Optimizing frontline immunotherapy for advanced NSCLC

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Overview

Optimizing frontline immunotherapy for advanced NSCLC
ASCO Annual Meeting 2021 + ESMO Congress 2021

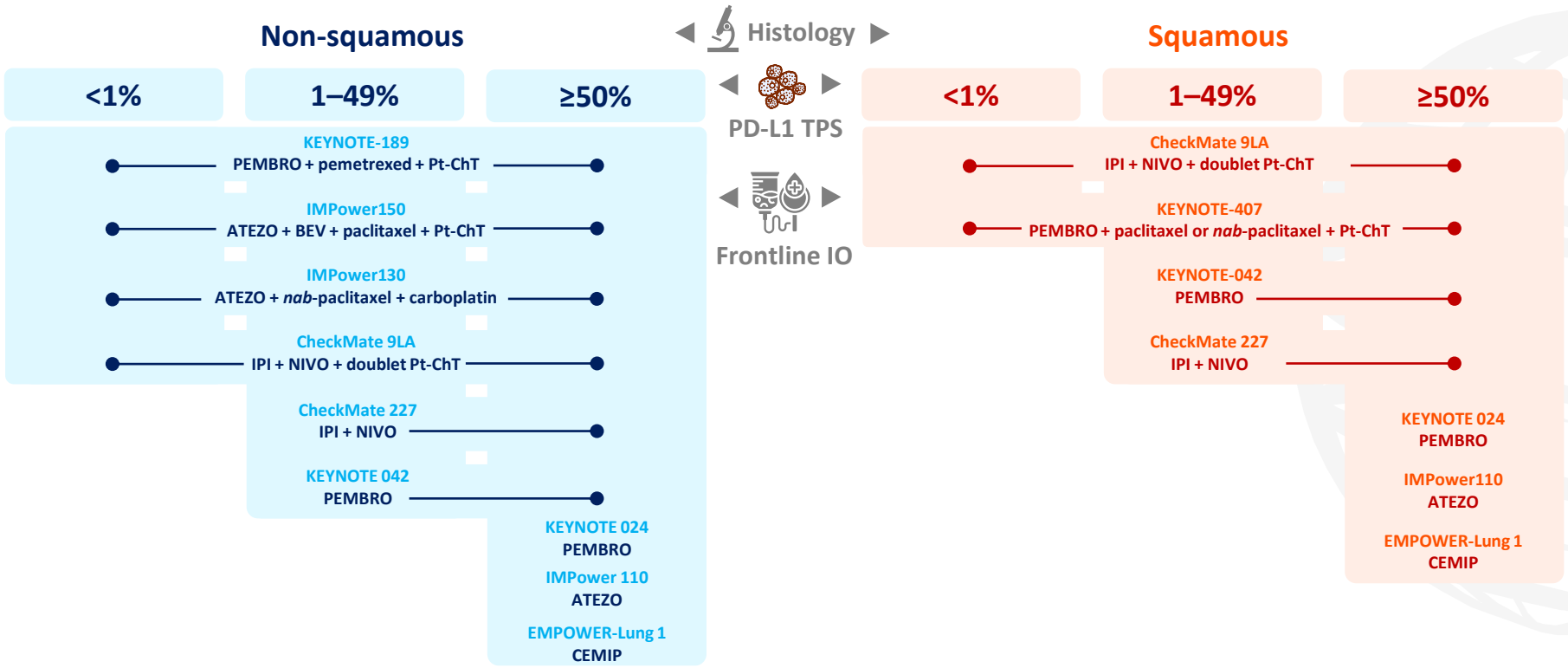
- **Part 1:** Update on immunotherapy in the frontline setting in advanced NSCLC
- **Part 2:** Emerging biomarkers guiding immunotherapy treatment decisions in advanced NSCLC
- **Part 3:** Optimizing frontline immunotherapy in the management of advanced NSCLC

ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; NSCLC, non-small cell lung cancer.

ASCO Annual Meeting 2021 + ESMO Congress 2021

Update on immunotherapy in the frontline setting in advanced NSCLC

Frontline IO in advanced NSCLC: Where are we now?



IO agents FDA-approved for frontline treatment of advanced NSCLC and landmark trials leading to regulatory approval.
ATEZO, atezolizumab; BEV, bevacizumab; CEMIP, cemiplimab; ChT, chemotherapy; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; PEMBRO, pembrolizumab; Pt-, platinum-based; TPS, tumour proportion score.
Shields MD, et al. *Am Soc Clin Oncol Educ Book.* 2021;41:e105–27.

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CheckMate 227 (Part 1) 4-year update: Frontline NIVO plus IPI vs ChT in advanced NSCLC (1/2)

Paz-Ares LG, et al.

Updated 4-year efficacy results of NIVO + IPI dual IO support use as a frontline treatment in advanced NSCLC†

- Treatment-naive stage IV or recurrent NSCLC **without** oncogene driver mutations (*ALK* or *EGFR*)

N=1,739

PD-L1 ≥1%
n=1,189
- **NIVO + IPI** (n=396)
- **ChT** (n=397)
- **NIVO** (n=396)

PD-L1 <1%
n=550
- **NIVO + IPI** (n=187)
- **ChT** (n=186)
- **NIVO + ChT** (n=177)

PD-L1	NIVO + IPI		ChT	NIVO†	NIVO + IPI vs ChT
4-year OS (months)					
<1%	17.2	vs	12.2	15.2†	HR 0.64 (95% CI 0.51–0.81)
≥1%	17.1	vs	14.9	15.7	HR 0.76 (95% CI 0.65–0.90)
≥50%	21.2	vs	14.0	18.1	HR 0.66 (95% CI 0.52–0.84)
4-year DOR (months)					
<1%	18.0	vs	4.8	8.3†	
≥1%	23.2	vs	6.7	15.5	
≥50%	31.8	vs	5.8	16.8	

HR (95% CI) by histology and PD-L1 expression
(NIVO + IPI vs ChT)

PD-L1	SQ	NSQ
<1%	0.53 (0.34–0.84)	0.69 (0.53–0.89)
≥1%	0.68 (0.51–0.89)	0.81 (0.67–0.99)

NIVO+IPI demonstrated durable long-term benefit regardless of histology or PD-L1 expression, compared with ChT

Dual IO with NIVO+IPI continued to improve efficacy benefit at 4 years compared with single-agent NIVO (PD-L1 ≥1%) and NIVO + ChT (PD-L1 <1%)

PFS and DOR benefits maintained at 4 years

†Based on Kaplan-Meier estimates. *NIVO + ChT regimen for PD-L1 <1% cohort only. *ALK,* anaplastic lymphoma kinase; ChT, chemotherapy; DOR, duration of response; *EGFR,* epidermal growth factor receptor; HR, hazard ratio; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer; NSQ, non-squamous; OS, overall survival; PD-L1, programmed cell death ligand-1; SQ, squamous; TRAE, treatment-related adverse event.

Paz-Ares LG, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9016. Presented at: ASCO21 Virtual, 4–8 June 2021.

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CheckMate 227 (Part 1) 4-year update: Frontline NIVO plus IPI vs ChT in advanced NSCLC (2/2)

Paz-Ares LG, et al.

