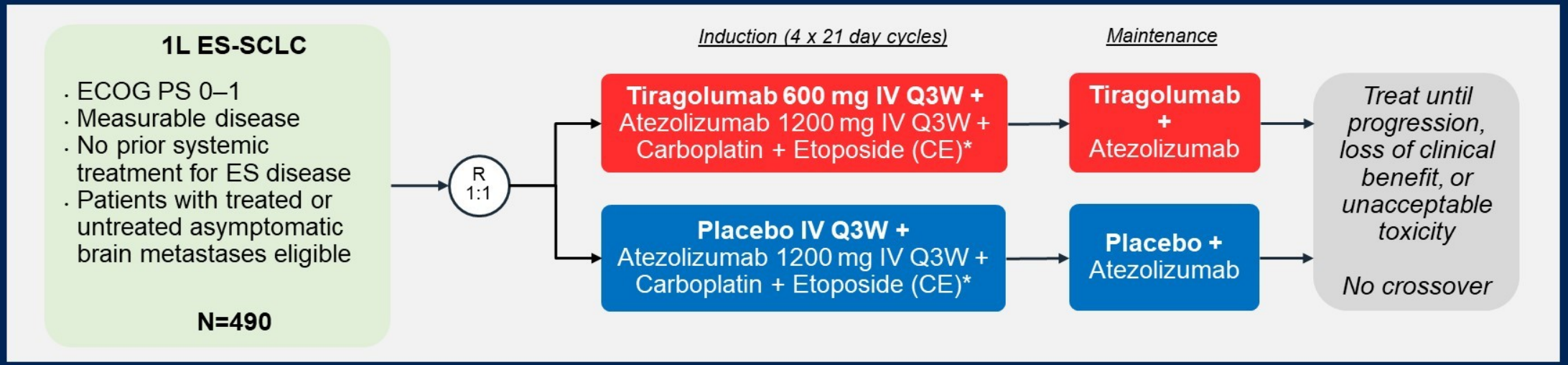


- DNA damage repair alterations and TMB significantly higher in the EA cohort than in the Caucasian cohort
- Resting lymphocytes significantly enriched in the EA cohort

Lin A, Cancer Cell Int. 2022 Apr 29;22(1):173

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

SKYSCRAPER-02: Randomized, double-blind, placebo-controlled study of tiragolumab + atezolizumab + chemotherapy in patients with untreated ES-SCLC



Stratification Factors:

- **ECOG PS** (0 vs. 1)
- **Brain metastases** (Yes vs. No)
- **LDH** (≤ ULN vs > ULN)

Co-Primary Endpoints:

- Investigator-assessed OS and PFS in **Primary Analysis Set** (all randomized patients without presence or history of brain metastases at baseline)

Secondary Endpoints:

- PFS and OS in **Full Analysis Set** (all randomized patients)
- Confirmed ORR
- Duration of response
- Safety
- Pharmacokinetics
- PROs

Primary analysis

- Cut-off date of 6 Feb 2022
- Median follow-up of 14.3 months (Primary Analysis Set)

