Evolving role of Immunotherapy in ES-SCLC

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ES-SCLC: Extensive Stage Small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related death worldwide, SCLC represents ~15% of all lung cancer cases

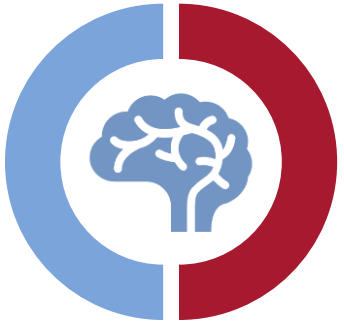
Lung cancer is categorized into two main types[1,4]

~15% Small Cell Lung Cancer (SCLC)

~85% Non-small Cell Lung Cancer (NSCLC)

Incidence: ***India = 16%***

Brain metastases occur in ~50% of patients with SCLC and are associated with poor outcomes[5,34]

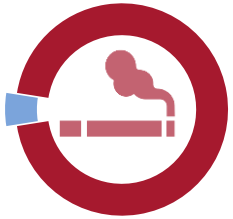


~50% Brain Metastases

Median age of SCLC patients at diagnosis[1,36]

~70 years

SCLC occurs almost exclusively in smokers[2]

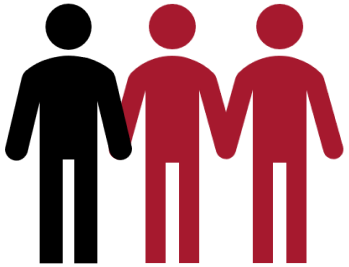


~90-97% Smokers

1. American Cancer Society: Key Statistics for Lung Cancer; 2. Muscat JE, et al. Cancer Letters 1995; 4. Bray F, et al. IARC 2017; 5. National Comprehensive Cancer Network. NCCN Guidelines v3.2020. SCLC; 34. Lukas RV, et al. Oncotarget 2017;8:71223–71233; 36. Khakwani A, et al. PLOS One 2014, Mohan etal Lung India 2021

Approximately two in three patients have ES-SCLC at diagnosis and their life-expectancy is less than a year when treated with EP alone

Two in three patients with SCLC have **ES-SCLC at diagnosis**[3,6]



Patients with ES-SCLC have **poor prognoses when taking EP alone, the current first-line standard of care treatment**[7-9,41]

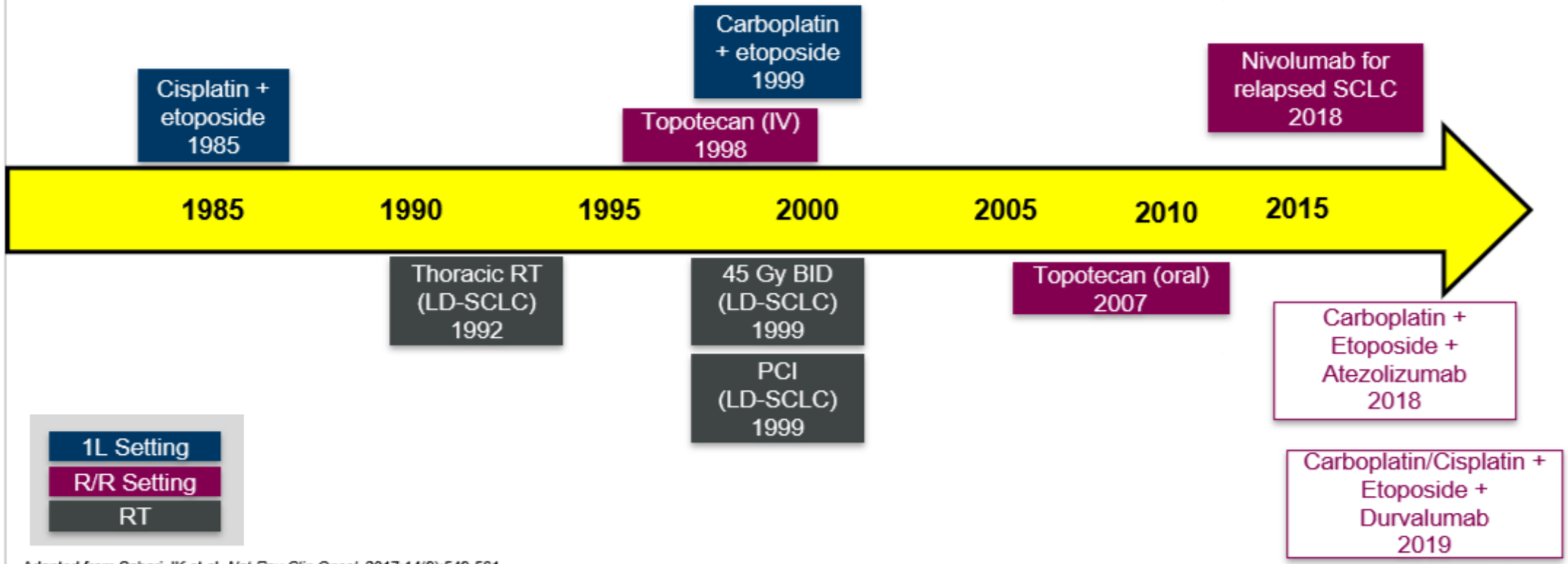
Survival rate
3-year: 5.8%
5-year: 1–3%

EP: platinum-etoposide

3. American Cancer Society. Small Cell Lung Cancer Stages 2020; 6. Oronsky B, et al. Neoplasia 2017; 7. Sundstrøm S, et al. J Clin Oncol 2002; 8. Gaspar LE, et al. Clin Lung Cancer 2012. 9. American Cancer Society. Lung Cancer Survival Rates Accessed July 2020. 41: Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the Phase 3 CASPIAN study. Presented at Virtual ESMO 2021, 16–21 September 2021: Abstract LBA61