Post-hoc efficacy analysis of patients discontinuing IO due to TRAEs demonstrates sustained clinical response for ≥3 years†

- Participants in CheckMate 227 experiencing TRAEs leading to treatment discontinuation of full NIVO + IPI regimen

N=163

Experienced TRAE

- **PD-L1 ≥1%** n=66
- **All PD-L1 <1% and ≥1%** n=97

NIVO + IPI regimen

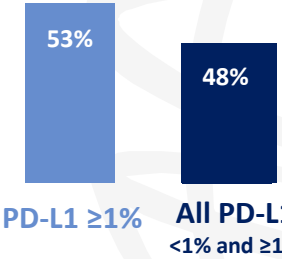
Clinical outcomes in patients discontinuing NIVO + IPI due to TRAEs

	Median OS	4-year OS rate
PD-L1 ≥1%	30.6 months	44%
All PD-L1 <1% and ≥1%	41.5 months	44%

Median DOR after discontinuation

PD-L1 ≥1%	52.6 months
All PD-L1 <1% and ≥1%	34.2 months

Ongoing response ≥3 years after discontinuation



Discontinuation of NIVO + IPI due to TRAEs did not negatively impact long-term benefits seen in all randomized patients

Almost half of responders experiencing a TRAE leading to discontinuation maintained their response for ≥3 years post-discontinuation†

†Based on Kaplan-Meier estimates.

ChT, chemotherapy; DOR, duration of response; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand-1; TRAE, treatment-related adverse events.

Paz-Ares LG, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9016. Presented at: ASCO21 Virtual, 4–8 June 2021.

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CheckMate 9LA 2-year update: Frontline NIVO plus IPI plus ChT (2 cycles) vs ChT (4 cycles) in advanced NSCLC (1/2)

Reck M, et al.

Updated 2-year efficacy results support NIVO plus IPI plus 2 cycles of ChT as a frontline treatment in advanced NSCLC

- Treatment-naive stage IV or recurrent NSCLC **without** oncogene driver mutations (*ALK* or *EGFR*)

N=719

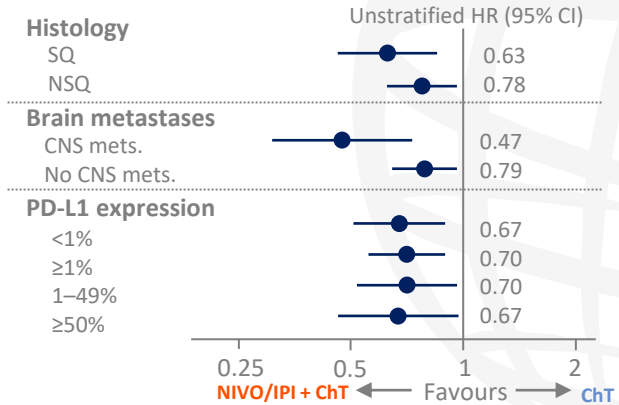
n=361 — **NIVO** 360 mg Q3W + **IPI** 1 mg/kg Q6W + **ChT (2 cycles)*** Q3W

n=358 — **ChT (4 cycles)*** Q3W; NSQ: optional pemetrexed maintenance

Survival outcomes at 2 years
(all randomized patients)

	NIVO/IPI + ChT		ChT	
Median OS	15.8 months	vs	11.0 months	HR 0.72 (95% CI 0.61–0.86)
Median PFS	6.7 months	vs	5.3 months	HR 0.67 (95% CI 0.56–0.79)
Median DOR	13.0 months	vs	5.6 months	
ORR	38.0%	vs	25.4%	

Median OS by subgroup



NIVO/IPI + ChT maintained clinical benefit at 2 years, including across key subgroups (e.g. PD-L1 expression, histology, presence of CNS metastases)

*ChT regimen by histological subtype: NSQ—pemetrexed plus cisplatin or carboplatin; SQ—paclitaxel plus carboplatin. adv., advanced; *ALK,* anaplastic lymphoma kinase; ChT, chemotherapy; CI, confidence interval; CNS, central nervous system; DOR, duration of response; *EGFR,* epidermal growth factor receptor; HR, hazard ratio; IO, immunotherapy; IPI, ipilimumab; mets., metastases; NIVO, nivolumab; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; SQ, squamous; TRAE, treatment-related adverse events.

Reck M, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9000. Presented at: ASCO21 Virtual, 4–8 June 2021.

CheckMate 9LA 2-year update: Frontline NIVO plus IPI plus ChT (2 cycles) vs ChT (4 cycles) in advanced NSCLC (2/2)

Reck M, et al.

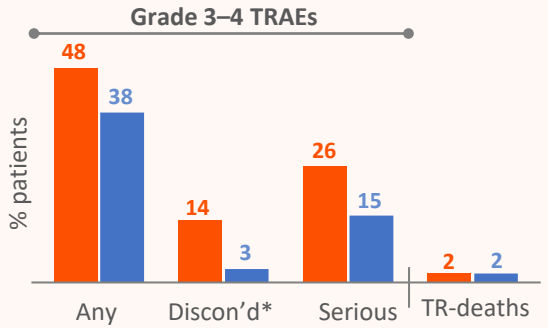
Discontinuation of NIVO/IPI + ChT due to TRAEs did not negatively impact long-term benefits of treatment

- Treatment-naive stage IV or recurrent NSCLC **without** oncogene driver mutations (*ALK* or *EGFR*)

n=707

- NIVO/IPI + ChT n=358
- ChT n=349

No new safety signals observed during long-term follow-up



Onset of grade ≥3 symptoms with NIVO/IPI + ChT regimen occurred during ChT cycles

Efficacy following NIVO/IPI + ChT discontinuation due to TRAEs

n=61

Median OS after discontinuation†: **27.5 months**

Median DOR after discontinuation†: **14.5 months**

2-year OS rate 54%

ORR 51%

Ongoing response for ≥1 year after discontinuation 56%

Over half of responders experiencing a TRAE leading to discontinuation maintained their response for >1 year following discontinuation

2-year update analyses support NIVO/IPI + ChT as an effective treatment option in the frontline setting for patients with advanced NSCLC

*TRAEs leading to discontinuation of all components of treatment regimen. †Based on Kaplan-Meier estimates. *ALK,* anaplastic lymphoma kinase; ChT, chemotherapy; CI, confidence interval; CNS, central nervous system; DOR, duration of response; *EGFR,* epidermal growth factor receptor; HR, hazard ratio; IO, immunotherapy; IPI, ipilimumab; mets., metastases; NIVO, nivolumab; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand-1; SQ, squamous; TR, treatment-related; TRAE, treatment-related adverse event.

Reck M, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9000. Presented at: ASCO21 Virtual, 4–8 June 2021.

New horizons for frontline IO in advanced NSCLC

Agents targeting immune checkpoints beyond CTLA-4 and the PD-1/PD-L1 axis are undergoing evaluation[1–3]

TIGIT

CITYSCAPE[1] (NCT03563716)
phase II study (N=135)

- Frontline TIRA + ATEZO vs **PBO + ATEZO**
- Locally advanced or metastatic NSCLC PD-L1 TPS ≥1%

	TIRA + ATEZO	PBO + ATEZO
ORR	31.3%	16.2%
mPFS	5.4 months	3.6 months

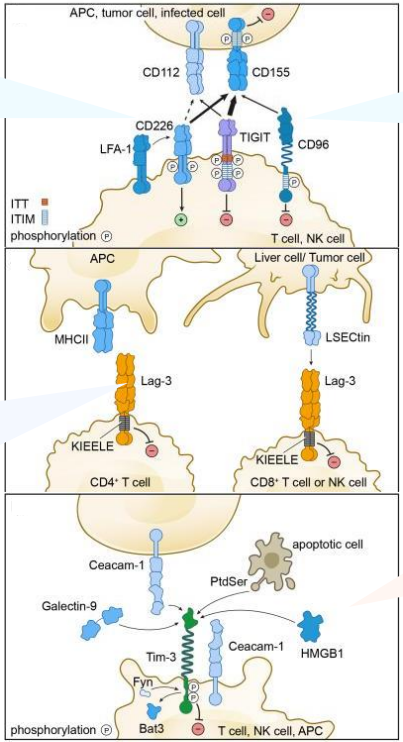
LAG-3

TACTI-002 (NCT03625323)
Ongoing phase II study

- Includes frontline **EFTI + PEMBRO**
- Locally advanced or metastatic NSCLC

RELATIVITY-047 (NCT03470922)
Frontline **RELA + NIVO + ChT** vs **NIVO + ChT**

- Metastatic NSCLC with measurable disease



TIGIT *Ongoing phase III studies*

SKYSCRAPER-01 (NCT04294810)