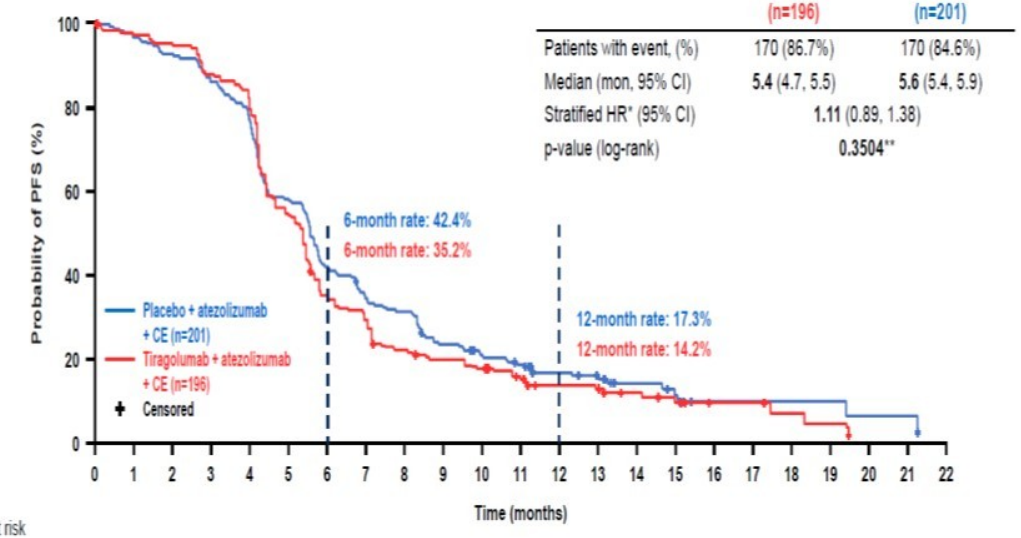
NCT04256421

*Carboplatin IV AUC 5 mg/mL per min Q3W and etoposide IV 100mg/m² body surface area days 1–3 Q3W

PRESENTED BY:
Dr Charles M. Rudin

SKYSCRAPER-02: Randomized, double-blind, placebo-controlled study of tiragolumab + atezolizumab + chemotherapy in patients with untreated ES-SCLC

PFS: Primary Analysis Set



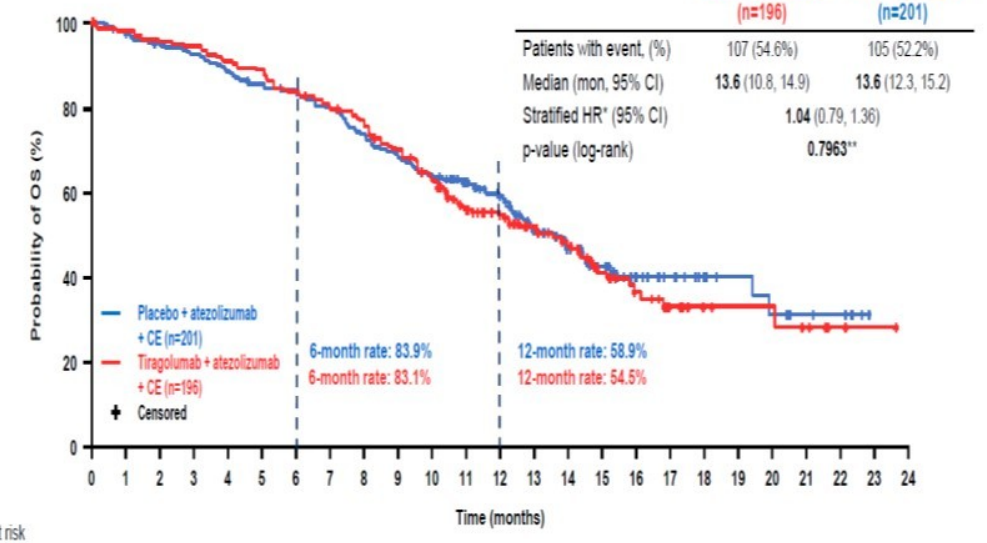
	Tiragolumab + atezolizumab +CE (n=196)	Placebo + atezolizumab + CE (n=201)
Patients with event, (%)	170 (86.7%)	170 (84.6%)
Median (mon, 95% CI)	5.4 (4.7, 5.5)	5.6 (5.4, 5.9)
Stratified HR* (95% CI)	1.11 (0.89, 1.38)	
p-value (log-rank)	0.3504**	

No. at risk																							
Placebo + atezo + CE	201	192	184	171	152	115	84	68	62	46	39	34	26	20	11	8	3	3	3	3	2	2	NE
Tiragolumab + atezo + CE	196	189	183	170	154	105	67	54	41	37	33	25	17	17	11	8	5	5	3	2	NE	NE	NE

Median follow-up: 14.3 months

* Stratification factors are: ECOG, LDH; ** Statistical boundary: 0.001
Data cut-off: 6 February 2022

