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Conference Coverage: ASCO 2022 – Focus on Lung Cancer

June 13, 2022

Report Contents

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Meeting Snapshot

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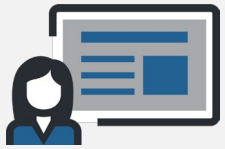
VIRTUAL CLOSED-DOOR ROUNDTABLE

DATE:
June 13, 2022



DISEASE STATE AND DATA PRESENTATIONS by key experts

INSIGHTS REPORT including postmeeting analyses and actionable recommendations

PANEL: Key experts in lung cancer
- > 6 from US
- > 2 from Europe

LUNG CANCER-SPECIFIC DISCUSSIONS on therapeutic advances and their application in clinical decision-making

Panel Consisting of 6 US and 2 European Lung Cancer Experts

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Paul Paik, MD
Memorial Sloan Kettering Cancer Center

Lynette Sholl, MD
Dana-Farber Cancer Institute

CHAIR:
Corey Langer, MD, FACP
University of Pennsylvania

Roy Herbst, MD, PhD
Yale Cancer Center

David Spigel, MD
Sarah Cannon Research Institute

Solange Peters, MD, PhD
University Hospital of Lausanne

Mark Socinski, MD
AdventHealth Cancer Institute

Enriqueta Felip, MD, PhD
Vall d'Hebron University Hospital

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Meeting Agenda

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Time (EDT)	Topic	Speaker/Moderator
10.00 AM – 10.05 AM (5 min)	Welcome and Introductions	Corey J. Langer, MD, FACP
10.05 AM – 10.10 AM (5 min)	Immunotherapy in Resectable NSCLC	Roy Herbst, MD, PhD
10.10 AM – 10.30 AM (20 min)	Discussion – Immunotherapy in Resectable NSCLC	All
10.30 AM – 10.40 AM (10 min)	Immunotherapy in Unresectable Stage III NSCLC	Mark Socinski, MD
10.40 AM – 10.50 AM (10 min)	Discussion – Immunotherapy in Unresectable Stage III NSCLC	All
10.50 AM – 11.00 AM (10 min)	Immunotherapy in Stage IV NSCLC	Solange Peters, MD, PhD
11.00 AM – 11.25 AM (25 min)	Discussion – Immunotherapy in Stage IV NSCLC	All
11.25 AM – 11.30 AM (5 min)	BREAK	
11.30 AM – 11.40 AM (10 min)	*EGFR* Mutations	David Spigel, MD
11.40 AM – 11.50 AM (10 min)	Discussion – *EGFR* Mutations	All
11.50 AM – 12.05 PM (15 min)	Oncogenic Drivers: Mutations	Enriqueta Felip, MD, PhD
12.05 PM – 12.20 PM (15 min)	Discussion – Oncogenic Drivers: Mutations	All
12.20 PM – 12.25 PM (5 min)	Oncogenic Drivers: Fusions	Paul Paik, MD
12.25 PM – 12.35 PM (10 min)	Discussion – Oncogenic Drivers: Fusions	All
12.35 PM – 12.45 PM (10 min)	SCLC/Other Targets in Lung Cancer	Corey J. Langer, MD, FACP
12.45 PM – 12.55 PM (10 min)	Discussion – SCLC/Other Targets in Lung Cancer	All
12.55 PM – 1.00 PM (5 min)	Summary and Closing Remarks	Corey J. Langer, MD, FACP

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Congress Highlights

Association of pathological regression with event-free survival (EFS) in CheckMate 816

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Provencio M, et al. 2022, ASCO LBA8511

STUDY POPULATION

> Pts with resectable stage IB–IIIA NSCLC

OUTCOME

> Posthoc evaluation of EFS by pathologic response and percentage residual viable tumor (RVT)

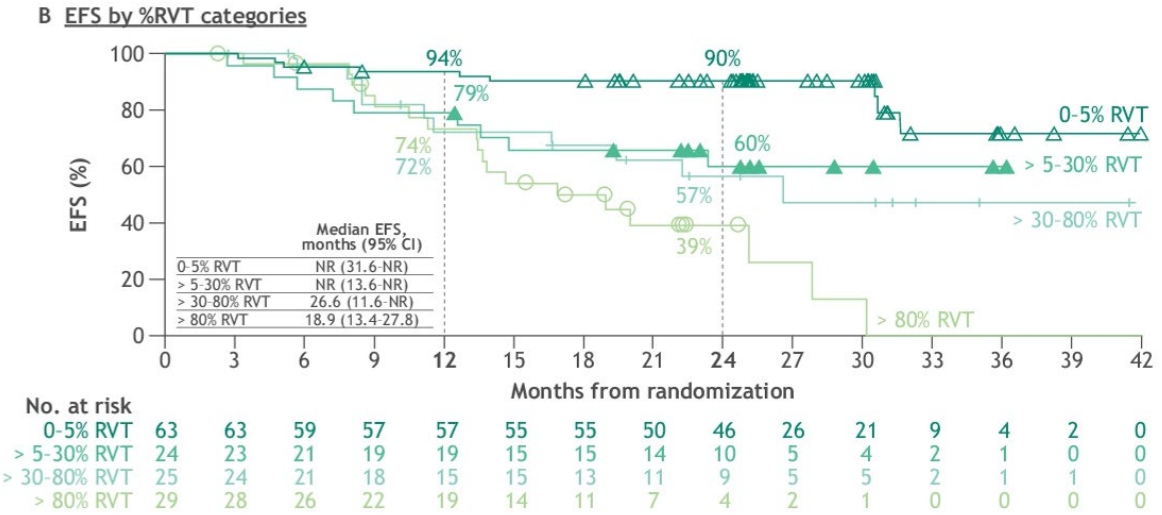
Efficacy

> 24-month EFS by %RVT
  - 0%–5%: 90%
  - 5%–30%: 60%
  - 30%–80%: 57%
  - >80%: 39%

Safety

> Grade 3/4 TREAEs
  - Nivo-chemo: 34%
  - Chemo: 37%

EFS BY RESIDUAL VIABLE TUMOR PERCENTAGE



AUTHOR CONCLUSIONS

> Patients with a deeper pathologic response appear to have better EFS at 2 years
> Results are consistent with pathologic response as an early indicator of EFS benefit with neoadjuvant immunotherapy plus chemotherapy

Outcomes in subgroups related to surgery, disease burden, and adjuvant chemotherapy use in EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091

O'Brien M, et al. 2022, ASCO 8512

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STUDY POPULATION

> Pts with completely resected, stage IB–IIIA NSCLC

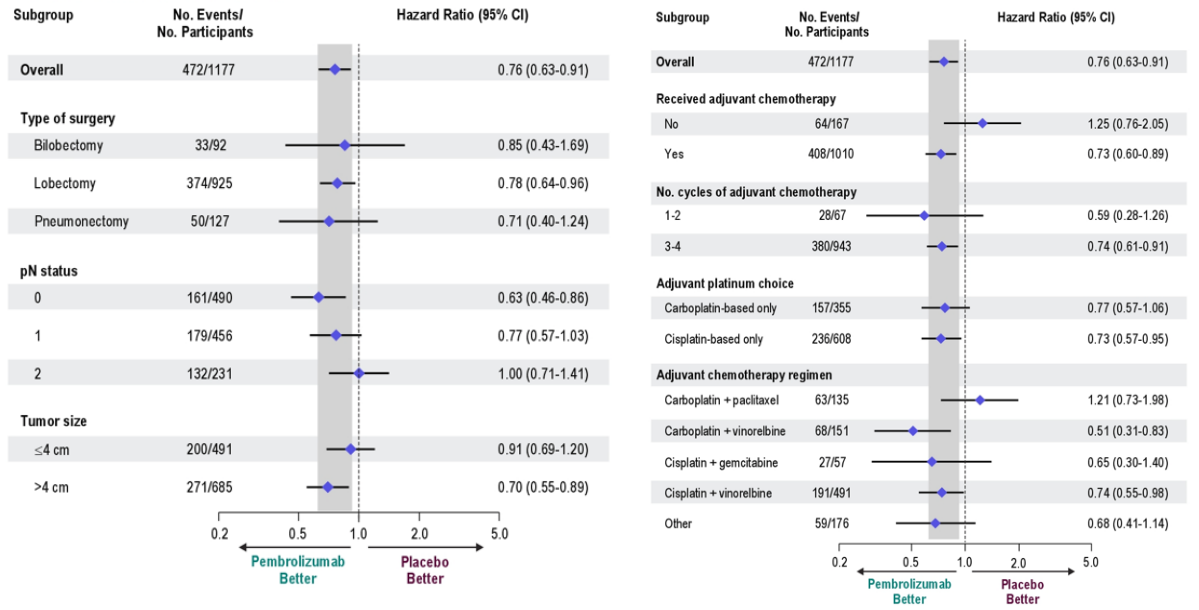
OUTCOME

> Exploratory analysis of DFS by type of surgery, disease burden, and use of adjuvant chemotherapy

Efficacy

> DFS favored pembrolizumab across types of surgery, pN0/1, and patients receiving adjuvant chemotherapy

DFS BY SURGERY, DISEASE BURDEN, CHEMOTHERAPY USE



AUTHOR CONCLUSIONS

> Pembrolizumab generally improved DFS compared with placebo across categories of surgical resection, tumor size, and adjuvant chemotherapy approaches

Nivolumab + chemotherapy versus chemotherapy as neoadjuvant treatment for resectable stage IIIA NSCLC: Phase 2 NADIM II

Provencio M, et al. 2022, ASCO 8501

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STUDY POPULATION

> Pts with potentially resectable stage IIIA/B NSCLC
> N=90

OUTCOME

> Improved outcome with the addition of nivolumab to neoadjuvant chemotherapy

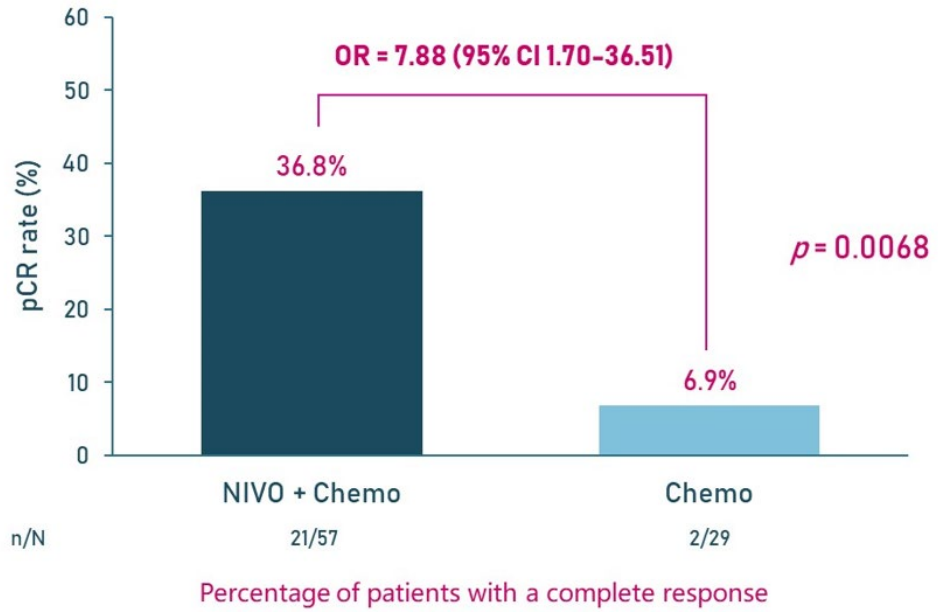
Efficacy (nivo-chemo vs chemo)