- Frontline TIRA + ATEZO vs **PBO + ATEZO**
- Locally advanced unresectable or metastatic NSCLC with high TPS PD-L1

SKYSCRAPER-06 (NCT04619797)

- TIRA + ATEZO + ChT vs **PBO + PEMBRO + ChT**
- Treatment-naive locally advanced or metastatic NSQ NSCLC (inoperable/ChT ineligible)

TIM-3

NCT03744468
Ongoing phase I/II study

- **Anti-TIM3 + TISL**
- Includes PD-L1-positive NSCLC

NCT02608268
Ongoing phase I/II study

- **Anti-TIM3 + Anti-PD-L1 ± ChT**
- Includes PD-L1-naive advanced or metastatic NSCLC

Figure reproduced with permission from:
Anderson AC, et al. *Immunity.* 2016;44:989.

APC, antigen presenting cell; ATEZO, atezolizumab; CD, cluster of differentiation; ChT, chemotherapy; EFTI, eftilagimod alpha; Ig, immunoglobulin, IO, immunotherapy; ITIM, immunoreceptor tyrosine-based inhibitory motif; LAG-3, lymphocyte-activation gene-3; LFA-1, leucocyte function antigen-1; MHC, major histocompatibility complex; mPFS, median progression-free survival; NIVO, nivolumab; NSQ; non-squamous; NSCLC, non-small cell lung cancer; ORR, objective response rate; PBO, placebo; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; RELA, relatlimab; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TIM-3, T cell Ig mucin-3; TIRA, tiragolumab; TISL, tislelizumab; TPS, tumour proportion score.

1. Rodriguez-Arbeau D, et al. *J Clin Oncol.* 2020;38(Suppl. 15)9503; 2. Anderson AC, et al. *Immunity.* 2016;44:989; 3. Horvath L, et al. *Mol Cancer.* 2020;19:141.

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EMPOWER-Lung 1 subgroup analysis: Frontline CEMIP monotherapy in patients with brain mets from advanced NSCLC with PD-L1 ≥50%

Ozguroglu M, et al.

1L CEMIP monotherapy improved OS, PFS and ORR in patients with advanced NSCLC expressing PD-L1 ≥50% and clinically stable brain mets at baseline, compared with ChT

- Treatment-naive advanced NSCLC with PD-L1 ≥50% **without** oncogene driver mutations (*ALK, EGFR, ROS1* negative)
- Patients with brain metastases included if adequately treated/neurologically returned to baseline ≥2 weeks prior to randomization

N=68*

n=34 → CEMIP IV 350 mg Q3W → PD → Optional: continue CEMIP + 4 cycles ChT

n=34 → ChT (investigator choice) 4–6 cycles → PD → crossover to CEMIP

Clinical activity at ~9 months follow-up†

	CEMIP n=34	ChT n=34	
Median DoT	24.0 months (IQR 11.9–45.0)	13.4 months (IQR 9.3–21.1)	
Median OS	18.7 months	11.7 months	HR 0.17 (95% CI 0.04–0.76)
Median PFS	10.4 months	5.3 months	HR 0.45 (95% CI 0.22–0.92)
ORR	41.2%	8.8%	OR 6.9 (95% CI 1.7–27.8)

Rates of intracranial disease progression

CEMIP		ChT
5.9%	vs	11.8%
2 patients		4 patients

CEMIP monotherapy represents a suitable option for a subgroup of patients with clinically stable brain mets from advanced NSCLC with PD-L1 ≥50%

*12.1% (n=68/563) of the PD-L1 ≥50% population meeting brain mets criteria at time of randomization. Data cut-off for analysis: 01 March 2020.
†Median duration of follow-up: CEMIP, 9.2 months; ChT, 9.3 months.
1L, frontline; *ALK,* anaplastic lymphoma kinase; CEMIP, cemiplimab; ChT, chemotherapy; CI, confidence interval; DoT, duration of treatment exposure; HR, hazard ratio; *EGFR*, epidermal growth factor receptor; IV, intravenous; mets, metastases; NSCLC, non-small cell lung cancer; OR, odds ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; Q3W, every 3 weeks; *ROS1*, ROS Proto-Oncogene 1.
Ozguroglu M, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9085. Presented at: ASCO21 Virtual, 4–8 June 2021.

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EMPOWER-Lung 3 interim analysis: CEMIP in combination with Pt/Pt-ChT for frontline treatment of advanced NSCLC

Gogishvili M, et al.

Second interim analysis of a randomized phase III clinical trial (EMPOWER-Lung 3) assessing the efficacy and safety of CEMIP in combination with Pt/Pt-ChT in patients with advanced NSCLC

- Treatment-naive advanced NSCLC (SQ or NSQ) with any PD-L1 expression and **without** oncogene driver mutations (*ALK, EGFR, ROS1*)
- Treated and stable CNS metastases

N=466

- CEMIP 350 mg Q3W + ChT Q3W for 4 cycles (n=312)
- R 2:1
- PBO Q3W + ChT Q3W for 4 cycles (n=154)

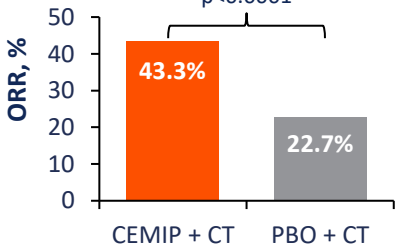
Clinical activity at ~16 months follow-up*

OS and PFS

	CEMIP + ChT	PBO + ChT
mOS, mo	21.9	13.0
HR (95% CI)	**0.71** (0.53–0.93) p=0.014	
mPFS, mo	8.2	5.0
HR (95% CI)	**0.56** (0.44–0.70) p<0.0001	

Tumour response

OR (95% CI): 2.68 (1.72–4.19)
p<0.0001



⚠ Safety

- Low rates of AEs leading to discontinuation
- Safety profile consistent with previously reported AEs for CEMIP + Pt/Pt-ChT

CEMIP in combination with Pt/Pt-ChT showed significant improvements in survival and tumour response vs PBO in 1L treatment of patients with advanced NSCLC, with an acceptable safety profile

*Median duration of follow-up (range): 16.4 (8.5–24.0) months.
AE, adverse event; CEMIP, cemiplimab; ChT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, Hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; NSQ, non-squamous; OR, odds ratio; ORR, objective response rate; PBO, placebo; PD-L1, programmed death ligand 1; PT/Pt-ChT, platinum doublet-based ChT; Q3W, every 3 weeks; SQ, squamous.

Gogishvili M, et al. Abstract/presentation number: LBA51. Presented at: ESMO Virtual Congress 2021, 16–21 September 2021.