Interim OS: Primary Analysis Set



	Tiragolumab + atezolizumab +CE (n=196)	Placebo + atezolizumab + CE (n=201)
Patients with event, (%)	107 (54.6%)	105 (52.2%)
Median (mon, 95% CI)	13.6 (10.8, 14.9)	13.6 (12.3, 15.2)
Stratified HR* (95% CI)	1.04 (0.79, 1.36)	
p-value (log-rank)	0.7963**	

No. at risk																							
Placebo + atezo + CE	201	195	188	183	175	168	164	156	144	134	125	115	97	70	47	36	26	19	12	9	7	5	4	NE	NE
Tiragolumab + atezo + CE	196	191	186	184	177	172	162	154	146	133	116	93	80	62	51	32	21	14	9	7	7	5	2	1	NE

Median follow-up: 14.3 months

* Stratification factors are: ECOG, LDH; ** Statistical boundary: 0.0175
Data cut-off: 6 February 2022

PRESENTED BY:
Chandra P. Belani, MD

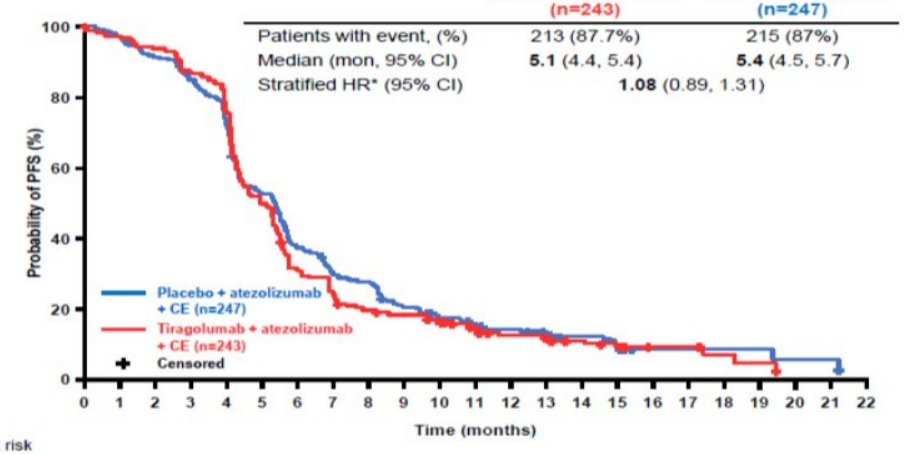
SKYSCRAPER-02: Randomized, double-blind, placebo-controlled study of tiragolumab + atezolizumab + chemotherapy in patients with untreated ES-SCLC

4

PFS and OS: Full Analysis Set

PFS in the Full Analysis Set

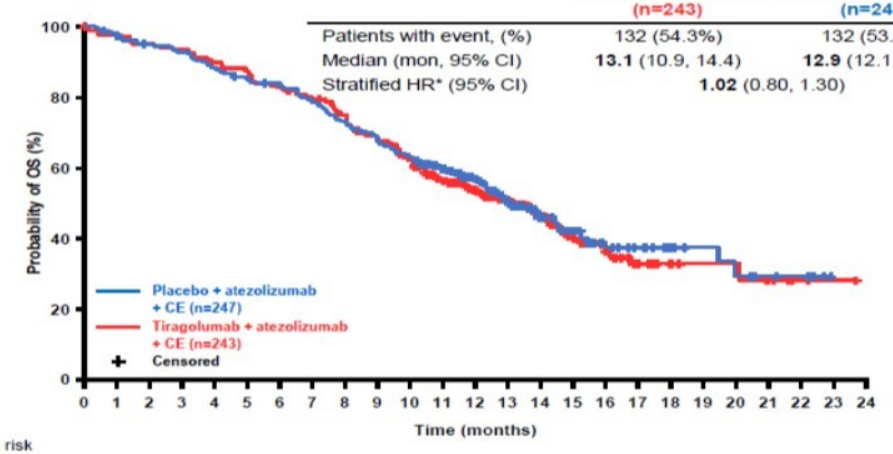
	Tiragolumab + atezolizumab + CE (n=243)	Placebo + atezolizumab + CE (n=247)
Patients with event, (%)	213 (87.7%)	215 (87%)
Median (mon, 95% CI)	**5.1** (4.4, 5.4)	**5.4** (4.5, 5.7)
Stratified HR* (95% CI)	**1.08** (0.89, 1.31)	