> pCR: 37% vs 7%; *P*=.0068
> MPR: 53% vs 14%; *P*=.0012

Safety

> G3/4 AEs: 25% vs 10%

PATHOLOGIC COMPLETE RESPONSE



(EXPERT) CONCLUSIONS

> Following on NADIM, the NADIM II trial shows superiority of neoadjuvant nivolumab plus chemotherapy compared with chemotherapy alone in patients with resectable stage IIIA/B NSCLC without impeding the feasibility of surgery

Two-year update from KEYNOTE-799: Pembrolizumab plus concurrent chemoradiation therapy

Reck M, et al. 2022, ASCO 8508

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STUDY POPULATION

- Pts with unresectable, stage IIIA–C NSCLC
  - Cohort A: Both histologies (pembro plus pac-carbo)
  - Cohort B: Nonsquamous (pembro plus pem-cis)

OUTCOME (Cohort A; Cohort B)

Efficacy

- 2-yr DOR: 64%; 69%
- 2-yr PFS: 55%; 61%
- 2-yr OS: 64%; 71%

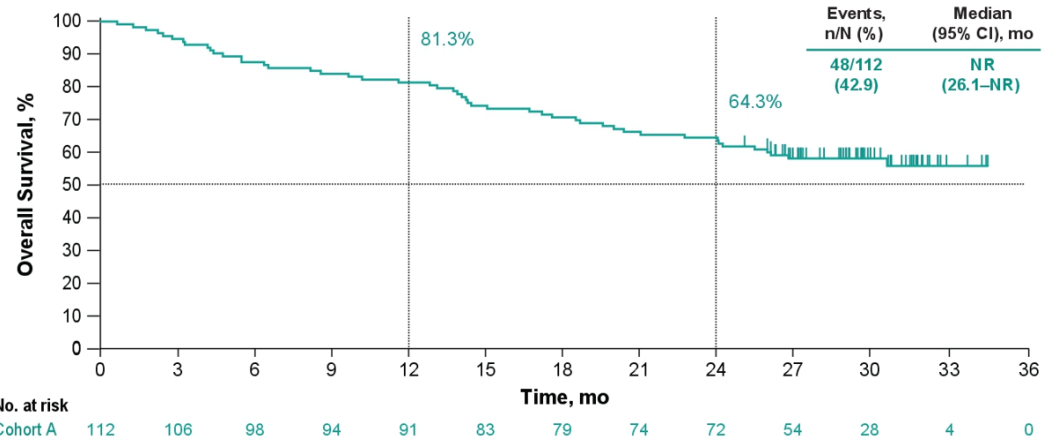
Safety

- G≥3 pneumonitis: 6%; 6%

OVERALL SURVIVAL

Figure 4. Overall survival

A. Cohort A (squamous and nonsquamous histology)



EXPERT CONCLUSIONS

- Induction/concurrent chemo-IO with pembrolizumab appears feasible and safe
- Outcomes are promising, but randomized trials will be needed against the current SOC

Consolidation nivolumab +/- ipilimumab cCRT for unresectable stage III non-small cell lung cancer: BTCRC LUN 16-081

Durm G, et al. 2022, ASCO 8509

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STUDY POPULATION

> Pts with unresectable stage IIIA/B NSCLC completing cCRT with a ≥SD
> N=105

OUTCOME (nivo-ipi vs nivo)

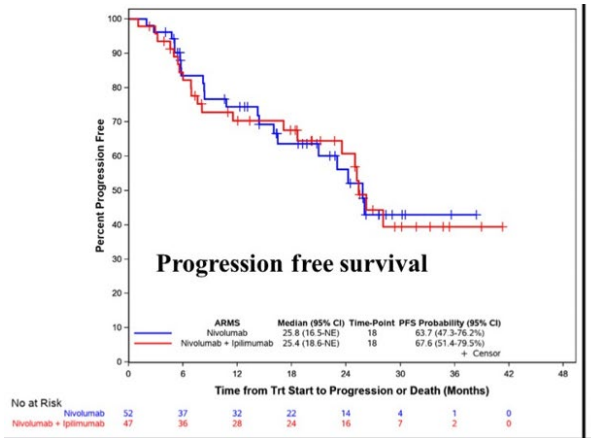
Efficacy

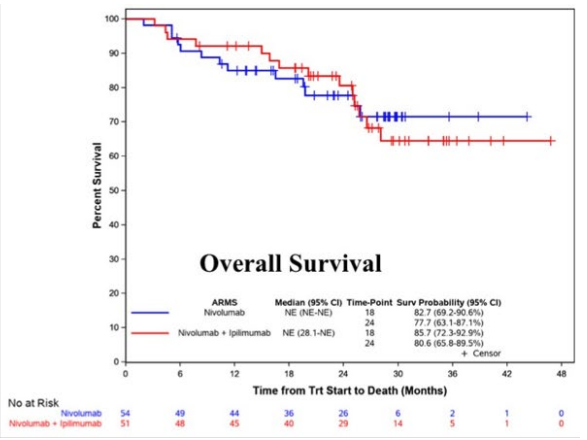
> mPFS: 25.8 mo vs 25.4 mo
> 24-mo OS: 78% vs 81%

Safety

> Any G≥3 TRAE: 18.5% vs 27.5%
> G3 pneumonitis: 9% vs 18%

PFS AND OS





EXPERT CONCLUSIONS

> Consolidation nivolumab for 6 months was feasible, and outcomes look promising
> However, ipilimumab added nothing but toxicity

A post hoc subgroup analysis of patients with *EGFR* mutations from PACIFIC

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Naidoo J, et al. 2022, ASCO 8541

STUDY POPULATION

> Pts with *EGFR* mutations enrolled in PACIFIC (n=35)

OUTCOME (durvalumab vs placebo)

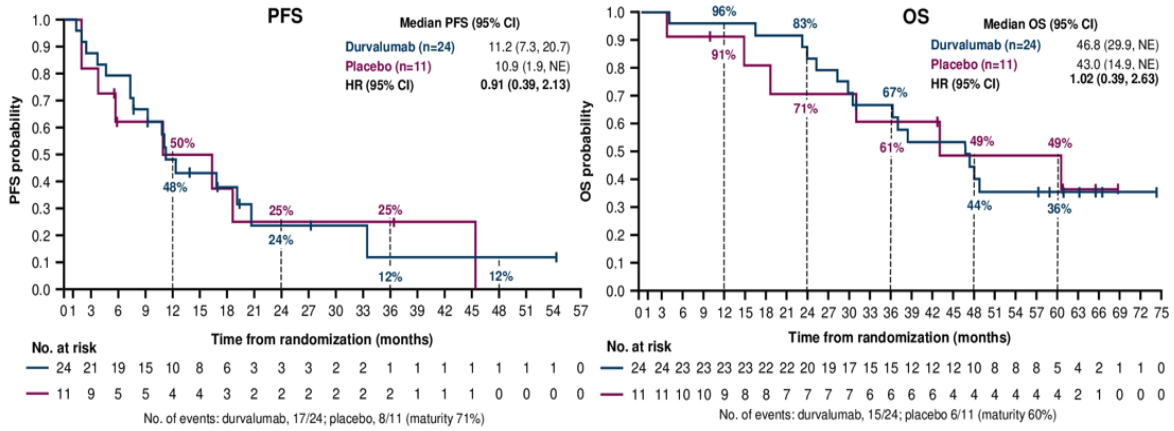
Efficacy

> PFS: 11.2 mo vs 10.9 mo
  – HR, 0.91
> OS: 46.8 mo vs 43.0 mo
  – HR, 1.02

Safety

> irAEs: 8 (33%) vs 2 (18%)

PFS AND OS



AUTHOR CONCLUSIONS

> Although patient numbers were limited, this exploratory analysis suggests that consolidation durvalumab after cCRT did not improve PFS or OS in patients with *EGFR* mutation-positive, unresectable stage III NSCLC
> The use of osimertinib in this setting is being explored in the phase III LAURA trial

Outcomes of immunotherapy with or without chemotherapy for first-line treatment of advanced NSCLC with PD-L1 score ≥ 50%: FDA pooled analysis

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Akinboro O, et al. 2022, ASCO 9000

STUDY POPULATION

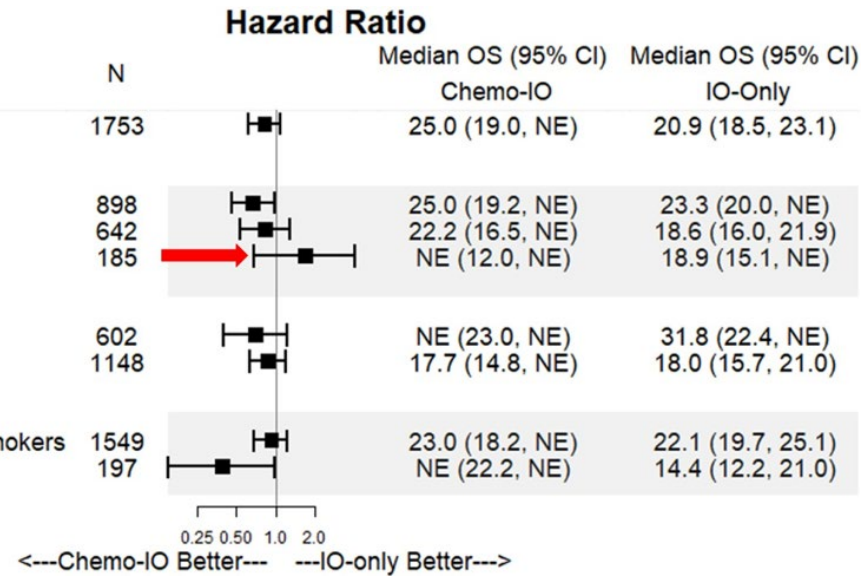
> Pts with advanced NSCLC and PD-L1 ≥50%
  - Chemo-IO (n=455)
  - IO alone (n=1,298)