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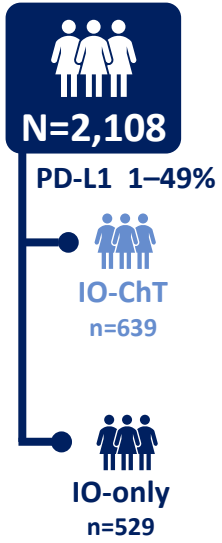
FDA pooled analysis: Clinical outcomes with frontline IO-ChT vs IO-only in advanced NSCLC expressing PD-L1 1–49%

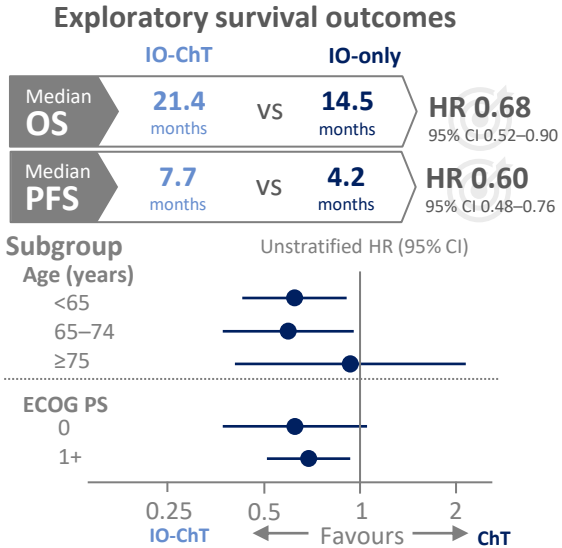
Akinboro O, et al.

Pooled analysis from 8 RCTs supporting FDA-approvals to determine efficacy of frontline IO-based regimens in PD-L1 1–49% cohorts

- Treatment-naive advanced or metastatic NSCLC expressing PD-L1 1–49% and **without** oncogene driver mutations (*ALK or EGFR*)

Trial*	Active treatment
IO-ChT	
KEYNOTE-189	PEMBRO + Pt/Pt-ChT
KEYNOTE-407	PEMBRO + Pt/Pt-ChT
KEYNOTE-021‡	PEMBRO + Pt/Pt-ChT
IMpower150†	ATEZO + BEV + Pt/Pt-ChT
IMpower130	ATEZO + Pt/Pt-ChT
CA2099LA	NIVO + IPI + Pt/Pt-ChT
IO-only	
KEYNOTE-042	PEMBRO
CheckMate 227	NIVO + IPI





FDA-approved IO-ChT regimens may improve OS and PFS compared with IO-only in advanced NSCLC PD-L1 1–49%, including in certain patient groups (e.g. aged 65–75 years, ECOG PS 1)

No evidence older adults (aged ≥75 years) have worse outcomes with IO-ChT compared with IO-only

Results raise questions regarding utility of IO-only as controls in RCTs evaluating 1L treatment of advanced NSCLC PD-L1 1–49%

*Control arms comprise Pt/Pt-ChT except †IMpower150 control arm comprised BEV plus Pt/Pt-ChT. ‡KEYNOTE-021 Cohort G data.
ALK, anaplastic lymphoma kinase; ATEZO, atezolizumab; BEV, bevacizumab; ChT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR,* epidermal growth factor receptor; HR, hazard ratio; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand-1; PEMBRO, pembrolizumab; PFS, progression-free survival; Pt/Pt, platinum-doublet ChT; RCT, randomized controlled trial.

Akinboro O, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9001. Presented at: ASCO21 Virtual, 4–8 June 2021.

Summary: Update on frontline IO in NSCLC

- Updates from CheckMate 227[1] and CheckMate 9LA[2] demonstrate long-term clinical benefit with combination IO (NIVO/IPI) ± ChT:
  - Durable PFS and DOR regardless of tumour PD-L1 status, and across key patient subgroups (e.g. histological subtypes, presence of CNS metastases)
  - Treatment response endures even after treatment discontinuation following TRAEs[1,2]
- FDA pooled analyses suggest IO-ChT combination regimens improve survival outcomes compared with IO-monotherapy in PD-L1 1–49% cohorts[3]
  - No evidence that older age (65–75 years) or ECOG PS (1+) associated with worse outcomes[3]
- Second interim data analysis from EMPOWER-Lung 3 demonstrates IO (CEMIP) in combination with Pt-based doublet ChT improves survival and tumour response[4]
- Subgroup analysis of EMPOWER-Lung 1 demonstrates upfront IO monotherapy (CEMIP) is a feasible treatment option in patients with brain metastases arising from NSCLC PD-L1 ≥50%[5]

1L, frontline; ASCO, American Society of Clinical Oncology; CEMIP, cemiplimab; ChT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESMO, European Society of Medical Oncology; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; Pt, platinum; QoL, quality of life; TRAE, treatment-related adverse event.

1. Paz-Ares LG, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9016; 2. Reck M, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9000; 3. Akinboro O, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9001; 4. Gogishvili M, et al. LBA51. ESMO21; 5. Ozguroglu M, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9085.

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Emerging biomarkers guiding immunotherapy treatment decisions in advanced NSCLC

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Role of PD-L1 guiding 1L IO treatment decisions in advanced NSCLC

Consider within clinical context of oncogene mutation status (e.g. *ALK/BRAF/EGFR/ROS1*)[1–3]

TPS ≥50%

- ATEZO
- CEMIP
- PEMBRO

Target for inhibitor
CTLA-4,
PD-1
PD-L1
VEGF

TPS 1–49%
PEMBRO?

*'The **NCCN NSCLC Panel** also **recommends single-agent PEMBRO** as a **frontline therapy option** in eligible patients with metastatic NSCLC regardless of histology, **PD-L1 levels 1–49%,** and **negative** test results for **specific molecular variants**'.*[3]

PD-L1 TPS ≥1%

- NIVO/IPI
- PEMBRO

No indicated PD-L1 threshold

- NSQ histology: ATEZO/BEV + Carbo/[*nab*-]P
- NIVO/IPI + Pt/Pt ChT
- NSQ histology: PEMBRO + Pt/Pem ChT
- SQ histology: PEMBRO + Carbo/[*nab*-]P

Approval of PD-1 inhibitors as SoC frontline treatment in selected patients renders PD-L1 testing mandatory in advanced NSCLC[1,2]

1L, frontline; *ALK*, anaplastic lymphoma kinase; ATEZO, atezolizumab; BEV, bevacizumab; BRAF, v-Raf murine sarcoma viral oncogene homologue B; Carbo, carboplatin; CEMIP, cemiplimab; ChT, chemotherapy; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; *EGFR*, epidermal growth factor receptor; IO, immunotherapy; IPI, ipilimumab; *nab*-P, *nab*-paclitaxel; NIVO, nivolumab; NSCLC, non-small cell lung cancer; NSQ, non-squamous; P, paclitaxel; Pem, pemetrexed; PEMBRO, pembrolizumab; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; Pt, platinum; *ROS1*, ROS Proto-Oncogene 1; SoC, standard of care; SQ, squamous; TPS, tumour proportion score; VEGF, vascular epidermal growth factor.

1. Planchard D, et al. *Ann Oncol.* ESMO Guidelines 2020 update; 2. Mathew M, et al. *Ann Transl Med.* 2017;5:375; 3. NCCN Clinical Practice Guidelines in Oncology: Non-small cell lung cancer. Version 5.2021. FDA Prescribing information for agents available/searchable online at: www.fda.gov/; EMA Summary of product characteristics available/searchable at: www.ema.europa.eu/en

Role of PD-L1 guiding 1L IO treatment decisions in advanced NSCLC

Challenges remain with PD-L1 testing to guide IO treatment in NSCLC[1,2]

Assay-specific

- Accessibility, costs, inter-assay variability

Biopsy-specific

- Histology vs cytology, biopsy site, inter-/intra-tumoural heterogeneity

Patient-specific

- Impact of concurrent oncogene driver mutations

IO, immunotherapy; NSCLC, non-small cell lung cancer;PD-L1, programmed cell death ligand-1.