No. at risk																						
Placebo + atezo + CE	247	237	224	207	185	128	92	73	66	49	40	34	26	20	11	8	3	3	3	3	2	2	NE
Tiragolumab + atezo +CE	243	232	224	209	188	120	74	59	45	41	35	27	18	18	12	9	5	5	3	2	NE	NE	NE

Interim OS in the Full Analysis Set

	Tiragolumab + atezolizumab + CE (n=243)	Placebo + atezolizumab + CE (n=247)
Patients with event, (%)	132 (54.3%)	132 (53.4%)
Median (mon, 95% CI)	**13.1** (10.9, 14.4)	**12.9** (12.1, 14.5)
Stratified HR* (95% CI)	**1.02** (0.80, 1.30)	



No. at risk																									
Placebo + atezo +CE	247	240	232	226	215	207	202	190	176	165	152	134	109	80	52	40	26	19	12	9	7	5	4	NE	NE
Tiragolumab + atezo +CE	243	235	228	225	216	210	199	190	176	161	141	114	90	70	56	36	24	14	9	7	7	5	2	1	NE

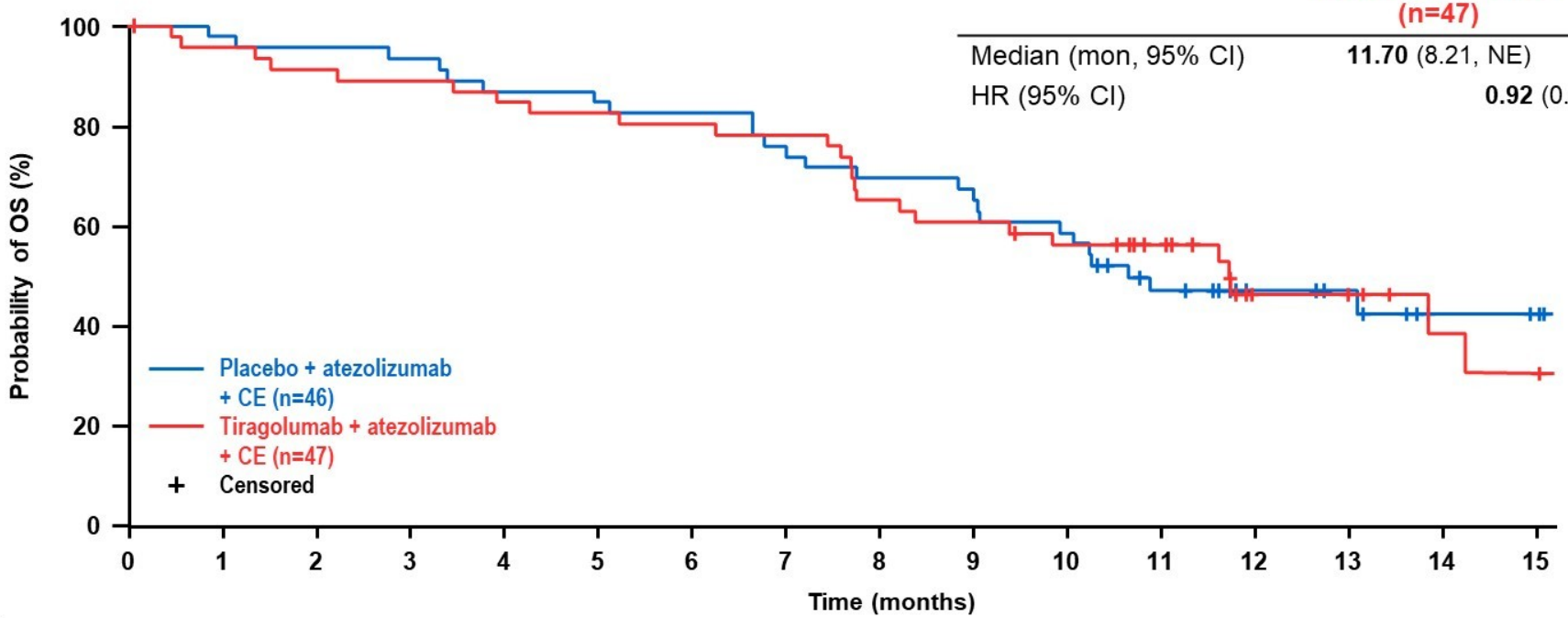
Median follow-up: 13.9 months

* Stratification factors are: ECOG, LDH
Data cut-off: 6 February 2022

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Subgroup OS: Patients with brain metastases