OUTCOME (chemo-IO vs IO alone)

Efficacy

> OS: 25.0 mo vs 20.9 mo
> PFS: 9.6 mo vs 7.1 mo

OS IN PD-L1 ≥50% BY SELECTED SUBGROUPS



AUTHOR CONCLUSIONS

> This exploratory pooled analysis does not suggest that the addition of chemotherapy to immunotherapy improves OS compared with immunotherapy alone, although there is a numeric benefit with chemotherapy

Outcomes of first-line immunotherapy with or without chemotherapy by *KRAS* mutational status and PD-L1 expression in patients with advanced NSCLC: FDA pooled analysis

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Nakajima E, et al. 2022, ASCO 9001

STUDY POPULATION

- Pts with advanced NSCLC
  - *KRAS* wt (n=875)
  - *KRAS* mut (n=555); G12C (n=157)

OUTCOME

Efficacy

- ORR ~50% for all subgroups
- OS
  - *KRAS* wt: 18.7 mo
  - *KRAS* mut: 22.4 mo
  - *KRAS* G12C: 20.8 mo

OS BY *KRAS* MUTATION STATUS

Study Therapy	Median OS, mos (95% CI)		
	KRASwt	*KRASm*	*KRAS G12C*
ICI+chemo	**18.7** (16.0, 25.2) N=313	**22.4** (18.2, NE) N=219	**20.8** (11.3, NE) N=58
	HR 1.12 (95% CI: 0.86, 1.46)		
ICI alone	**16.4** (13.4, 19.7) N=240	**16.2** (11.1, NE) N=135	**11.8** (8.2, NE) N=45
	HR 1.01 (95% CI: 0.76, 1.34)		
Chemo alone	14.9 (12.2, 16.6) N=322	17.1 (12.3, 18.9) N=201	17.5 (10.7, 21.1) N=54
	HR 1.02 (95% CI: 0.81, 1.29)		

AUTHOR CONCLUSIONS

- Patients with *KRAS* mutations benefit from immunotherapy plus chemotherapy to a similar extent as those with wild-type *KRAS*
- The optimal control arm for first-line studies may be immunotherapy plus chemotherapy

Association of PFS and ORR with OS in first-line randomized trials of immunotherapy-based regimens for metastatic NSCLC: An FDA pooled analysis

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Goulart B, et al. 2022, ASCO 9029

STUDY POPULATION

> Pts in randomized trials of immunotherapy in metastatic NSCLC submitted to the FDA between 7/2016 and 3/2021 (N=9,285)

CORRELATION (R^2) OF ORR or PFS WITH OS BY PD-L1

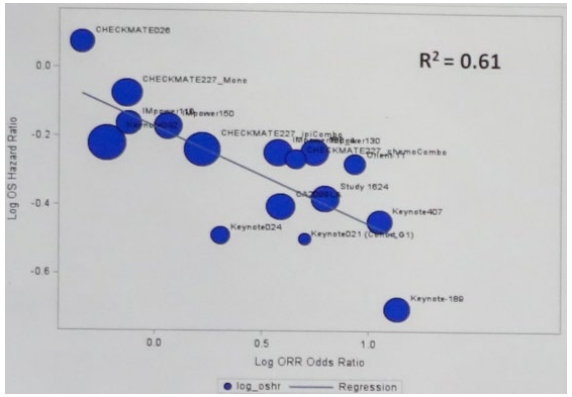
ORR

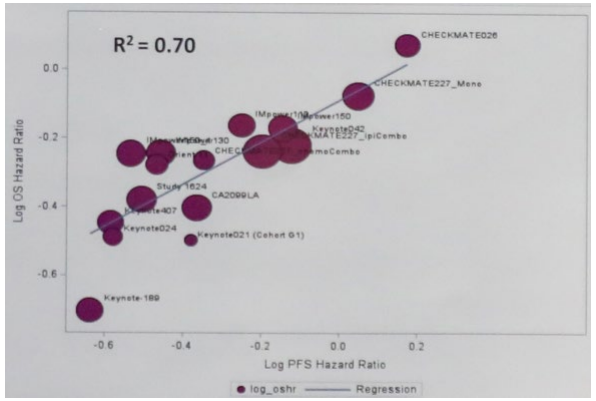
> <1%: 0.69
> ≥1%: 0.55
> 1%–49%: 0.49
> ≥50%: 0.31

PFS

> <1%: 0.62
> ≥1%: 0.70
> 1%–49%: 0.63
> ≥50%: 0.61

CORRELATION OF ORR/PFS AND OS





AUTHOR CONCLUSIONS

> Early clinical endpoints, such as ORR or PFS, may not predict for OS from immunotherapy

Five-year survival outcomes with nivolumab plus ipilimumab versus chemotherapy as first-line treatment for metastatic NSCLC: Results from CheckMate 227

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Brahmer J, et al. 2022, ASCO LBA9025

STUDY POPULATION

> Pts with stage IV NSCLC and no prior chemotherapy

OUTCOME (PD-L1 ≥1%; nivo-ipi vs chemo)

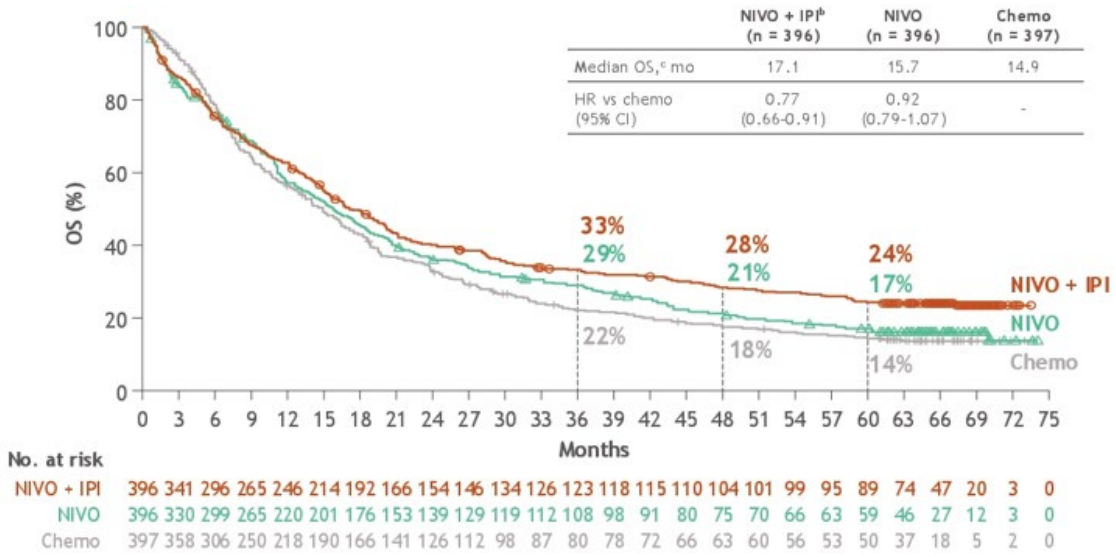
Efficacy

> OS: 17.1 mo vs 14.9 mo
> PFS: 5.1 mo vs 5.6 mo
> DOR: 24.5 mo vs 6.7 mo

Safety

> No new safety signals were reported

OS IN PD-L1 ≥1%



AUTHOR CONCLUSIONS

> Long-term benefit was observed with nivolumab-ipilimumab vs chemotherapy

Three-year update from first-line nivolumab plus ipilimumab + 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in patients with metastatic NSCLC: CheckMate 9LA

EPICS

Paz-Ares L, et al. 2022, ASCO LBA9026

STUDY POPULATION

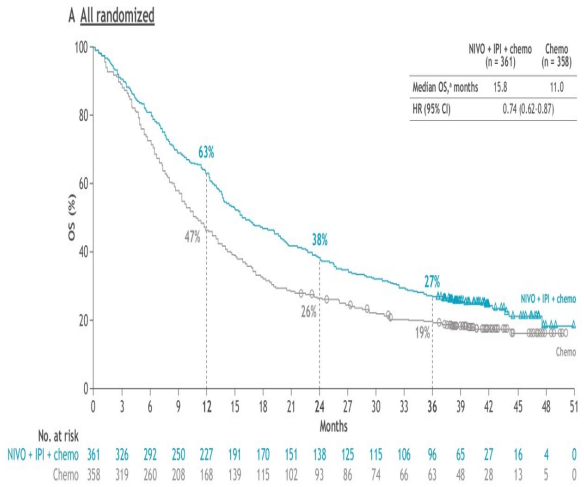
> Pts with stage IV NSCLC and no prior chemotherapy

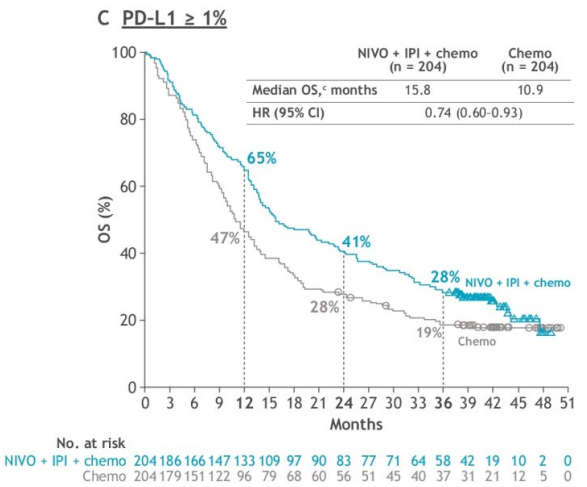
OUTCOME (nivo-ipi-chemo vs chemo)

OS by PD-L1 expression

> All patients: 15.8 mo vs 11.0 mo
> <1%: 17.7 mo vs 9.8 mo
> ≥1%: 15.8 mo vs 10.9 mo
> 1%–49%: 15.2 mo vs 10.4 mo
> ≥50%: 18.9 mo vs 12.9 mo

OS (all randomized patients/PD-L1 ≥1%)





EXPERT CONCLUSIONS

> While continued benefit with nivolumab-ipilimumab plus chemotherapy compared with chemotherapy alone was demonstrated, it is unclear whether chemotherapy is needed (cf 3-year OS in PD-L1 ≥1%)

Phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced NSCLC previously treated with immunotherapy: Lung-MAP nonmatched substudy S1800A

EPICS

Reckamp K, et al. 2022, ASCO 9004

STUDY POPULATION

> Pts with stage IV/recurrent NSCLC and previous platinum chemotherapy and inhibitor of PD-1/PD-L1 (N=130)

OUTCOME (pembrolizumab-ramucirumab vs SOC)

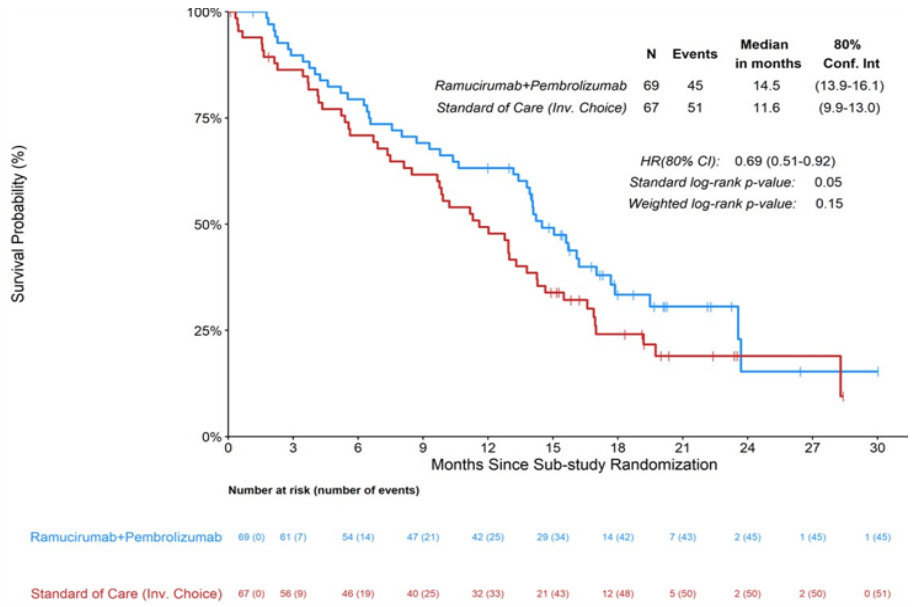
Efficacy

> OS: 14.5 mo vs 11.6 mo
> PFS: 4.5 mo vs 5.2 mo
> ORR: 22% vs 28%

Safety

> G≥3 TRAEs: 42% vs 60%

OVERALL SURVIVAL



EXPERT CONCLUSIONS

> OS benefit with ramucirumab-pembrolizumab, but no PFS or ORR benefit
> Better safety profile with ramucirumab-pembrolizumab (42% vs 60% grade 3–5 TRAEs)
> Defines a new, exciting treatment opportunity – waiting for high-level evidence from ongoing trials (eg, SAPPHIRE [sitravatinib-nivolumab], CONTACT-01 [cabozantinib-atezolizumab], LEAP-008 [lenvatinib-pembrolizumab])

Cabozantinib with or without atezolizumab in patients with advanced NSCLC previously treated with immunotherapy: Results from Cohorts 7 and 20 of the COSMIC-021 study

EPICS

Neal J, et al. 2022, ASCO 9005

STUDY POPULATION

> Pts with stage IV, nonsquamous NSCLC and PD after 1 prior line of immunotherapy and 2 or fewer prior lines of therapy (N=112)

OUTCOME (cabo-atezo vs cabo)

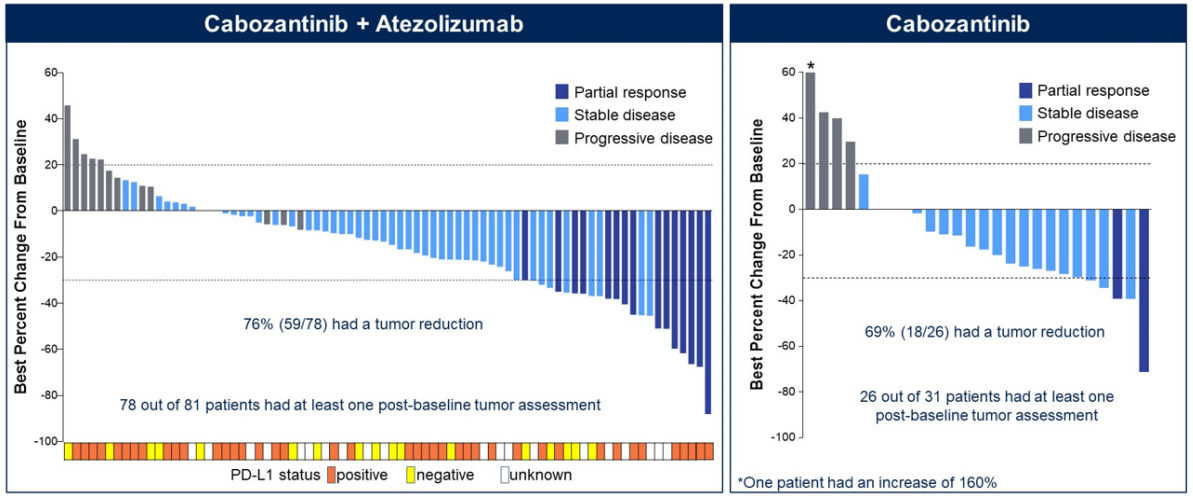
Efficacy

> ORR: 19% vs 6%
> PFS: 4.5 mo vs 3.4 mo
> OS: 13.8 mo vs 9.4 mo

Safety (G3/4)

> HTN: 6% vs 23%
> Pneumonitis: 0 vs 0
> Diarrhea: 1% vs 10%

BEST CHANGE IN TARGET LESIONS



EXPERT CONCLUSIONS

> Cabozantinib with atezolizumab showed encouraging clinical activity; cabozantinib alone showed minimal activity
> Unclear whether a phase III trial of cabozantinib-atezolizumab vs docetaxel is reasonable

Amivantamab and lazertinib in patients with *EGFR*-mutant NSCLC after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2.

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Shu C, et al. 2022, ASCO 9006

STUDY POPULATION

> Pts with *EGFR* mutation-positive NSCLC progressing after osimertinib and platinum-based chemotherapy (N=162)

OUTCOME

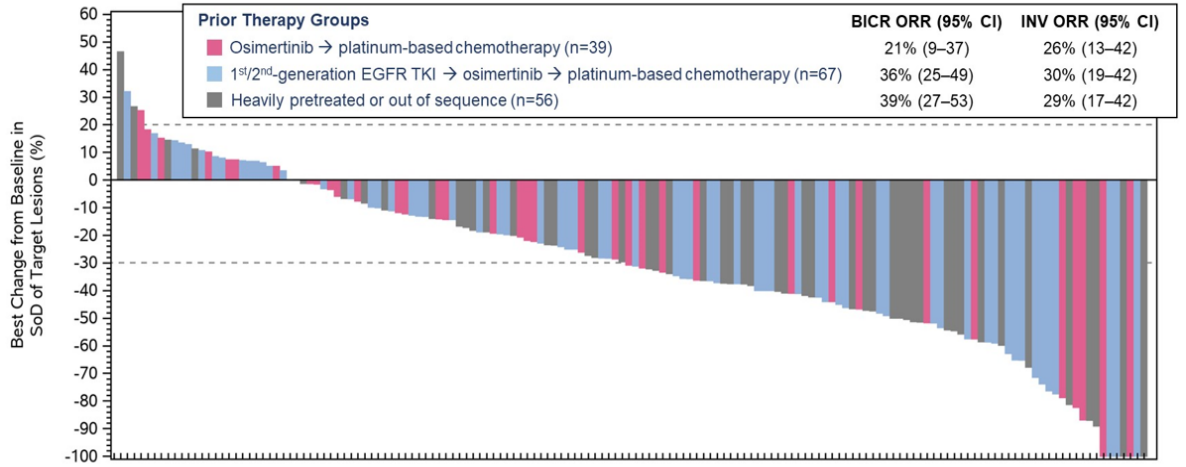
Efficacy

> ORR (BICR): 33%
> DOR: 8.4 mo
> PFS: 5.1 mo
> OS: 14.8 mo

Safety (G≥3)

> Dermatitis acneiform: 5%
> Edema: 1%
> Pneumonitis/ILD: 4%

TUMOR CHANGE BY PRIOR THERAPY



AUTHOR CONCLUSIONS

> The combination of amivantamab and lazertinib demonstrated durable activity in patients with *EGFR* mutation-positive NSCLC after progression on osimertinib and platinum-based chemotherapy
> Phase III trials are ongoing to further investigate amivantamab plus lazertinib (first line and post-osimertinib)

Phase 1/1b study of telisotuzumab vedotin (Teliso-V) + osimertinib (Osi), after failure on prior Osi, in patients with advanced, c-Met overexpressing, *EGFR*-mutated non-small cell lung cancer (NSCLC)

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Goldman J, et al. 2022, ASCO 9013

STUDY POPULATION

> Pts with metastatic, c-Met–overexpressing, nonsquamous NSCLC progressing on prior osimertinib (N=25)

OUTCOME

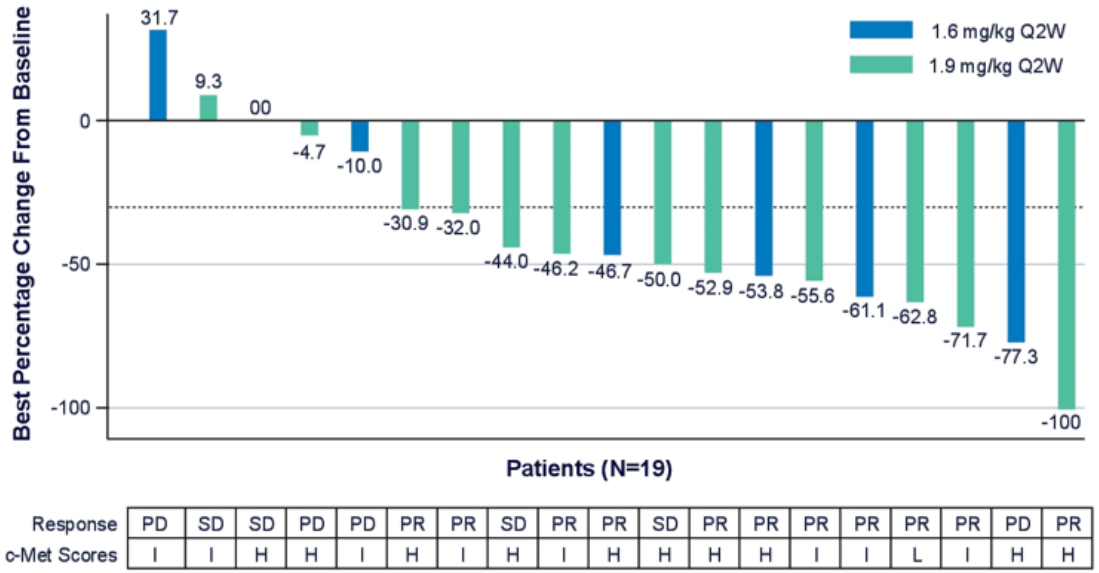
Efficacy (ORR)