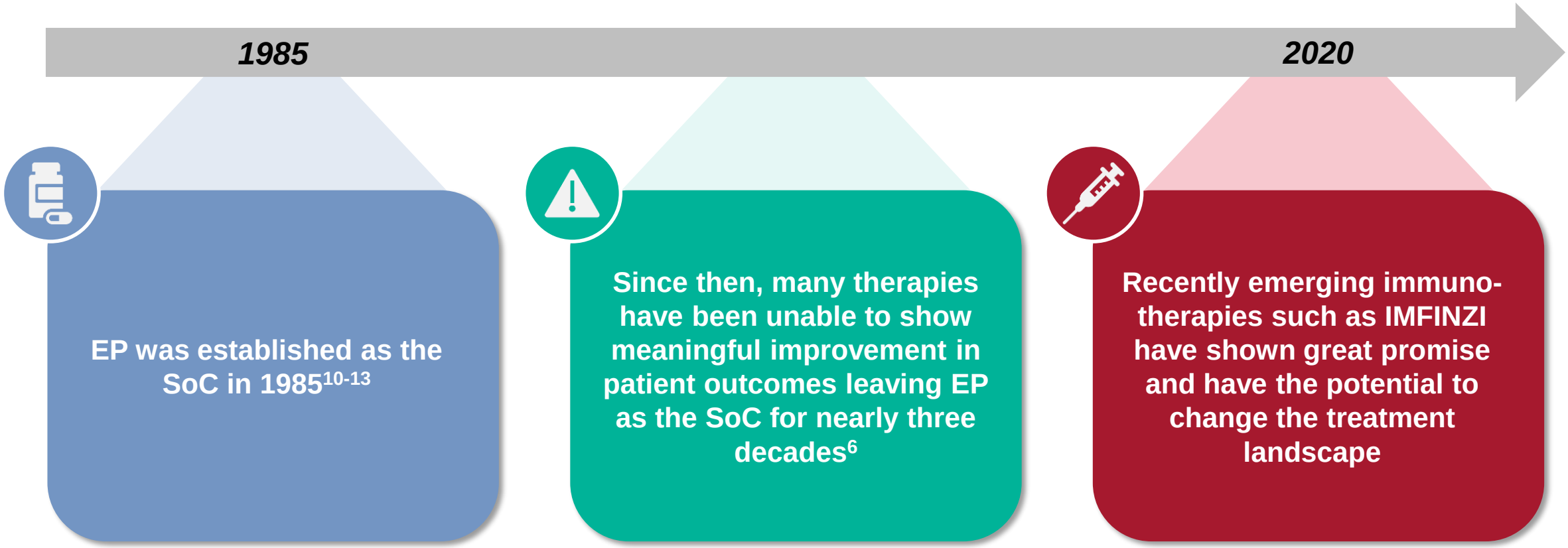
Advances in the Treatment of SCLC

The SoC for treatment of ES-SCLC, often given palliatively, is a standard combination regimen of cisplatin or carboplatin + etoposide or irinotecan and had not changed in more than 30 years.



Adapted from Sabari JK et al. *Nat Rev Clin Oncol.* 2017;14(9):549-561.

Since EP was established as the SoC nearly 30 years ago, there has been limited progress until the addition of immuno-oncology agents



EP: platinum-etoposide; SCLC: small-cell lung cancer;

6. Oronsky B, et al. Neoplasia 2017; 10. Demedts IK, et al. Eur Respir J 2010; 11. Farago AF, et al. Transl Lung Cancer Res 2018; 12. Fukuoka M, et al. J Natl Cacner Inst 1991; 13. Roth BJ, et al. J Clin Oncol 1992

Etoposide + cisplatin/carboplatin is the current standard of care; IOs are emerging 1L options that will change the treatment paradigm

First-line[5,6,14,39,40,42]

Combination platinum-doublet (EP) chemotherapy (4–6 cycles)

PCI and radiotherapy at physician's discretion† to prevent and treat brain metastases, respectively

Second-line and beyond[6,15,16]

Sensitive or resistant response to first-line chemotherapy

>6 months

- Platinum re-challenge
- Non-platinum chemotherapy

Refractory, no response to first-line chemotherapy

≤6 months

Topotecan, lurbinectedin, or clinical trial
If no treatment is available, best supportive care,‡ palliative care, localized radiotherapy or clinical trial is recommended[6,39]

IOs have recently become available, showing improved outcomes vs chemotherapy and changing the treatment paradigm