1. Planchard D, et al. *Ann Oncol.* ESMO Guidelines 2020 update; 2. Mathew M, et al. *Ann Transl Med.* 2017;5:375.

Beyond PD-L1: Emerging IO biomarkers in NSCLC[1–3]

Tissue markers

Tumour mutational burden

- Higher TMB associated with IO clinical benefit
- Prior ChT may compromise predictive value

Tumour-infiltrating lymphocytes

- Higher TIL density associated with improved survival
- Extent of TIL PD-L1 associated with IO response

Gene expression profiles

- High expression of T-effector and IFN-γ related gene signature associated with improved survival

Tumour-specific genotypes

- *ALK* and *EGFR* mutations associated with poorer IO outcomes
- *STK11/LKB1* co-mutation associated with IO resistance

Serum markers

Full blood count markers

- Higher NLR associated with poorer prognosis
- NLR correlated to treatment response

Blood tumour mutational burden

- Higher bTMB associated with clinical benefit

Circulating tumour DNA

- Changes in ctDNA associated with TMB and cancer progression

Ongoing need for improved biomarkers predictive of treatment response and toxicities[1,2]

ALK, anaplastic lymphoma kinase; bTMB, blood TMB; ChT, chemotherapy; ctDNA, circulating tumour DNA; *EGFR*, epidermal growth factor receptor; IFN-γ, interferon-gamma; IO, immunotherapy; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; *STK11/LKB1*, liver kinase B1; TIL, tumour-infiltrating lymphocyte; TMB, tumour mutational burden.

1. Bodor JN, et al. *Cancer.* 2020;126:260–70; 2. Yang J, et al. *Front Oncol.* 2021;11:725938; 3. Lei Y, et al. *Front Oncol.* 2021;11:617335.

Very high TMB associated with increased CD8$^+$ and PD-1$^+$ TILs and improved clinical response to IO in advanced NSCLC across different PD-L1 thresholds

Ricciuti B, et al.

Pooled analysis of DFCI and MSKCC cohorts to determine TMB categories associated with IO efficacy in advanced NSCLC

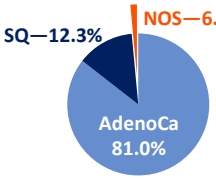
- Patients at the DFCI and MSKCC with advanced NSCLC (regardless of oncogene driver status) consenting to IRB-approved protocols

N=1,386

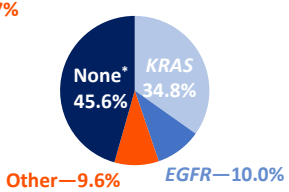
- DFCI n=714
- MSKCC n=672

Cohort characteristics

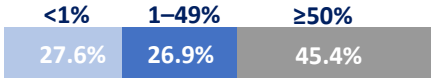
Histology



Oncogene



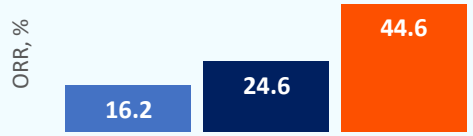
Known PD-L1 expression*



(n/N=925/1386)

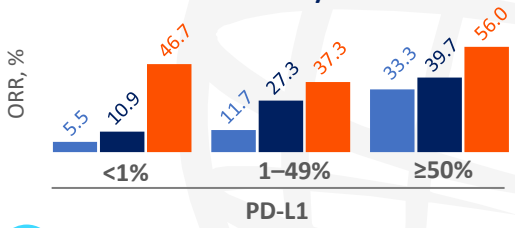
Line of therapy

Three optimal TMB groupings identified† with respect to ORR that correlate with OS and PFS



TMB:	Low n=797	Intermediate n=430	High n=159
Median OS	10.9 months	12.1 months	35.4 months
Median PFS	2.5 months	3.2 months	9.8 months

Increasing TMB associated with improved IO efficacy



RNAseq data showed association between increasing TMB and TILs, and total CD8$^+$, PD1$^+$, Foxp3$^+$ and PD-L1$^+$ cells

Increasing TMB may promote TILs, increasing IO sensitivity in NSCLC, notably in tumours with high PD-L1

*PD-L1 expression not assessed in n=461. †TMB groupings identified by unbiased recursive partitioning for ORR to IO identified in three TMB groupings: Low (≤56th percentile), intermediate (56–88th percentile), high (>88th percentile).1L, frontline; 2L, second-line; AdenoCa, adenocarcinoma; CD, cluster of differentiation; DFCI, Dana-Farber Cancer Institute; *EGFR*, epidermal growth factor receptor; IRB, Institutional Review Board; *KRAS*, Kirsten Rat Sarcoma Viral Oncogene Homolog; MSKCC, Memorial Sloan Kettering Cancer Center; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death-1; PD-L1, PD-ligand-1; PFS, progression-free survival; RNAseq, RNA sequencing; SQ, squamous cell carcinoma; TIL, tumour infiltrating lymphocyte; TMB, tumour mutational burden.

Ricciuti B, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9018. Presented at: ASCO21 Virtual, 4–8 June 2021.

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BFAST phase III trial (cohort C): Frontline ATEZO vs Pt-ChT in bTMB^{+} patients with advanced/metastatic NSCLC

Dziadziuszko R, et al.

Evaluation of TMB as a predictive biomarker for 1L ATEZO vs Pt-ChT in patients with bTMB^{+} NSCLC identified by FM-bTMB-CTA

- Treatment-naive unresectable, stage IIIB or IV NSCLC **without** oncogene driver mutation (*EGFR/ALK*) and bTMB^{+} (≥10 mut/Mb)*

N=471

ATEZO n=234
- ATEZO 1,200 mg Q3W until PD or loss of clinical benefit

Pt-ChT n=237
- Pt-ChT Q3W 4 or 6 cycles
  - NSQ: maintenance pemetrexed permitted

bTMB ≥10

bTMB ≥16

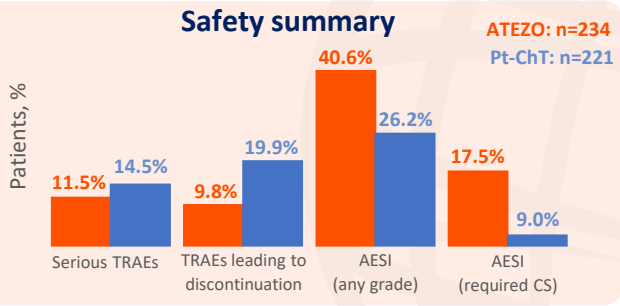
Clinical outcomes in bTMB ≥16 cohort

	ATEZO n=145		Pt-ChT n=146	
Median OS	13.3 months	vs	10.3 months	HR 0.87 (95% CI 0.64–1.17)
Median PFS	4.5 months	vs	4.3 months	HR 0.77 (95% CI 0.59–1.00)

Confirmed ORR

ATEZO	25.5% (95% CI 18.7–33.4)
Pt-ChT	17.8% (95% CI 12.0–25.0)

Safety summary



Primary PFS endpoint not reached in bTMB ≥16 cohort

ATEZO shows tolerable safety profile consistent with ATEZO monotherapy experience across indications

Further evaluation is needed of TMB clinical utility and thresholds relevant for predicting 1L IO clinical benefit in NSCLC

*bTMB score of 10 ≈9.1 mut/mb. 1L, frontline; AE, adverse event; AESI, AE of special interest; *ALK* , anaplastic lymphoma kinase; ATEZO, atezolizumab; BFAST, Blood First Assay Screening Trial; bTMB, blood-based TMB; ChT, chemotherapy; CI, confidence interval; CS, corticosteroids; FM-bTMB-CTA, Foundation Medicine bTMB clinical trial assay; HR, hazard ratio; IO, immunotherapy; mut/Mb, mutations per megabase; NSCLC, non-small cell lung cancer; NSQ, non-squamous; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Pt, platinum; Pt-ChT, Pt-based ChT; TMB, tumour mutational burden; TRAE, treatment-related AE.