> Overall: 58%
> C-Met high: 50%
> C-Met int: 63%

Safety

> Any grade
  – Peripheral sensory neuropathy: 36%
  – Peripheral edema: 24%
> Grade ≥3
  – Pulmonary embolism: 12%

TUMOR CHANGE FROM BASELINE



AUTHOR CONCLUSIONS

> Teliso-V with osimertinib demonstrated promising efficacy in patients with *EGFR* mutation-positive NSCLC who had progressed on prior osimertinib
> The main AEs observed were peripheral sensory neuropathy, nausea, and peripheral edema

Phase 1/2a study of CLN-081 in patients with NSCLC with *EGFR* exon 20 insertion mutations

Yu H, et al. 2022, ASCO 9007

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STUDY POPULATION

> Pts with recurrent/metastatic NSCLC with an *EGFR* exon 20 insertion and prior chemotherapy (N=73)

OUTCOME

Efficacy

> ORR: 38%
> DOR: 10.0 mo
> PFS: 10.0 mo

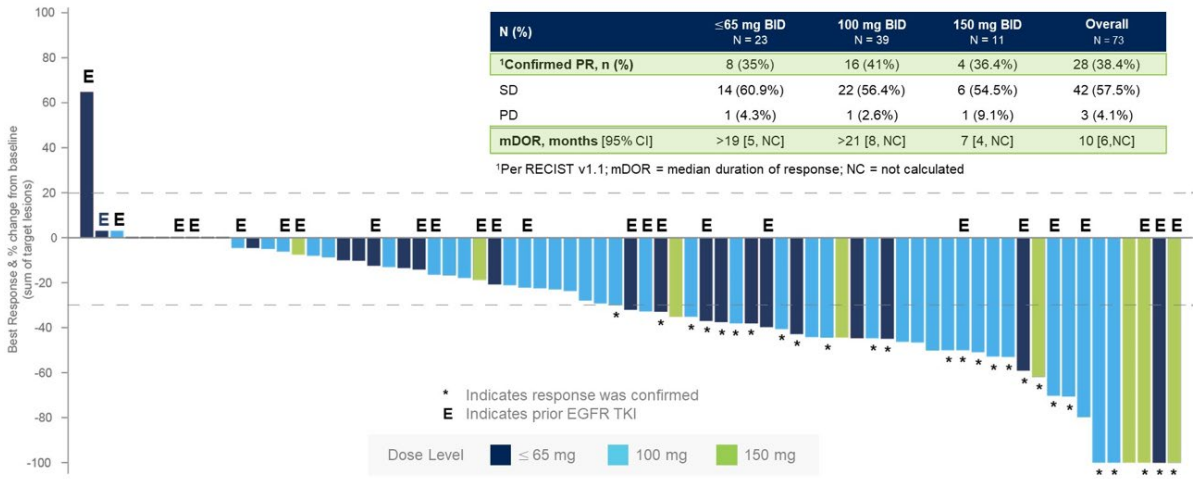
Safety (G≥3)

> Rash: 1%
> Diarrhea: 3%
> Paronychia: 0

TUMOR CHANGE FROM BASELINE

N (%)	≤65 mg BID N = 23	100 mg BID N = 39	150 mg BID N = 11	Overall N = 73
[1]Confirmed PR, n (%)	8 (35%)	16 (41%)	4 (36.4%)	28 (38.4%)
SD	14 (60.9%)	22 (56.4%)	6 (54.5%)	42 (57.5%)
PD	1 (4.3%)	1 (2.6%)	1 (9.1%)	3 (4.1%)
mDOR, months [95% CI]	>19 [5, NC]	>21 [8, NC]	7 [4, NC]	10 [6,NC]

[1]Per RECIST v1.1; mDOR = median duration of response; NC = not calculated



AUTHOR CONCLUSIONS

> Objective responses observed even in heavily pretreated patients, including those with prior EGFR TKIs
> Safety profile of CLN-081 is compatible for long-term therapy

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Mobocertinib (TAK-788) in *EGFR* exon 20 insertion+ metastatic NSCLC: Treatment beyond PD in platinum-pretreated patients with and without intracranial PD.

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Janne P, et al. 2022, ASCO 9099

STUDY POPULATION

> Pts with NSCLC and an *EGFR* exon 20 insertion treated with prior platinum chemotherapy; analysis of mobocertinib beyond PD (N=114)

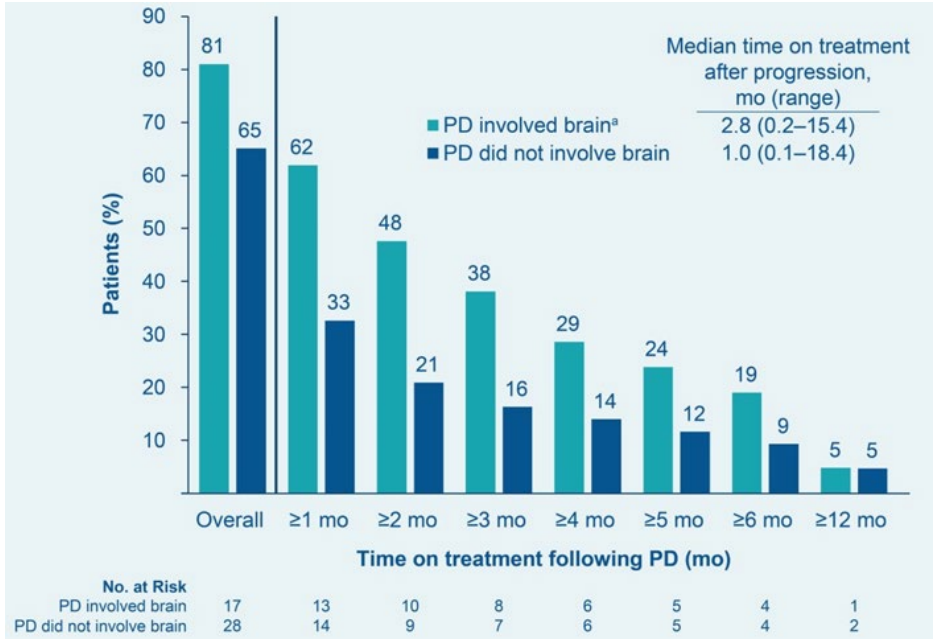
OUTCOME

> 21 patients (33%) had first site of PD involving the brain

Subsequent therapy

> 17 of 21 patients continued mobocertinib after PD, with 4 patients continuing for ≥6 months
> 7 of 21 patients also underwent brain RT; 3 patients continued for ≥6 months and 1 patient for ≥12 months

PATIENTS ON THERAPY AFTER PD BY SITE OF PROGRESSION



AUTHOR CONCLUSIONS

> Patients with *EGFR* exon 20 insertions and disease progression on mobocertinib may derive benefit from continuing mobocertinib in combination with local therapy

KRYSTAL-1: Activity and safety of adagrasib (MRTX849) in patients with advanced/metastatic NSCLC harboring a *KRAS* G12C mutation

EPICS

Spira A, et al. 2022, ASCO 9002

STUDY POPULATION

> Pts with advanced NSCLC, a *KRAS* G12C mutation, and prior immunotherapy-chemotherapy (N=116)

OUTCOME

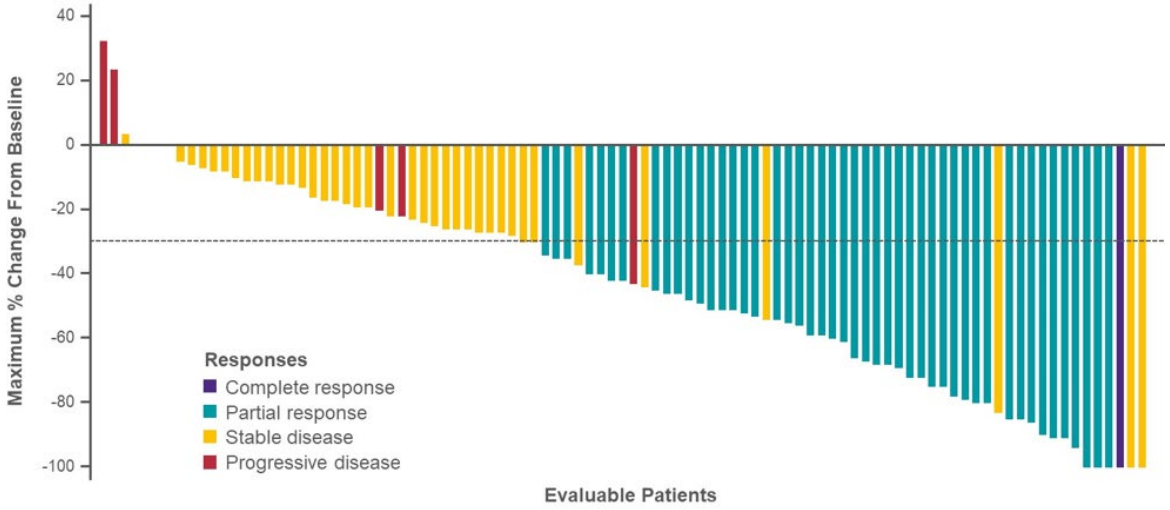
Efficacy

> ORR: 43%
> DOR: 8.5 mo
> PFS: 6.5 mo
> OS: 12.6 mo
> Intracranial ORR in patients with treated CNS metastases: 33%

Safety (G3/4)

> Diarrhea: <1%
> Nausea: 4%
> Vomiting: <1%

TUMOR CHANGE FROM BASELINE



AUTHOR CONCLUSIONS

> Adagrasib demonstrated promising activity in this phase II trial, with data in regulatory review
> Confirmatory phase III trial of adagrasib vs docetaxel (KRYSTAL-12) is ongoing

KRYSTAL-1: Active, untreated CNS metastases cohort

Sabari J, et al. 2022, ASCO LBA9009

EPICS

STUDY POPULATION

> Pts with *KRAS* G12C mutation-positive solid tumors and active, untreated CNS metastases; NSCLC cohort, n=25