- IMFINZI+EP
- Atezolizumab+EP

- FDA / EMA / NMPA / PMDA approved

NCCN cat 1

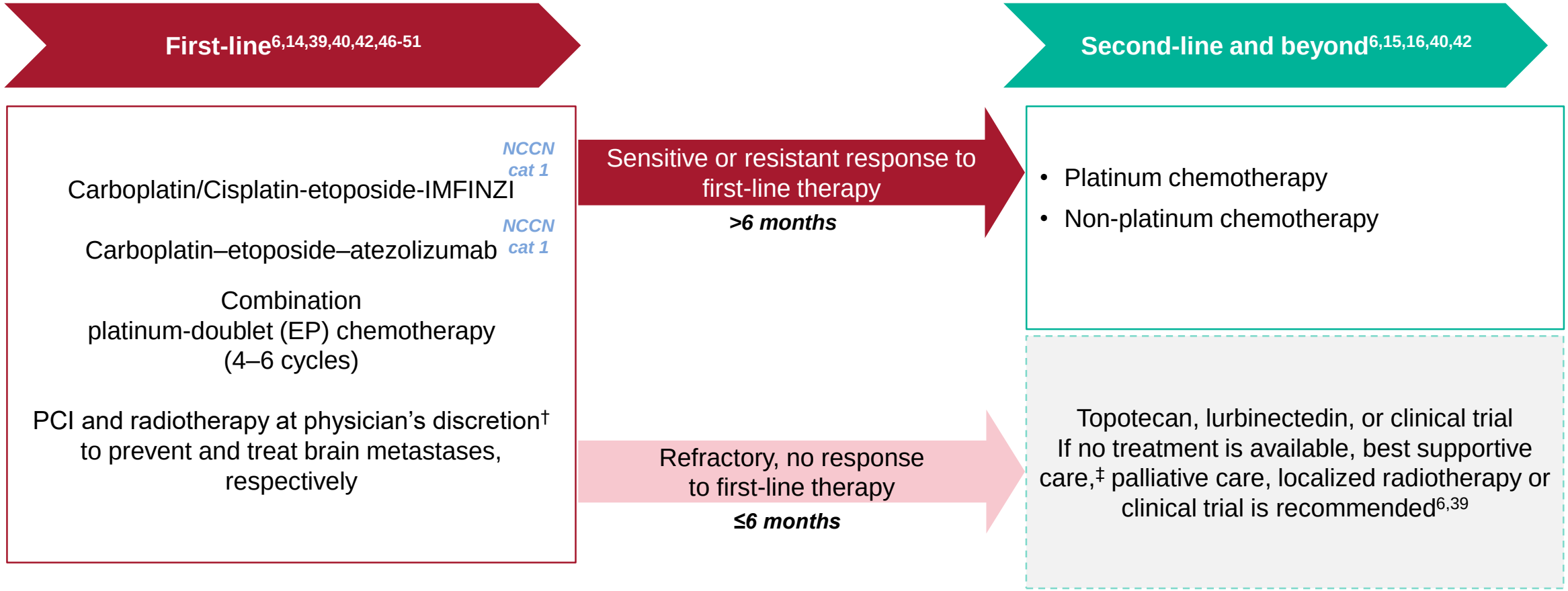
FDA: Food and Drug Administration; EMA: European Medicines Agency; NMPA: National Medical Products Administration; PMDA: Pharmaceuticals and Medical Devices Agency

† Some patients with limited stage SCLC may not benefit from PCI and PCI is not recommended for patients with poor performance status or impaired neurocognitive function; ‡ Pain medications and other non-specific palliative treatments, including radiotherapy with explicitly palliative intention (<5 0 Gray of radiation).[9,10]

DoR: duration of response; ES-SCLC: extensive-stage small cell lung cancer; EP: platinum-etoposide; FDA: food and drug administration; IO: immuno-oncology; NCCN: National Comprehensive Cancer Network; ORR: objective response rate; PCI: prophylactic cranial irradiation; SCLC: small cell lung cancer

5: NCCN. NCCN Guidelines for SCLC, Version 3. 20206. Oronsky B, et al. Neoplasia 2017; 14: "Resources for Information on Approved Drugs." U.S. Food and Drug Administration, FDA, 2021; 15: ESMO press release. 3 September 2018. 16: MERCK News Release, June 2019; 39: "NCCN Guidelines for SCLC, Version 1.2022."; 40. "Lung & Chest Tumors." ESMO Interactive Guidelines, 2021; 42: "Download Medicine Data." *European Medicines Agency*, 13 Oct. 2021; 46: The ASCO Post Staff. "Nivolumab Indication in Small Cell Lung Cancer Withdrawn in U.S. Market." 2021; 47: The ASCO Post Staff. "Pembrolizumab's Indication in Small Cell Lung Cancer Is Withdrawn." 2021

Immuno-oncology products have replaced etoposide + cisplatin/carboplatin as the SoC for 1L ES-SCLC in many markets



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6. Oronsky B, et al. Neoplasia 2017; 14. "Resources for Information on Approved Drugs." U.S. Food and Drug Administration, FDA, 2021; 15: ESMO press release. 3 September 2018. 16: MERCK News Release, June 201939: "NCCN Guidelines for SCLC, Version 1.2022."; 40: "Lung & Chest Tumors." *ESMO Interactive Guidelines*; 42: "Download Medicine Data." European Medicines Agency, 13 Oct. 2021; 46: The ASCO Post Staff. "Nivolumab Indication in Small Cell Lung Cancer Withdrawn in U.S. Market." 2021; 47: The ASCO Post Staff. "Pembrolizumab's Indication in Small Cell Lung Cancer Is Withdrawn." 2021; 48: "Review Report Pharmaceuticals and Medical Devices ... - PMDA."; 49: "Pharmaceuticals and Medical Devices Agency - PMDA.GO.JP." 50: "IMFINZI Approved in China for the Treatment of Extensive-Stage Small Cell Lung Cancer." 51: "China National Medical Products Administration Grants Approval of Roche's Tecentriq in Combination with Chemotherapy as First-Line Treatment of People with Extensive-Stage Small Cell Lung Cancer."