Dziadziuszko R, et al. Abstract/presentation number: 1281O. Presented at: ESMO Virtual Congress 2021, 16–21 September 2021.

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Impact of *STK11* mutation on frontline IO outcomes in a real-world cohort of patients with *KRAS*^{G12C} mutant lung adenocarcinoma

Heist RS, et al.

Real-world analysis of a clinical genomic database to assess impact of concurrent *STK11* + KRAS^{G12C} mutations on 1L IO outcomes

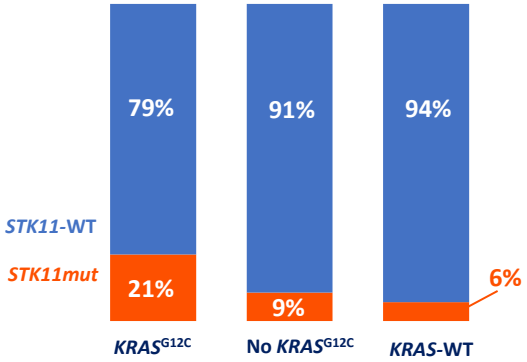
- TKI-naive patients with lung adenocarcinoma harbouring *KRAS*^{G12C} mutation receiving IO ≤90 days of index

N=330

STK11mut n=70

STK11-WT n=260

Prevalence of concurrent *STK11mut* by *KRAS* status



Real-world clinical outcomes by *STK11* and *KRAS* mutation status

	KRAS^{G12C}		*KRAS*-WT	
	STK11mut n=70	*STK11*-WT n=260	*STK11mut* n=49	*STK11*-WT n=705
median RW-OS (days)	411	NR	889	893
	HR 3.2 (95% CI 2.0–5.1)		HR 1.4 (95% CI 0.8–2.4)	
median TNTT (days)	224	975	301	514
	HR 2.7 (95% CI 1.8–4.0)		HR 1.7 (95% CI 1.1–2.6)	

***STK11* mutations concurrent with *KRAS* ^{G12C} are associated with poor clinical outcomes in patients with lung adenocarcinoma treated with 1L IO regimens**

1L, frontline; IO, immunotherapy; HR, hazard ratio; *KRAS,* Kirsten Rat Sarcoma Viral Oncogene Homolog; *mut,* mutant; NR, not reached; RW-OS, real-world overall survival; *STK11,* serine/threonine kinase-11; TKI, tyrosine kinase inhibitor; TNTT, time to next treatment; WT, wild-type.

Heist RS, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9016. Presented at: ASCO21 Virtual, 4–8 June 2021.

MYSTIC trial: Early ctDNA dynamics for predicting and monitoring response to frontline dual-IO vs mono-IO vs ChT in metastatic NSCLC

Peters S, et al.

Analysis of prognostic value of ctDNA in BEP* cohorts in the MYSTIC trial assessing dual-IO vs mono-IO vs SoC ChT in adv. NSCLC

- Treatment-naive metastatic NSCLC **without** oncogene driver mutation (*EGFR/ALK*)

N=1,118

Baseline ctDNA availability-defined

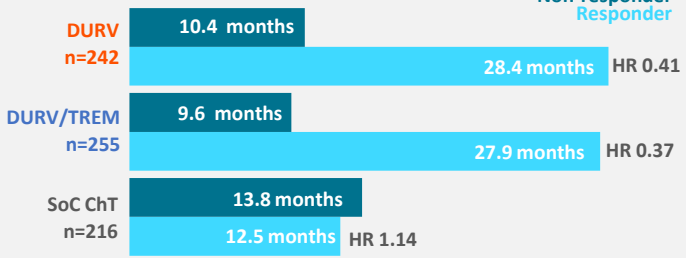
- DURV
- DURV + TREM
- SoC ChT

BEP 1 n=932

BEP 2 n=732

BEP 1: mOS by median baseline mean VAF status

BEP 2: mOS by molecular response status



Baseline ctDNA prognostically associated with survival outcomes regardless of treatment

MR may be an early predictor and a complementary metric to radiologic disease assessment to determine patients likely to derive long-term IO benefit, and facilitate early clinical decision-making

BEPs definition based on availability of ctDNA data at baseline (BEP 1) or both baseline and pre-dose cycle 2 of IO/cycle 3 of ChT (BEP 2).
1L, frontline; adv., advanced; BEP, biomarker evaluable population; ChT, chemotherapy; ctDNA, circulating tumour DNA; DURV, durvalumab; mOS, median overall survival; MR, molecular responder; NSCLC, non-small cell lung cancer; SoC, standard of care; TREM, tremelimumab; VAF, variant allele frequency.

Peters S, et al. Abstract/presentation number: 1264P. Presented at: ESMO Virtual Congress 2021, 16–21 September 2021.

Summary: Emerging biomarkers

- Biomarkers beyond PD-L1 are emerging in advanced NSCLC
- Data presented across ASCO and ESMO 2021 have shown:
    i. TMB as a predictor of IO efficacy, immune infiltrates and tumour response to IO-based regimens,[1] but more research is needed to determine utility and establish clinically meaningful TMB thresholds predictive of 1L IO response in advanced NSCLC[2]
    ii. Importance of concurrent tumour mutation status: *STK11* mutations concurrent with *KRAS*^{G12C} are associated with poor clinical outcomes[3]
    iii. Utility of baseline ctDNA as a predictor of survival outcomes[4]
    iv. Emerging role of the immune microenvironment in determining response to IO[1]

1L, frontline; ASCO, American Society of Clinical Oncology; ctDNA, circulating tumour DNA; ESMO, European Society of Medical Oncology; IO, immunotherapy; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; TMB, tumour mutational burden.

1. Ricciuti B, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9018; 2. Dziadziuszko R, et al. Abstract/presentation number: 1281O; Presented at the ESMO Virtual Congress 2021, 16–21 September 2021; 3. Heist RS, et al. *J Clin Oncol.* 2021;39 (Suppl. 15):9016; 4. Peters S, et al. Abstract/presentation number: 1264P. Presented at: ESMO Virtual Congress 2021, 16–21 September 2021.