OUTCOME

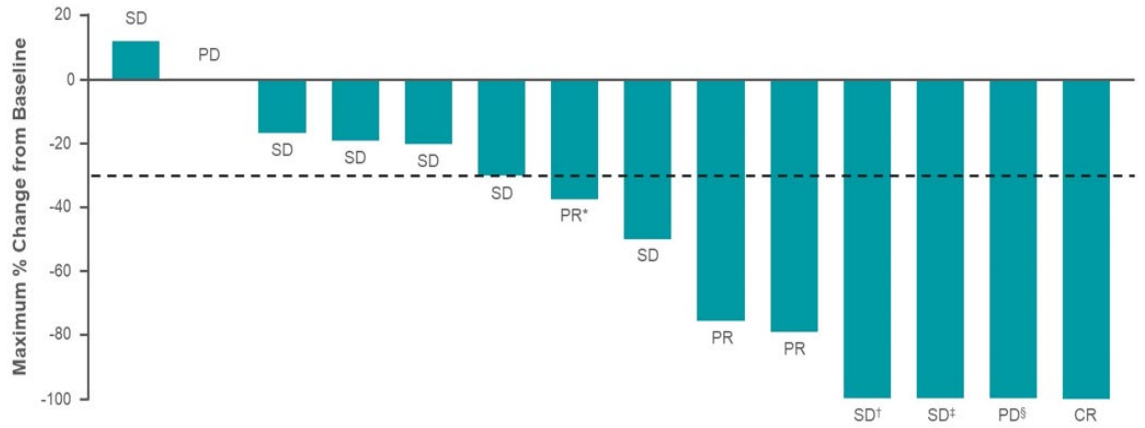
Efficacy

> Intracranial (IC) ORR: 32%
> Median IC PFS: 4.2 months

Safety (G3)

> Vomiting: 12%
> Nausea: 8%
> Diarrhea: 0

TUMOR CHANGE FROM BASELINE



AUTHOR CONCLUSIONS

> Adagrasib demonstrated encouraging CNS activity in patients with NSCLC and active, untreated CNS metastases
> Together with abstract 9002, adagrasib has demonstrated activity in patients with NSCLC and both treated and untreated CNS metastases

Amivantamab in patients with NSCLC with *MET* exon 14 skipping mutation: Updated results from the CHRYSALIS study

Krebs M, et al. 2022, ASCO 9008

EPICS

STUDY POPULATION

> Pts with advanced NSCLC and a *MET* exon 14 mutation, ineligible for standard therapy or standard therapy failed (N=55)

OUTCOME

> Patients had a median 2 prior regimens (range, 0–10 regimens)

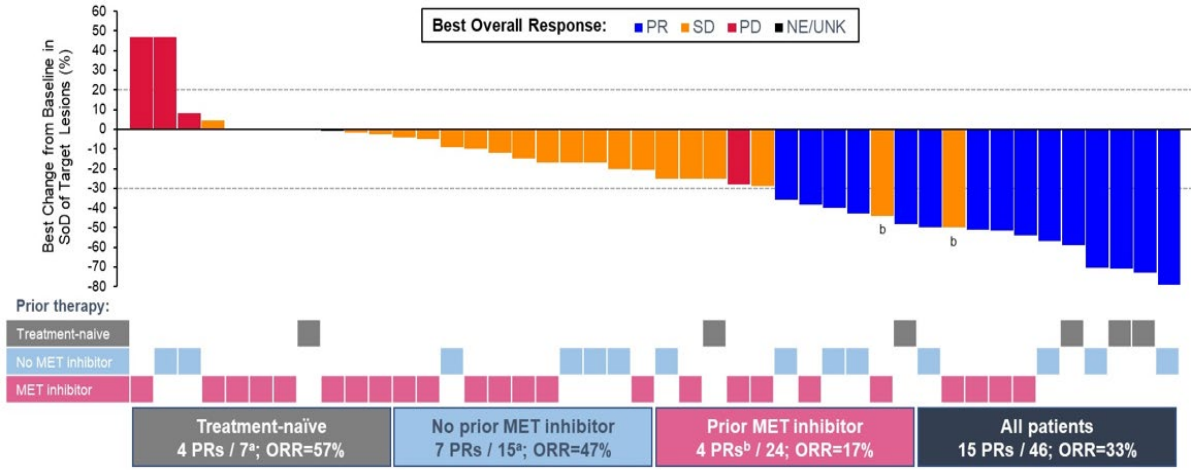
Efficacy

> ORR
  - All patients: 33%
  - Treatment naive: 57%

Safety (N=425; G≥3)

> Infusion reaction: 3%
> Dyspnea: 5%

TUMOR CHANGE FROM BASELINE



AUTHOR CONCLUSIONS

> Amivantamab as a single agent is active in patients with NSCLC and a *MET* exon 14 mutation
> The safety profile is similar between the *MET* exon 14 subset and the overall patient cohort

Telisotuzumab vedotin monotherapy in patients with previously treated c-Met–overexpressing advanced NSCLC

EPICS

Camidge R, et al. 2022, ASCO 9016

STUDY POPULATION

> Pts with advanced NSCLC and ≤2 prior lines of therapy (n=130 evaluable)

OUTCOME

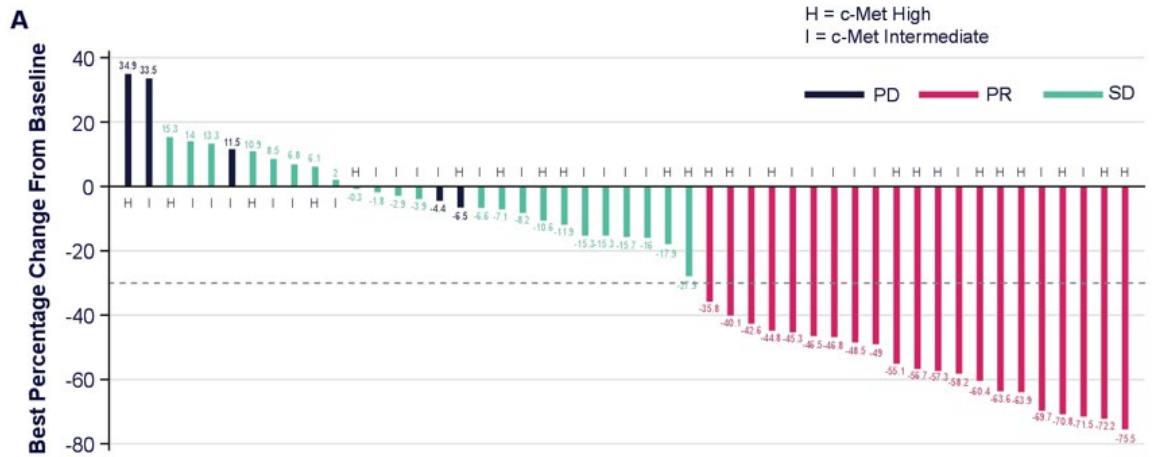
Efficacy (nonsquamous)

> *EGFR*wt, c-Met high: 52%
> *EGFR*wt, c-Met int: 24%
> *EGFR*mut, c-Met high: 17%
> *EGFR*mut, c-Met int: 0

Safety (G≥3)

> Peripheral sensory neuropathy: 4%
> Peripheral edema: 0

TUMOR CHANGE FROM BASELINE



AUTHOR CONCLUSIONS

> Telisotuzumab vedotin demonstrated promising efficacy, particularly in patients with nonsquamous, *EGFR* wild-type NSCLC and c-Met–high disease

Efficacy/safety of entrectinib in patients with *ROS1*-positive advanced/ metastatic NSCLC from the Blood First Assay Screening Trial (BFAST).

Peters S, et al. 2022, ASCO LBA9023

EPICS

STUDY POPULATION

> Pts with previously untreated, advanced NSCLC and a *ROS1* fusion detected through liquid biopsy (N=55)

OUTCOME

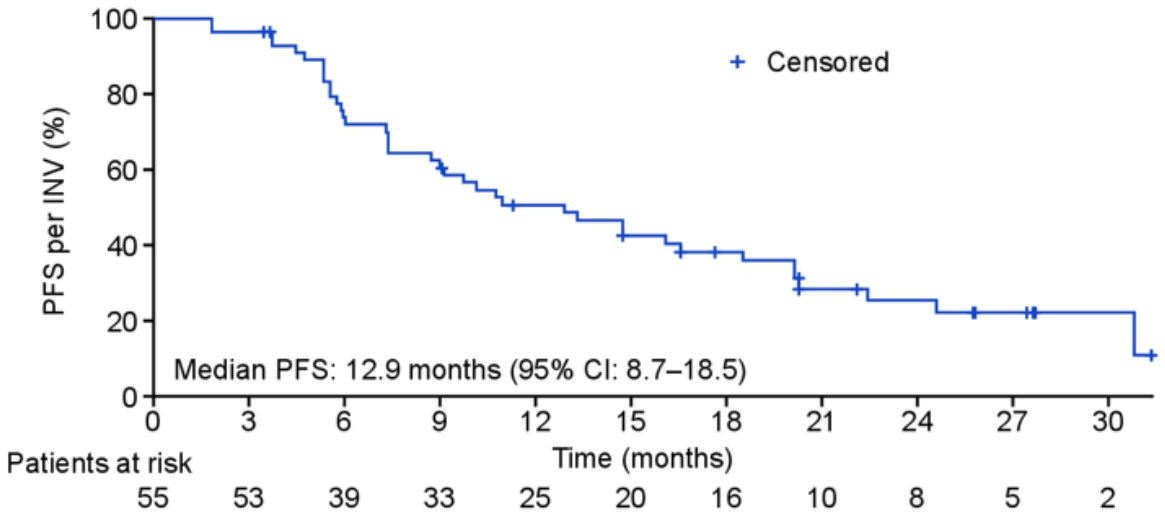
Efficacy

> ORR (INV): 81.5%
> DOR: 13.0 mo
> PFS: 12.9 mo
> 12-mo OS: 79%

Safety

> G3 weight gain: 7%

PFS WITH ENTRECTINIB IN *ROS1*-REARRANGED NSCLC



AUTHOR CONCLUSIONS

> Entrectinib therapy in patients with blood-based detection of *ROS1* fusions in NSCLC met its primary endpoint

Updated efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (TRK) fusion lung cancer.