Although most patients respond to 1L EP, they typically progress within 4.7-5.5 months and life expectancy is less than one year

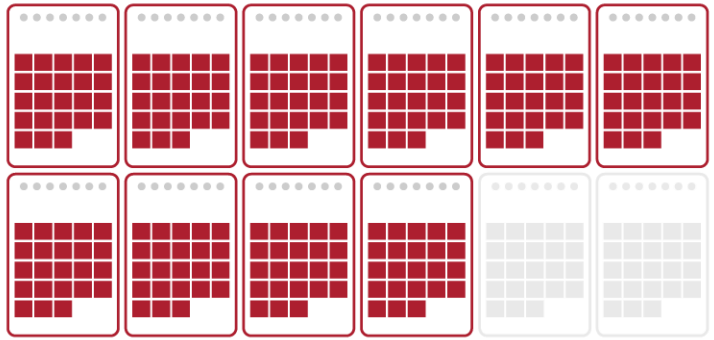
~60-70% of patients initially respond to EP

ORR 60–70%[21,22†]

However, patients typically relapse within 6 months

Median PFS 4.7-5.5 months[17,19]

Resulting in a poor overall survival rate



Median OS is 7–12 months
1 Year OS is ~40%[17,19,20,26]

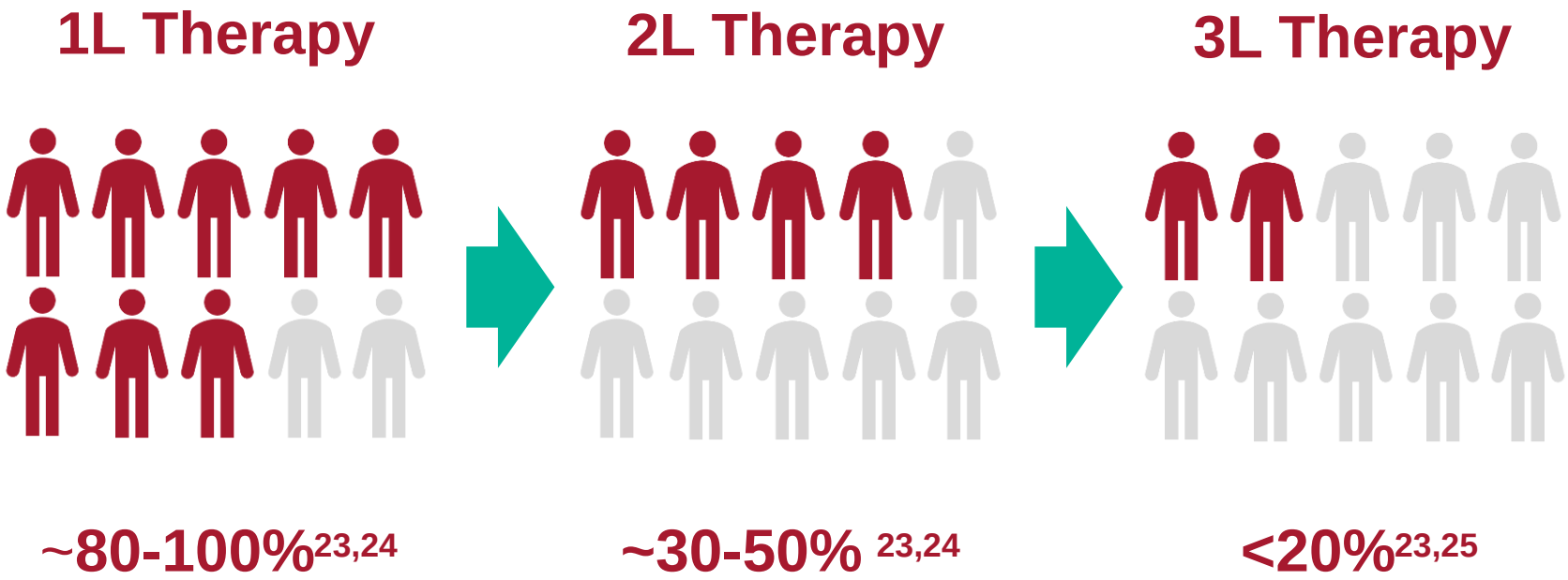
New treatments are needed to improve duration of response and OS for patients with ES-SCLC

† percentage of complete and partial responders; Complete response defined as no evidence of disease
EP: platinum-etoposide; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

17. Okamoto H, et al. Br J Cancer 2007;97:162– 9; 19. Foster NR, et al. Cancer 2011;117:1262–1271; 20. Tian S et al. Clin Lung Cancer 2019;20: 484-493.e6.; 21. Simon GR, et al. Diagnosis and Management of Lung Cancer: ACCP Guidelines 2007; 22. Früh M, et al. Annals of Oncology 2013; 26. Paz-Ares et al. Lancet 2019

Using the most effective first-line therapy is critical to patient outcomes as most patients receive only one line of treatment

Patients Eligible to Receive Treatment in Subsequent Lines of Therapy



Demonstrating sustained benefit in the 1L setting is paramount to improve patient outcomes

23. Froeschl S et al. J Thorac Oncol. 2008;3(2):163-169; 24. Aktas G et al. Onco Targets Ther. 2016;9:1921-1926; 25. de Jong WK et al. Lung Cancer. 2006;52(3):339-342.