	Tiragolumab + atezolizumab +CE (n=47)	Placebo + atezolizumab + CE (n=46)
Median (mon, 95% CI)	**11.70** (8.21, NE)	**10.64** (9.03, NE)
HR (95% CI)	**0.92** (0.53, 1.59)	



No. at risk																
Placebo + atezo + CE	46	45	44	43	40	39	38	34	32	31	27	19	12	10	5	4
Tiragolumab + atezo + CE	47	44	42	41	39	38	37	36	30	28	25	21	10	8	5	4

Data cut-off: 6 February 2022 (median follow-up: 13.9 months)

Content of this presentation is the property of the author, licensed by ASCO. Permission required for reuse.

Chemo-immunotherapy for First-line ES-SCLC

	N	OS (mos.)	HR	P-value	Median F/U
IMPOWER 133 *ATEZO (PDL-1)*	403 *1:1*	12.3/10.3	0.76	0.0154	22.9
CASPIAN *(PDL-1)* *Durva*	*805* *1:1*	12.9/10.5	0.71	0.003	39.4
ASTRUM-005 *SERP (PDL-1)*	*585* *2:1*	15.4/10.9	0.63	<0.001	12.3
SKYSCRAPER-02 *ATEZO+TIRA*	490 *1:1*	13.6/13.6	1.04	0.79	14.3

PRESENTED BY:
Chandra P. Belani, MD

Fazit

- **Chemoimmuntherapie bleibt weiterhin unser Standard**

Zusammenfassung

- Neoadjuvante Therapie in NSCLC
  - Nadim II
  - Checkmate 816
  - Neoscore
  - Neoadjuvante RCT

Neoadjuvante Therapie in NSCLC wird unsere jetzige Praxis ändern
3 Zyklen Chemoimmuntherapie ist besser als 2

Eine Verbesserung in OS sekundär zur pCR ist noch nicht erwiesen

Carboplatin könnte eine gute Option in diesem Setting sein
RCT hat keinen Stellenwert in einem neoadjuvanten Setting

- Adjuvante Therapie in NSCLC
  - Impower 010

Adjuvante Chemotherapie ist bereits zugelassen
Bei Frühstadien des NSCLC muss der EGFR, ALK und PD-L1 Status bestimmt werden
Alle Patienten sollen eine adjuvante Chemotherapie und 3-4 Wochen danach eine adjuvante Immuntherapie erhalten

Zusammenfassung

- Fortgeschrittenes Stadium NSCLC
  - Immunchemotherapie
    - Überlegenheit der Immuntherapie im fortgeschrittenem Stadium wurde nicht nachgewiesen
    - Immunchemotherapie für Patienten ≥ 75 und Nichtraucher vorteilhaft
    - In Abhängigkeit von Komorbidität und Tumorlast könnte Immunchemotherapie auch bei Patienten mit erhöhter PD-L1 Expression eingesetzt werden
  - TKI
    - Adagrasib ist eine Therapieoption für Patienten mit KRAS G12C und ZNS Metastasen
  - Post Immuntherapie
    - Ramucirumab in Kombination mit Pembrolizumab könnte eine mögliche Therapie bei Resistenz mit Immuntherapie werden
    - Phase III Studien sind vorher notwendig
  - Leptomeningeale Metastasen
    - Photon-Kraniospinale Bestrahlung ist eine neue vielversprechende Therapieoption
- SCLC
  - Chemoimmuntherapie bleibt weiterhin unser Standard


I REALLY
NEED A DAY
BETWEEN
SATURDAY
AND SUNDAY