Drilon A, et al. 2022, ASCO 9024

EPICS

STUDY POPULATION

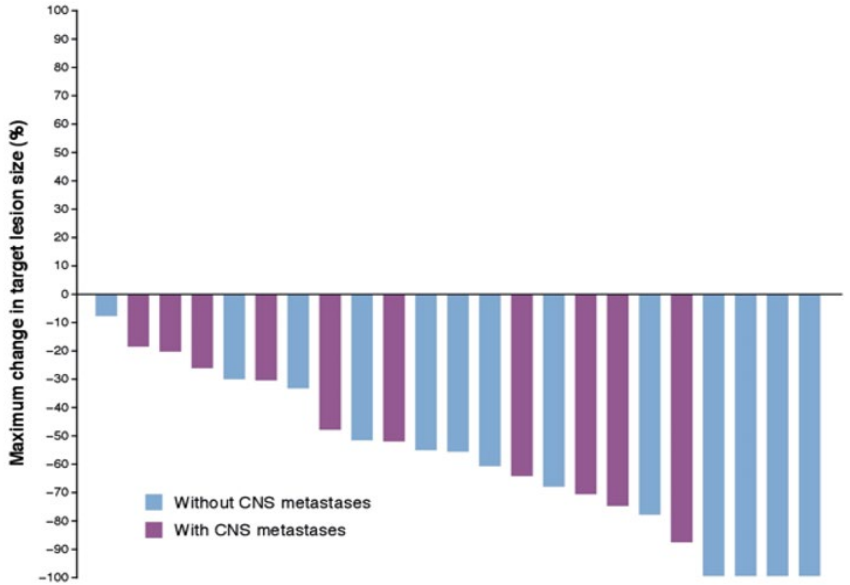
> Pts with *TRK* fusion-positive NSCLC (N=26)

OUTCOME

Efficacy

> ORR: 83%
> 24-mo DOR: 72%
> 24-mo PFS: 67%
> 24-mo OS: 72%

TUMOR CHANGE FROM BASELINE



(EXPERT) CONCLUSIONS

> With additional follow-up, larotrectinib demonstrated continued durable responses in patients with NSCLC and *TRK* fusions

SKYSCRAPER-02: Primary results of a phase III, randomized, double-blind, placebo-controlled study of atezolizumab + carboplatin + etoposide with or without tiragolumab in patients with untreated ES-SCLC

Rudin C, et al. 2022, ASCO LBA8507

EPICS

STUDY POPULATION

> Pts with previously untreated ES-SCLC (N=490)

OUTCOME (tiragolumab-ACE vs placebo-ACE)

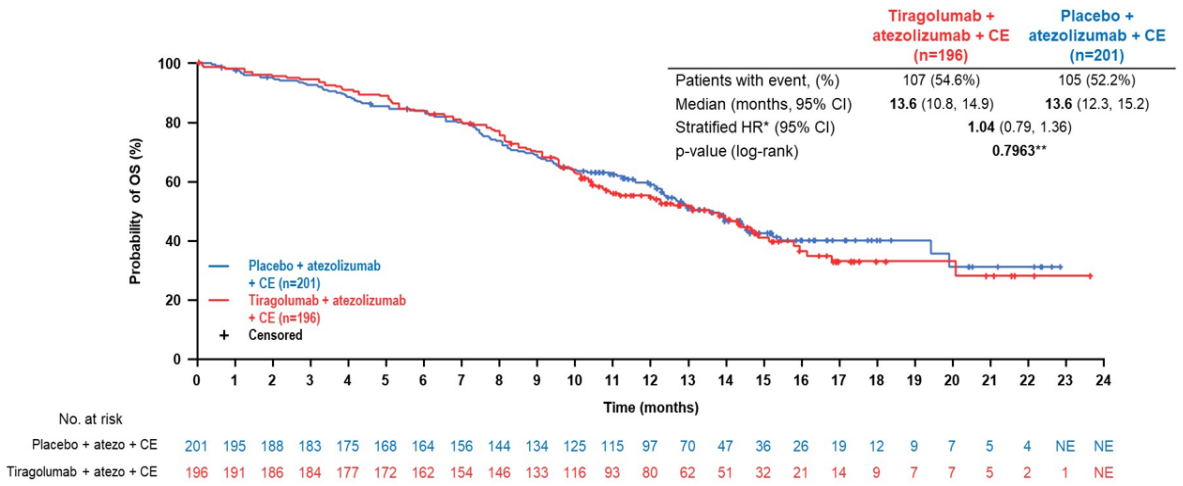
Efficacy

> OS: 13.6 mo vs 13.6 mo
> PFS: 5.4 mo vs 5.6 mo
> ORR: 71% vs 66%

Safety

> G3/4 TRAEs: 52% vs 56%

OVERALL SURVIVAL



AUTHOR CONCLUSIONS

> The addition of tiragolumab to atezolizumab-CE did not improve OS or PFS in patients with previously untreated ES-SCLC

Efficacy and safety of patritumab deruxtecan (HER3-DXd) in advanced/metastatic NSCLC without *EGFR*-activating mutations

Steuer C, et al. 2022, ASCO 9017

EPICS

STUDY POPULATION

> Pts with advanced NSCLC and without *EGFR* exon 19, L858R, L861Q, or G719X mutations (N=47)

OUTCOME

Efficacy

> ORR
  - With oncogenic drivers: 29%
  - Without oncogenic drivers: 27%

Safety

> G1/2 ILD: 11%

TUMOR CHANGE FROM BASELINE WITH (A) OR WITHOUT (B) ONCOGENIC DRIVERS

AUTHOR CONCLUSIONS

> HER3-DXd demonstrated promising clinical activity similar to observations seen in patients with *EGFR* mutation-positive NSCLC, with activity in patients with or without non-*EGFR* oncogenic drivers

Safety and efficacy of tusamitamab ravtansine (SAR408701) in long-term treated patients with nonsquamous NSCLC expressing CEACAM5

EPICS

Ricordel C, et al. 2022, ASCO 9039

STUDY POPULATION

> Pts with advanced solid tumors
> 92 patients with nonsquamous NSCLC

OUTCOME

> 11 patients were treated for ≥12 months
> Median 2 prior regimens (range, 1–6 regimens)

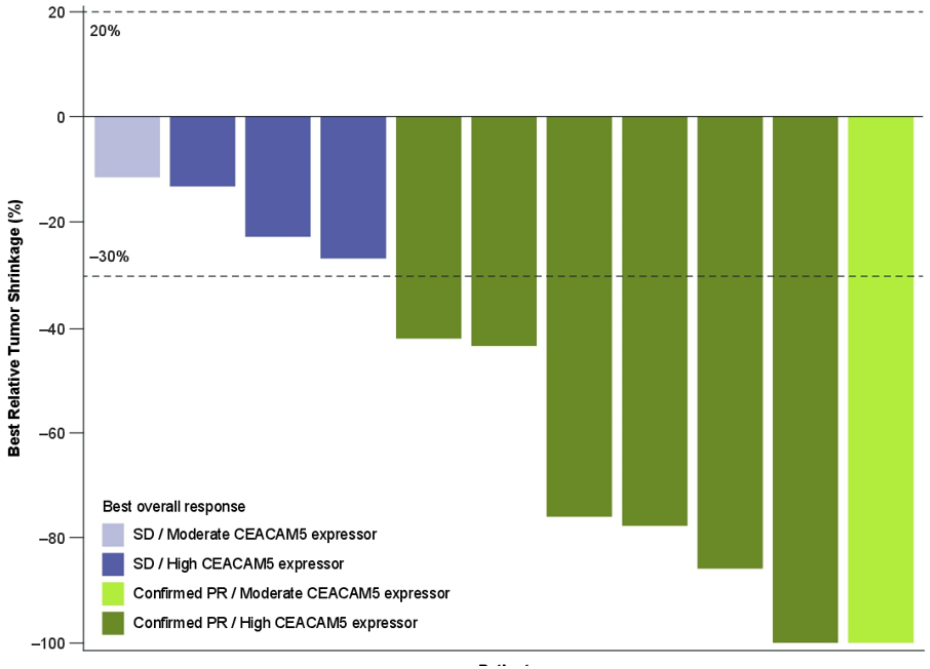
Efficacy

> ORR: 7 (64%)

Safety (G≥3)

> Keratitis: 4 (36%)
> Keratopathy: 2 (18%)

TUMOR CHANGE FROM BASELINE



AUTHOR CONCLUSIONS

> Tusamitamab ravtansine demonstrated activity in heavily pretreated patients
> Key adverse events included ocular toxicity

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Key Insights

Immunotherapy in Resectable NSCLC (1/2)

EPICS

The experts would implement the neoadjuvant immunotherapy strategy in their practices, with some patient selection

> One of the experts expects to implement the neoadjuvant approach most often in patients with stage IIIA disease, and less often in patients with earlier-stage disease, while another expert generally favors neoadjuvant therapy for the majority of patients with stage I–III disease
> The ideal amount of immunotherapy in patients with resectable disease is still not known, and expert opinion is that the strict neoadjuvant approach in CheckMate 816 (and therefore the strict adjuvant approach of IMpower010) may be supplanted by a regimen that also incorporates an adjuvant approach

For patients with a large primary tumor or pathologic N1 disease, expert opinion is that the adjuvant approach would be appropriate

Expert opinion is that image-based response assessment is less informative in the neoadjuvant setting

> In CheckMate 816, imaging showed a CR in ~1% of patients, but the pathologic CR (pCR) rate was actually ~30%
> This complicates decision-making for patients who only achieve a partial response by imaging

The experts think additional data will be needed before pCR can be considered a surrogate endpoint for EFS or OS in lung cancer

> Expert opinion is that there appears to be a correlation between pCR and EFS, with some retrospective data suggesting a correlation with OS
> However, one of the experts mentioned that the EMA has withdrawn reflex correlation between pCR and OS or PFS in breast cancer because post-surgery relapses have been observed in patients achieving a pCR after immunotherapy plus chemotherapy
> It was suggested by one of the experts that a correlation between EFS/DFS and OS in lung cancer should be solidified as a first step

“***Dr Sholl:***
I think obviously pCR is a powerful endpoint. I do think if we completely ignore MPR we could be throwing the baby out with the bathwater.”