Although most patients respond to 1L atezo + EP, they typically progress within 5.2 months and long-term (>2 yr) survival benefit is uncertain

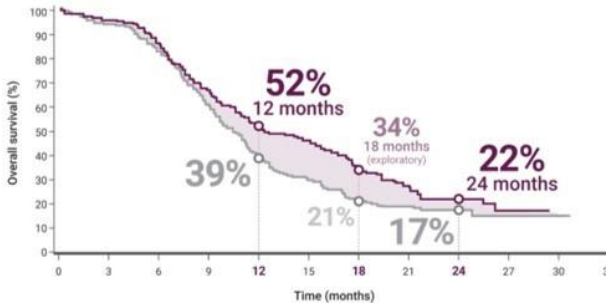
~60.2% of patients initially respond to atezolizumab[18]

ORR 60.2%[18]

However, patients typically relapse within 5.2 months[18]

Median PFS 5.2 months[18]

And long-term survival benefit has not been demonstrated[18]



2 year OS is ~22%; however, curves are trending towards convergence and long-term (>2 yr) survival benefit is uncertain[18]

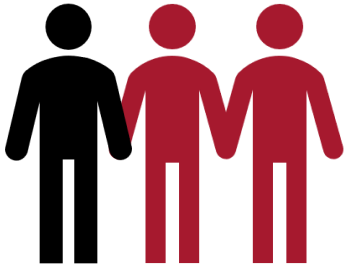
Long-term (>2 yr) OS data vs EP are needed to demonstrate sustained improvement in ES-SCLC patient survival

† percentage of complete and partial responders; Complete response defined as no evidence of disease
EP: platinum-etoposide; ORR: objective response rate; OS: overall survival; PFS: progression-free survival

18. Horn et al. N Engl J Med 2018

Approximately two in three patients have ES-SCLC at diagnosis; current survival data for atezolizumab + EP is limited to 2 years and longer-term benefit remains unclear

Two in three patients with SCLC have **ES-SCLC at diagnosis**[3,6]



Despite improving outcomes, treatment with atezolizumab **can only be used in combination with etoposide + carboplatin and survival data >2 yrs is currently lacking**[18,53]

2-year survival rate ~22%

EP: platinum-etoposide

3. American Cancer Society. Small Cell Lung Cancer Stages 2020; 6. Oronsky B, et al. Neoplasia 2017;18. Horn et al. N Engl J Med 2018; 53: Genentech. “Efficacy in Extensive-Stage Small Cell Lung Cancer (Es-SCLC): TECENTRIQ® (Atezolizumab).”

CASPIAN is the first and only approved IO regimen in ES-SCLC to allow up to 6 cycles of EP in the control arm and use of cisplatin or carboplatin

CASPIAN Study Design[5,26]

NEWLY DIAGNOSED ES-SCLC
n=805

- WHO/ECOG performance status 0 or 1
- Life expectancy ≥12 weeks
- At least 1 target lesion by RECIST 1.1
- Stratification: cisplatin or carboplatin

R
1:1:1

Induction Phase	Maintenance Phase
IMFINZI + EP • Investigator's choice of cisplatin or carboplatin* • 4 Cycles; Q3W; n=268	• IMFINZI Q4W until progression
EP • Investigator's choice of cisplatin or carboplatin‡ • 4-6 cycles • Up to 6 Cycles; Q3W; n=269	
IMFINZI + EP (4 cycles) + Investigational Agent (5 cycles) followed by IMFINZI maintenance (n=268)	

Primary endpoint

- Overall Survival

Key secondary endpoints

- PFS
- ORR
- OS at 18 months
- PFS 6 / 12 months
- HRQoL

CASPIAN allowed for		The control arm allowed for	
			
Investigator's choice of platinum-based chemotherapy	Patients with asymptomatic or treated brain metastases	Up to 6 cycles of chemotherapy	PCI per investigator's discretion

*IMFINZI 1500 mg + carboplatin or cisplatin and etoposide for a maximum of 4 cycles, followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity; EP consisted of etoposide 80 to 100 mg/m^2 with either carboplatin AUC 5 to 6 mg/mL or cisplatin 75 to 80 mg/m^2; ‡Either carboplatin or cisplatin and etoposide
EP: platinum-etoposide; ES-SCLC: extensive-stage small-cell lung cancer; HRQoL: health-related quality of life; ORR: objective response rate; DR: duration of reponse OS: overall survival; PCI: prophylactic cranial irradiation; PFS: progression-free survival; Q3W: every three weeks, Q4W, every four weeks

5. NCCN Clinical Practice Guidelines in Oncology. Version 2.2020 – November 15, 2019; 26. Paz-Ares et al. Lancet 2019

CASPIAN reflected international ES-SCLC clinical guidelines which more closely aligns with how patients are treated in the real-world