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Optimizing frontline immunotherapy in the management of advanced NSCLC

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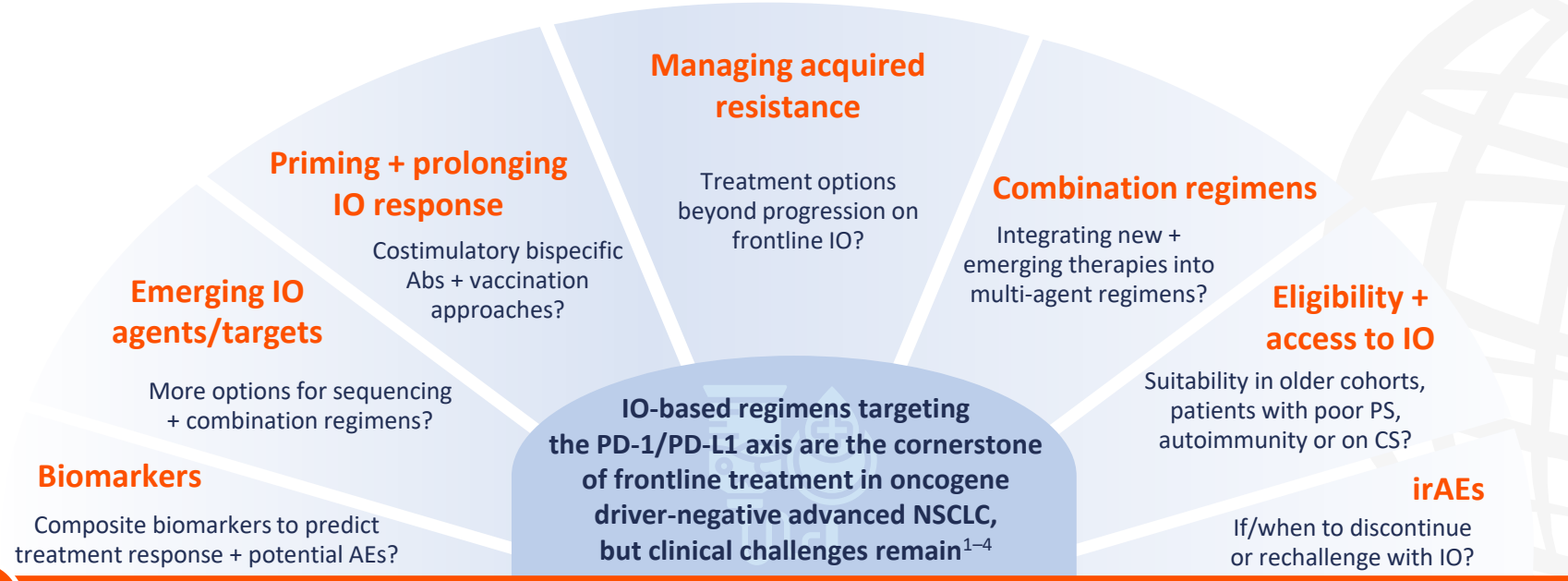
Optimizing frontline IO: Addressing clinical challenges



Many patients with NSCLC progress on IO therapy, therefore new agents and combination regimens are needed[1]

Ab, antibody; AE, adverse event; CS, corticosteroids; IO, immunotherapy; irAEs, immune-related AEs; NSCLC, non-small cell lung cancer; PD-1, programmed death protein-1; PD-L1, programmed cell death ligand-1; PS, performance status.

1. Horvath L, et al. *Mol Cancer.* 2020;19:141; 2. Grant MJ, et al. *Nat Rev Clin Oncol.* 2021; doi: 10.1038/s41571-021-00520-1 [online ahead of print];
3. Stock-Martineau S, et al. *JCO Oncol Prac.* 2021;17:465–71; 4. Hedge PS, Chen DS. *Immunity.* 2020;52:17–35.

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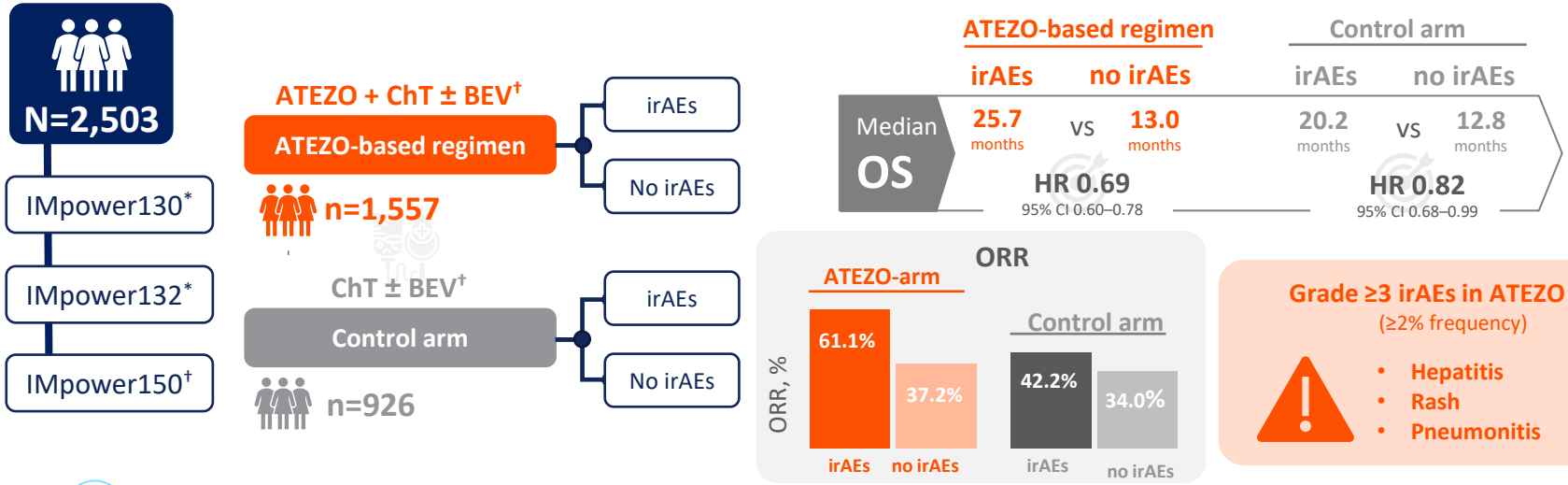
Pooled analyses of irAEs and efficacy from the phase III trials IMpower130, IMpower132 and IMpower150

Socinski MA, et al.

Exploratory analysis of irAEs and efficacy in ATEZO-based 1L regimens in three landmark phase III clinical trials



Grade ≥3 irAEs in ATEZO arm
(≥2% frequency)

- Hepatitis
- Rash
- Pneumonitis

Exploratory pooled analysis demonstrates patients with NSCLC who experienced irAEs had longer OS (at 1, 3, 6 and 12-month landmark analyses) compared with those who did not experience irAEs, for both ATEZO and control arms

*IMpower130 and -132 assessed ATEZO + ChT vs ChT; †IMpower150 assessed ATEZO + BEV + ChT vs ATEZO + ChT vs BEV + ChT. HRs are unstratified. Data cut-offs: 15 March 2018 (IMpower130); 22 May 2018 (IMpower132); 13 September 2019 (IMpower150)

1L, frontline; ATEZO, atezolizumab; HR, hazard ratio; irAE, adverse event; mo, months; NSCLC, non-small-cell lung cancer; OS, overall survival.

Socinski MA, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9002. Presented at: ASCO21 Virtual, 4–8 June 2021.

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EMPOWER-Lung 1: Impact of frontline CEMIP in advanced NSCLC PD-L1 ≥50% on symptom burden, functional status and QoL

Gümüs M, et al.