Immunotherapy in Resectable NSCLC (2/2)

EPICS

The opinion of the pathology expert is that MPR, with modifications, can be a valuable endpoint for neoadjuvant therapy

> Expert opinion is that MPR as an endpoint is currently impaired by unclear definitions, examination of only the tumor bed and excluding lymph node examination, and a lack of reproducibility regarding the cutoff of 10% viable tumor cells
> It was proposed to improve MPR by including nodal status, as well as standardizing grossing and microscopy protocols to improve reproducibility
> Given that some patients may have a good pathologic response, even if less than a pCR, collecting data on patients achieving a revised MPR might provide valuable and expanded information on the efficacy of neoadjuvant immunotherapy, since pCR rates can be low

There is enthusiasm from the experts for the potential use of ctDNA to guide postoperative therapy; however, in the ctDNA analysis from IMpower010 (Zhou et al. ESMO-IO 2021, abstract 2O), this approach appeared to be more prognostic than predictive, since a benefit with atezolizumab was observed both in ctDNA-negative and -positive patients

Expert opinion is that for patients with PD-L1 expression of 1%–49%, the trial design would favor the neoadjuvant approach

> One of the experts stated that IMpower010 was not properly stratified for PD-L1, with different scoring systems used for stratification vs the subgroup analysis
> On the other hand, CheckMate 816 is viewed as properly stratified for PD-L1 expression

Immunotherapy in Unresectable Stage III NSCLC

EPICS

For patients with unresectable stage III NSCLC and an *EGFR* mutation, the experts are eager to see the results of the LAURA trial

> Currently, the experts would not use immunotherapy
> The experts reported using osimertinib occasionally, even without phase III data; the rationale is that osimertinib is beneficial in both stage IV (FLAURA) and resectable disease (ADAURA)

Biomarker testing in stage III NSCLC varies between the different institutions; small biopsies were mentioned as an impairment to molecular testing

> The stage may not be apparent in small biopsies, so *EGFR* testing may not be done reflexively
> Furthermore, small biopsies may not be suitable for NGS-based testing or rapid *EGFR* testing

Expert opinion is that a concurrent approach with immunotherapy and chemoradiation therapy in unresectable stage III NSCLC is feasible, but phase III data are needed

There is enthusiasm for the combination approach in the COAST trial, which is moving to phase III investigation. While the control arm of durvalumab in COAST underperformed relative to the results seen with durvalumab in PACIFIC, the benefit of adding oleclumab or monalizumab to durvalumab in COAST was upheld by a propensity analysis

Expert opinion is that clarity is still needed in terms of the timing and duration of consolidation immunotherapy, given that not all patients are able to receive therapy as designed in PACIFIC

> While the goal is to start within 2 weeks, on the basis of PACIFIC, some patients need additional time to recover after chemoradiation therapy
> Evidence-based guidance on the optimal duration of consolidation immunotherapy is also needed, as it is unclear if the full year of therapy per the PACIFIC design is needed to obtain benefit

“***Dr Socinski:***
I think one of the key takeaways: is it time to address the duration question? Would less be more? We don’t know, but we have to be careful about that.”

Immunotherapy in Stage IV NSCLC (1/2)

EPICS

The experts think the combination of KRAS inhibitors with immunotherapy with or without chemotherapy should be explored in the first-line setting

> A note of caution from one of the experts was given regarding the potential for toxicity with the combination of sotorasib and immunotherapy, on the basis of 2 case reports showing liver toxicity when sotorasib was given immediately after immunotherapy
> In contrast, trials are ongoing with immunotherapy and adagrasib, suggesting a lack of toxicity with adagrasib-based combinations

The experts reported using immunotherapy beyond progression in certain patients

> One of the experts mentioned a retrospective analysis by Gandara et al showing benefit for this approach
> The most likely candidates would be those who have more-indolent progression or isolated oligometastases
> It is thought by experts that the National Comprehensive Cancer Network might include guidance on continuing immunotherapy after progression, since the guidelines are consensus based and do not require randomized phase III data

Expert opinion is that there are currently not enough data to use *STK11* or other mutations to choose therapy

> While *STK11* mutation status appears to have prognostic value, it is thought by experts that prospective data are needed regarding the predictive ability to determine benefit from immunotherapy
> The experts think clinical trials should continue to stratify by *STK11* mutational status to collect additional data
> The pathology expert mentioned that looking at any individual mutation in the context of immunotherapy would be an oversimplification; furthermore, translational work beyond genomics should be done, such as an examination of the immune milieu

“***Dr Peters:***
We know from ARC-7 and [SKYSCRAPER-01] there is a numerical difference, meaning not like small cell. TIGIT makes something in NSCLC. But in which patients, and is it enough for registration?”

Immunotherapy in Stage IV NSCLC (2/2)

EPICS

On the basis of the long-term analyses of CheckMate 227 and CheckMate 9LA, expert opinion is that the use of chemotherapy in CheckMate 9LA may not contribute much to the OS attained with immunotherapy alone (nivolumab-ipilimumab)

> It is thought that using the immunotherapy doublet alone in the frontline setting would allow for the use of chemotherapy in the next line of therapy

TIGIT is viewed by the experts as still having potential in NSCLC, despite the SKYSCRAPER-01 trial not meeting the PFS endpoint

> Since both ARC-7 and SKYSCRAPER-01 reported increases (“numeric” or “meaningful”) in efficacy with the addition of an anti-TIGIT antibody, expert opinion is that TIGIT appears to be a genuine target in NSCLC, as compared with SCLC
> It was pointed out by one of the experts that this trial was not powered to focus on PFS, but there is a large alpha for OS, so the readout on OS should happen soon
> Additionally, the lack of a biomarker other than PD-L1 for the TIGIT-based combination is seen as a potential weakness

The Lung-MAP combination of pembrolizumab-ramucirumab in patients with previously treated NSCLC is seen by the experts as a promising approach, with a favorable safety profile compared with the comparator arm

> The experts anticipate results of several phase III trials in the second-line setting by the end of 2022

EGFR Mutations

EPICS

For patients with *EGFR* exon 20 insertion mutations, expert opinion is that the current first-line standard of care is still chemotherapy with or without bevacizumab

> Expert opinion is that the toxicity seen with mobocertinib and amivantamab does not favor first-line use, so these are seen as second-line agents
> The experts want to see clinical data in the first-line setting before implementing any of the new agents in clinical practice
> Amivantamab and mobocertinib are seen as equally active, with toxicity being the differentiator in terms of choosing a treatment strategy
> CLN-081 is viewed by the experts as the most tolerable agent of those mentioned; while the patient number was still small, the adverse event profile of this agent is seen as favorable for first-line use, and the efficacy results were comparable with current options

Use of tissue- and liquid-based biopsy at diagnosis varies between the institutions, with most (n=4) requesting both types of biopsies simultaneously, and others (n=2) requesting tissue first

> The rationale for requesting both liquid and tissue biopsies is that the 2 methods are not 100% overlapping, and testing both compartments would maximize the chance to detect an oncogenic driver

The pathology expert mentioned a similar rationale for interrogating both liquid and tissue at the time of progression, namely the ability to evaluate both compartments for mechanisms of resistance

Dr Paik:
I think the data we have for amivantamab and mobocertinib, unless something really stands out, then we are talking about toxicity as the differentiating factor.

Oncogenic Drivers: Mutations

EPICS

The experts view the *KRAS* G12C inhibitors sotorasib and adagrasib as having similar efficacy

> Close monitoring of CNS activity as clinical trials progress may reveal a meaningful difference between the agents
> Expert opinion is that differences between the agents may appear with additional experience, particularly in terms of toxicity and the ability to combine with other agents such as immunotherapy

The evaluation of MET protein expression is seen as a challenge by the pathology expert

> The approach used to evaluate MET during the development of onartuzumab in the late 2010s is not viewed as optimal
> Expert opinion is that cutoff values will need to be carefully defined and strategies to conserve tissue are needed, given the already high demands for genetic and PD-L1 testing
> It will also be necessary to have clear nomenclature to differentiate between the different types of alterations (eg, MET protein expression, *MET* gene amplification, *MET* exon 14 skipping mutations). Furthermore, the experts think that most oncologists are not aware of the distinction between these different MET abnormalities, so education will be necessary

Dr Felip:
I think adagrasib, sotorasib are now probably standard of care in patients and we have to work to develop these agents in first line.

Oncogenic Drivers: Fusions

EPICS

The pathology expert mentioned that RNA-based testing is crucial for some fusions, such as *NTRK2* and *NTRK3*

> Nevertheless, it was acknowledged that while simultaneous DNA- and RNA-based testing is ideal for detection of fusions, there are practical considerations, such as the costs to extract DNA only, RNA only, or total nucleic acid extraction
> Expert opinion is that sending tissue to an external vendor, particularly for smaller centers, is the ideal approach to search for the widest array of oncogenic drivers
> The pathology expert stated that most blood-based tests are DNA based, so if the test is negative, it will be necessary to have reflex tissue-based testing
> IHC-based testing is not viewed by the pathology expert as having sufficient sensitivity or specificity for detecting *NTRK* fusions, although this approach is used for testing for *ROS1* fusions

For patients with *ROS1* fusions, the experts view entrectinib as having improved CNS activity compared with crizotinib

> The actual first-line agent varies by institution, with some having replaced crizotinib with entrectinib due to the CNS activity of the latter, and others preferentially using crizotinib unless the patient has brain metastases

Dr Sholl:
The vast majority of available blood-based assays . . . are DNA only. So, there is that risk of missing those fusions that are difficult to pick up by DNA-based testing.

SCLC/Other Targets in Lung Cancer

EPICS

The experts think the negative results from SKYSCRAPER-02 are a result of insufficient (pre)clinical rationale for simply adding an anti-TIGIT agent to standard immunotherapy-chemotherapy

Expert opinion is that there were some encouraging, although early, data with new agents and combinations in second-line SCLC (eg, sintilimab plus anlotinib, talazoparib plus temozolomide, bispecific agents)

> The large proportion of never-smoking patients in the East Asian trial of sintilimab plus anlotinib raised the possibility of *EGFR* mutation-positive disease that was histologically transformed into SCLC, which may have conferred a better prognosis than the typical patient with SCLC seen in the US
> In a related note, the experts think molecular testing should be carried out in patients with SCLC who are never-smokers; this will require paying closer attention to the demographics of the patients

Second-line approaches used by the experts vary and include lurbinectedin, clinical trials, chemotherapy (CAV), and taxanes

Antibody-drug conjugates (ADCs) are viewed by the experts as establishing a new therapeutic approach in lung cancer, with some caveats

> ADCs have unique toxicities associated with the payload that need to be considered for combination approaches
> The correlation between cell-surface expression of the target and activity of the agent is still unclear, given the positive results with trastuzumab deruxtecan in patients with HER2-low disease in the phase III DESTINY-Breast04 study

“***Dr Socinski:***
This year’s ASCO brought us another wave of a whole bunch of new therapies. It underscores the complexity and heterogeneity of the disease. We’re going to put a lot of pressure on our pathologists to help us . . .”