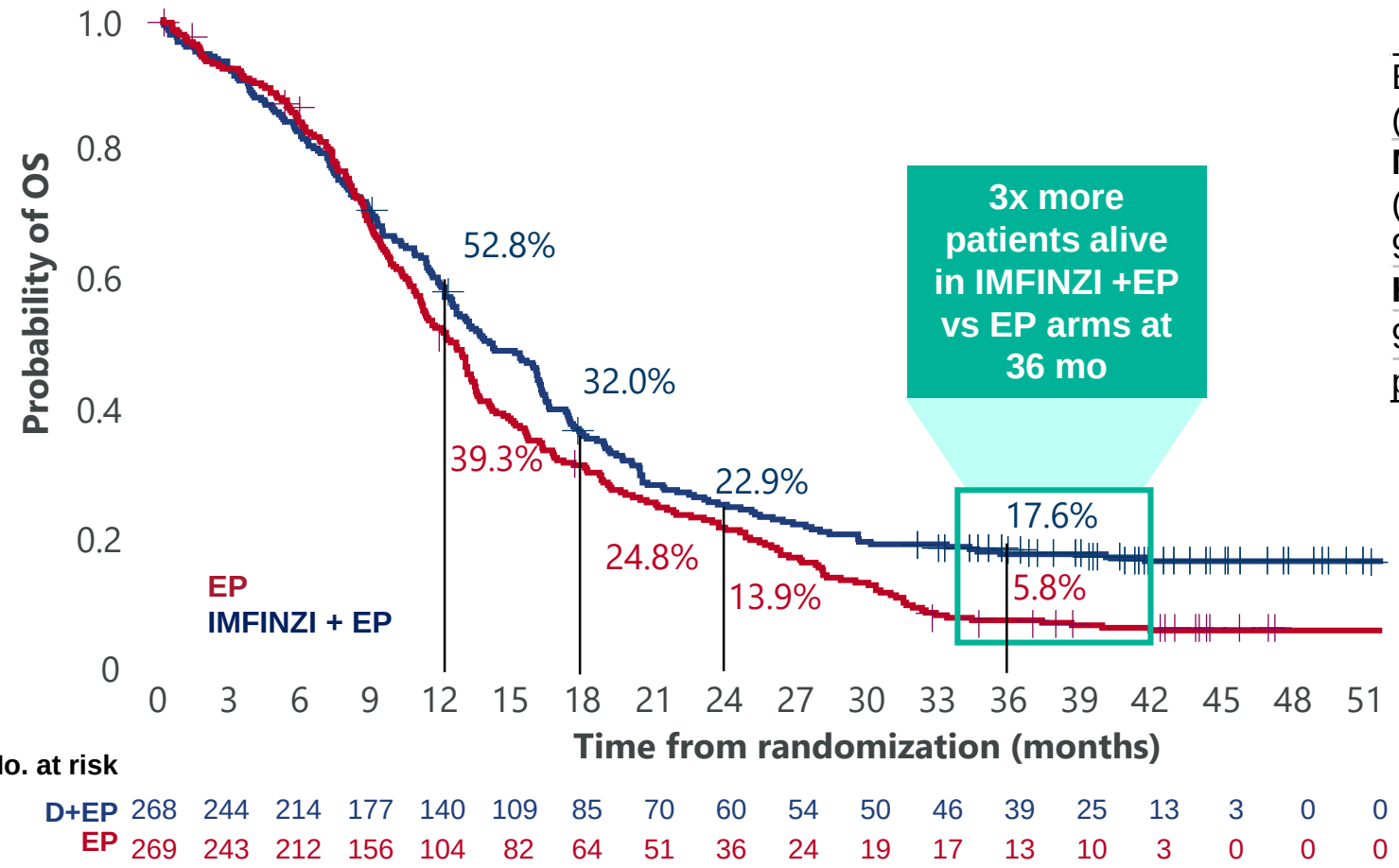
Clinical Guidelines[22,39]	IMpower133[18]	CASPIAN[29,41]
Carboplatin and cisplatin are both recommended; use is left up to physician discretion	Carboplatin was the only platinum therapy allowed	Use of either cisplatin or carboplatin was allowed to reflect real-world clinical practice across markets
Treatment for patients with symptomatic and asymptomatic brain metastases with radiotherapy is recommended before or after systemic therapy, respectively	Patients with brain metastases were only eligible if they had received prior treatment.	Patients with asymptomatic untreated and treated brain metastases were eligible
International guidelines recommend between 4 and 6 cycles of EP	Only 4 cycles of EP were allowed across all arms	The EP arm allowed for up to 6 cycles of treatment

*EP consists of etoposide 80–100 mg/m^2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m^2 **Patients could receive an additional two cycles of EP (up to six cycles total) and PCI at the investigator's discretion

618. Horn et al. N Engl J Med 2018; 22. Früh M, et al. Annals of Oncology 2013; 29: Paz-Ares, L et. al. 39: "NCCN Guidelines for SCLC, Version 1.2022."; 41: Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the Phase 3 CASPIAN study. Presented at Virtual ESMO 2021, 16–21 September 2021: Abstract LBA61

IMFINZI+EP is the first and only approved IO to demonstrate a statistically significant and sustained improvement in OS vs EP at 12, 24, and 36 mo

3-yr Overall Survival Analysis in the CASPIAN Trial[26,37,41]
(Median duration of follow-up 39.4 months)



3x more patients alive in IMFINZI +EP vs EP arms at 36 mo

	IMFINZI + EP	EP
Events, n/N (%)	221/268 (82.5)	248/269 (92.2)
Median OS (months) 95% CI	**12.9** 11.3–14.7	**10.5** 9.3–11.2
HR	**0.71**	
95% CI	0.60–0.86	
p-value	0.0003	