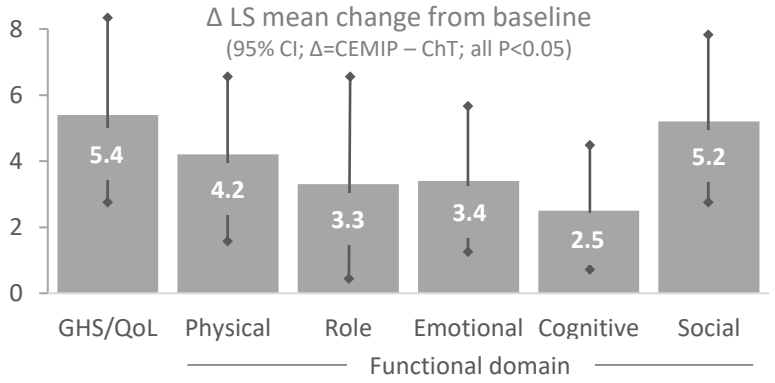
Assessment of GHS/QoL and symptom burden associated with 1L CEMIP compared with ChT in the EMPOWER-Lung 1 trial

- Patients with ECOG PS ≤1, histologically or cytologically confirmed stage IIIB/C or IV NSCLC **with** PD-L1 ≥50%

N=710

- **n=356** — **CEMIP** 350 mg Q3W (≤36 cycles)
- **n=354** — **Pt/Pt-ChT** (4–6 cycles) (investigator's choice)

CEMIP associated with overall improvement in GHS/QoL and functional measures



CEMIP associated with significantly* lower risk of deterioration of key symptoms:

- Dyspnoea
- Cough
- Chest pain
- Body pain
- Fatigue
- Nausea/vomiting
- Appetite loss
- Constipation

*all P<0.05

CEMIP significantly improved GHS/QoL, functioning and most symptoms compared with Pt/Pt-ChT in patients with advanced NSCLC and PD-L1 expression ≥50%

1L, frontline; CEMIP, cemiplimab; ChT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GHS, Global Health Status; LS, least squares; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; Pt/Pt-ChT, platinum doublet ChT; Q3W, every 3 weeks; QoL, quality of life.

Gümüs M, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9078. Presented at: ASCO21 Virtual, 4–8 June 2021.

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KEYNOTE-598: HR-QoL outcomes with frontline dual-IO (PEMBRO + IPI) compared with mono-IO (PEMBRO + PBO) in metastatic NSCLC PD-L1 ≥50%

Sendur MAN, et al.

Assessment of PROs in the phase III KEYNOTE-589 trial to evaluate HR-QoL associated with dual-IO versus mono-IO

- Treatment-naive metastatic NSCLC **with** PD-L1 ≥50% and **without** oncogene driver mutation (*EGFR/ALK*)

N=560*

***PRO analysis cohort**

- **PEMBRO** 200 mg Q3W **+ IPI** 1 mg/kg Q6W — n=280
- **PEMBRO** 200 mg Q3W **+ PBO** Q6W — n=280

Health function domains assessed

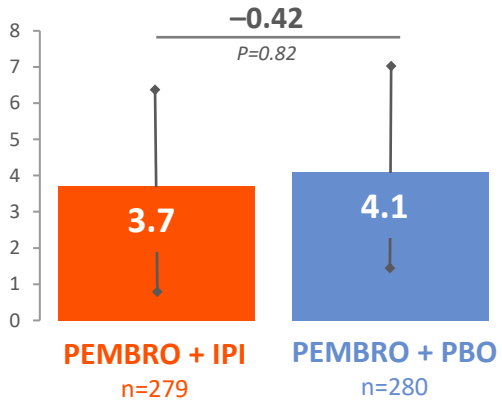
- Physical
- Role
- Emotional
- Cognitive
- Social

Symptom burdens assessed

- Fatigue
- Nausea/vomiting
- Appetite loss
- Constipation
- Diarrhoea
- Pain
- Dyspneoa
- Insomnia
- Financial

GHS/QoL improved, but no significant difference between groups

Δ LS mean change from baseline to week 18



No difference in HR-QoL nor time to deterioration in symptoms between dual-IO (PEMBRO + IPI) compared with mono-IO (PEMBRO)

GHS/QoL improved in both groups, but with no significant difference in improvement between groups

Results are consistent with previous PROs from prior primary efficacy analyses

No evidence of improved outcomes with addition of IPI to treatment in this setting

Data cut-off 01 Sept 2020.

1L, frontline; *ALK,* anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR,* epidermal growth factor receptor; GHS, Global Health Status; HR-QoL, health-related-QoL; LS, least squares; NSCLC, non-small cell lung cancer; PBO, placebo; PD-L1, programmed death ligand 1; PRO, patient reported outcomes; Q3W, every 3 weeks; Q6W, every 6 weeks; QoL, quality of life.

Şendur MAN, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9038. Presented at: ASCO21 Virtual, 4–8 June 2021.

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The time of anti-PD-1 infusion improves survival outcomes by fasting conditions simulation in NSCLC

Vilalta-Lacarra A, et al.

Correlation between fasting conditions and clinical outcomes (OS and PFS) in patients with NSCLC receiving PD-1 inhibitor

- Patients receiving PD-1 inhibitor-based treatment for metastatic NSCLC (infused before vs after 12 pm)

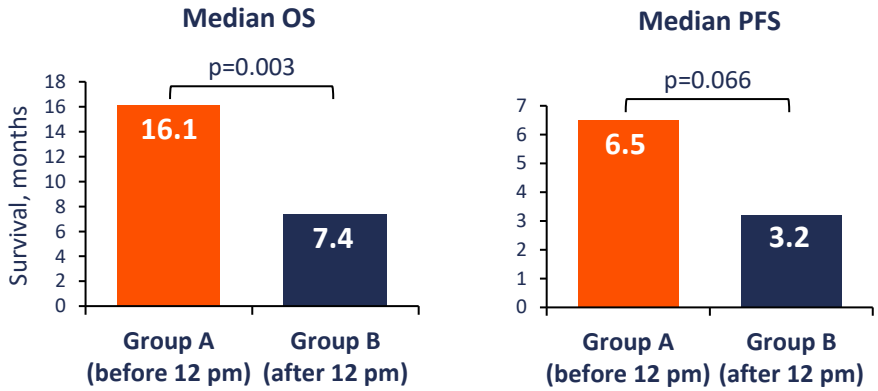
N=197

- 72.1% males
- 84.3% received PD-1-inhibitor monotherapy

Group A (n=104)
received PD-1 inhibitor **before 12 pm***

Group B (n=93)
received PD-1 inhibitor **after 12 pm***

Median follow-up
9.6 months



Administration of PD-1 inhibitor before 12 pm significantly improved OS and PFS in patients with NSCLC, suggesting a potential correlation with fasting

*Group A included patients who received ≥1 of first 4 cycles of PD-1 inhibitor infusion before 12 pm, Group B received all first four cycles after 12 pm.
mo, months; mNSCLC, metastatic non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein-1; PFS, progression-free survival.
Vilalta-Lacarra A, et al. Abstract/presentation number: 967P. Presented at: ESMO Virtual Congress 2021, 16–21 September 2021.

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Summary: Optimizing frontline IO in the management of NSCLC

- irAEs are associated with improved survival and response in advanced NSCLC, both with IO and ChT-based regimens, but improvements are more pronounced with IO-based regimens (e.g. ATEZO)[1]
- 1L IO (CEMIP) has been shown to improve global patient health status and functionality across multiple domains compared with CT[2]
- Addition of second IO agent (IPI) to PD-1-targeting regimens (PEMBRO) may not improve patient-reported outcome measures and functionality[3]
- Timing of IO infusions may impact survival outcomes, but not yet at a stage to influence clinical practice[4]

1L, frontline; ATEZO, atezolizumab; CEMIP, cemiplimab; ChT, chemotherapy; IO, immunotherapy; IPI, ipilimumab; irAE, immune-related adverse event; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein-1; PEMBRO, pembrolizumab.

1. Socinski MA, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9002; 2. Gümüs M, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9078; 3. Şendur MAN, et al. *J Clin Oncol.* 2021;39(Suppl. 15):9038; 4. Vilalta Lacarra A, et al. Abstract/presentation number: 967P. Presented at: ESMO Virtual Congress 2021, 16–21 September 2021.

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Thank you for watching

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