- IMFINZI + EP improved the estimated percentage of patients alive, with 3x more patients alive at 3 years vs. EP (17.6% vs 5.8%)
- Clear separation of the curves is sustained, with a notable flattening of the curve observed from ~27 months onwards, which further supports a sustained long-term OS benefit[41]

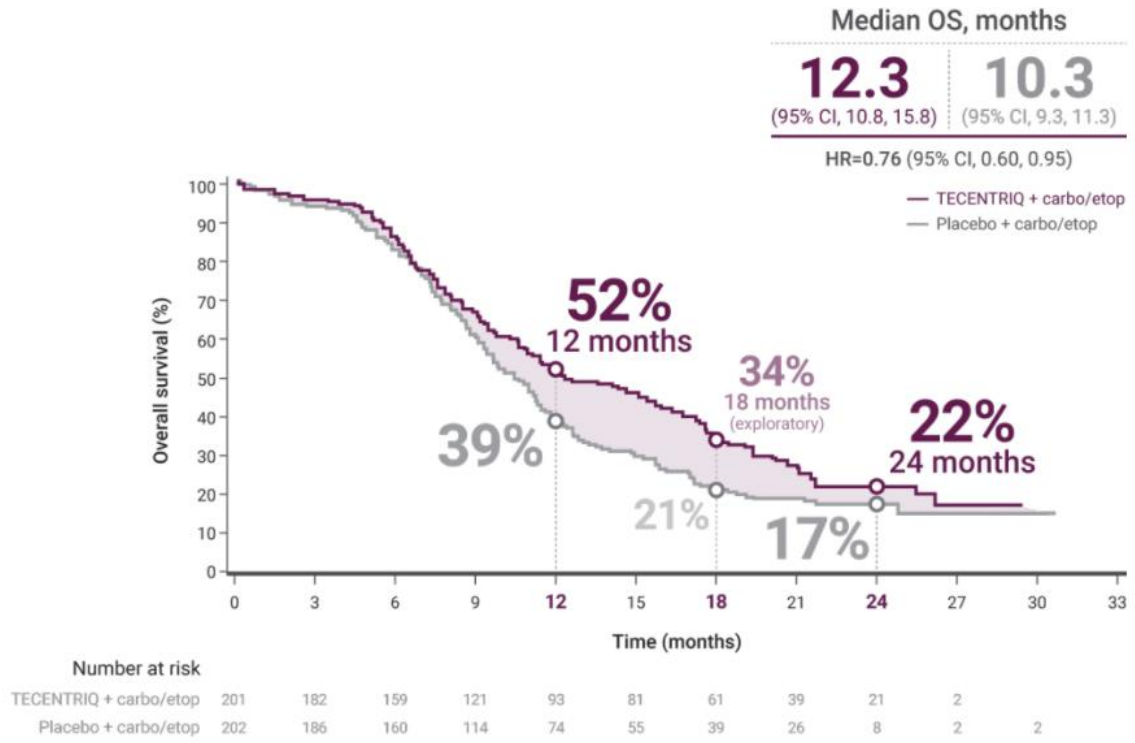
Data cut-off: 22 March 2021; CI: confidence interval; EP: platinum-etoposide; HR: hazard ratio; OS: overall survival

26. Paz-Ares et al. Lancet 2019; 37. Paz-Ares, L et al. Clinical Study Report 2019; 41: Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the Phase 3 CASPIAN study. Presented at Virtual ESMO 2021, 16–21 September 2021: Abstract LBA61

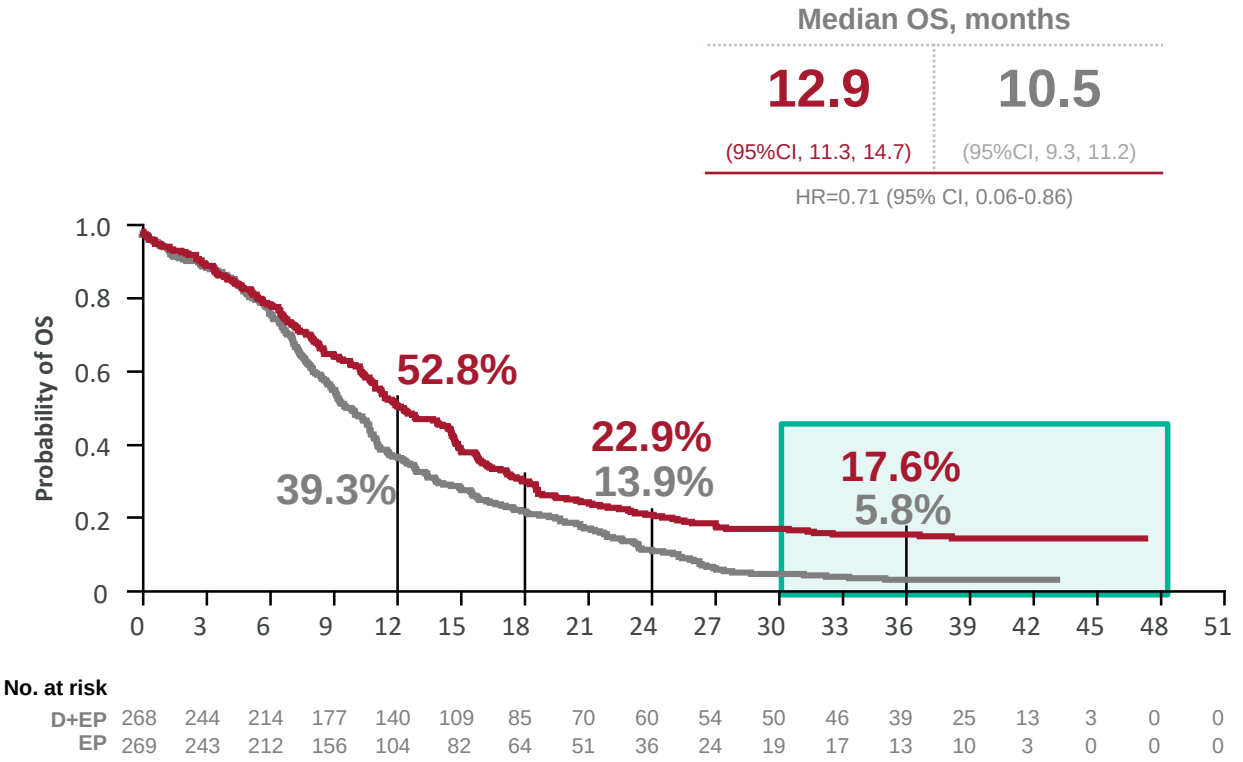
IMFINZI is the first and only immuno-oncology agent to show a sustained long-term survival benefit up to 3 years

ILLUSTRATIVE PURPOSES ONLY; SHOULD BE INTERPRETED WITH CAUTION AS DIRECT CROSS-TRIAL COMPARISONS CANNOT BE MADE

IMpower133 OS[18,53]



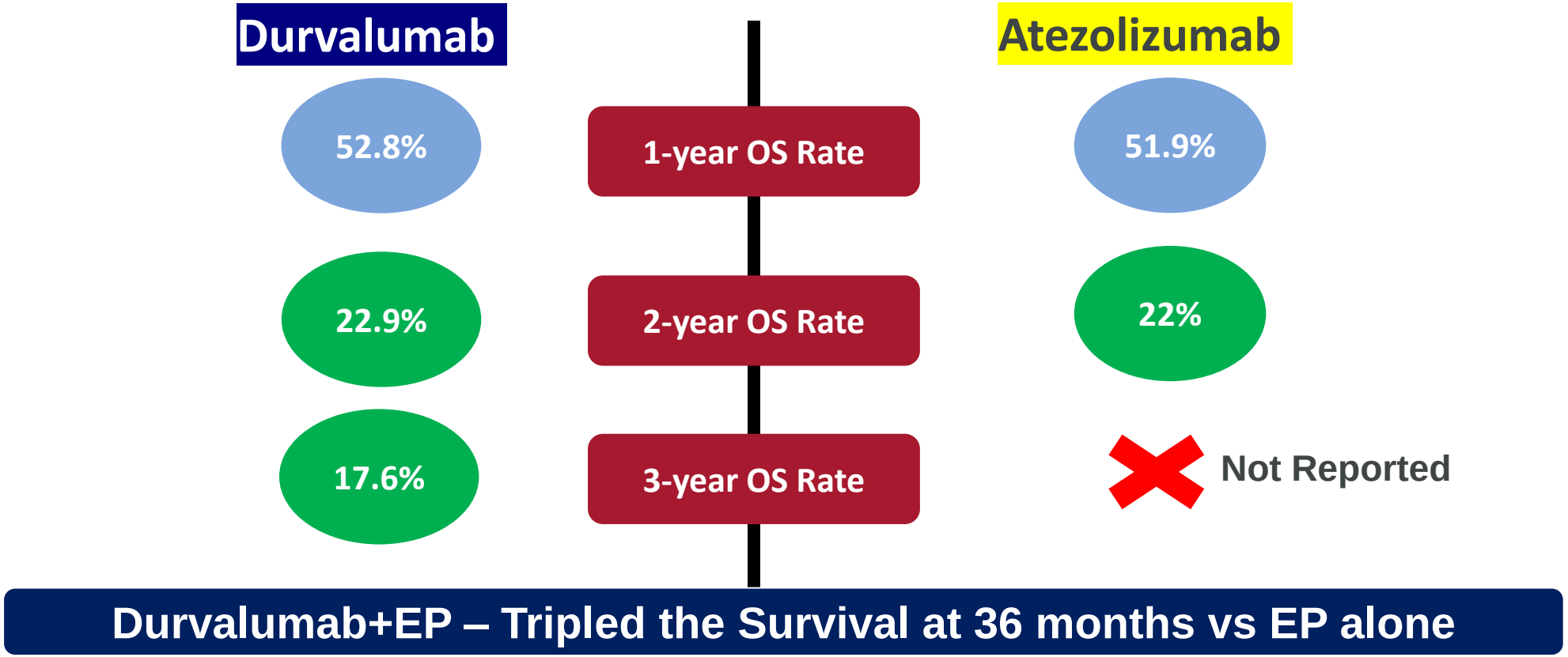
CASPIAN 3-year OS[41]



For internal reference purposes only; direct cross-trial comparison not appropriate

18. Horn et al. N Engl J Med 2018; 41: Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the Phase 3 CASPIAN study. Presented at Virtual ESMO 2021, 16–21 September 2021: Abstract LBA61; 53: Genentech. “Efficacy in Extensive-Stage Small Cell Lung Cancer (Es-SCLC): TECENTRIQ® (Atezolizumab).”

Is 2 year OS good enough to make the treatment choice for the sustained and durable response with IO ?



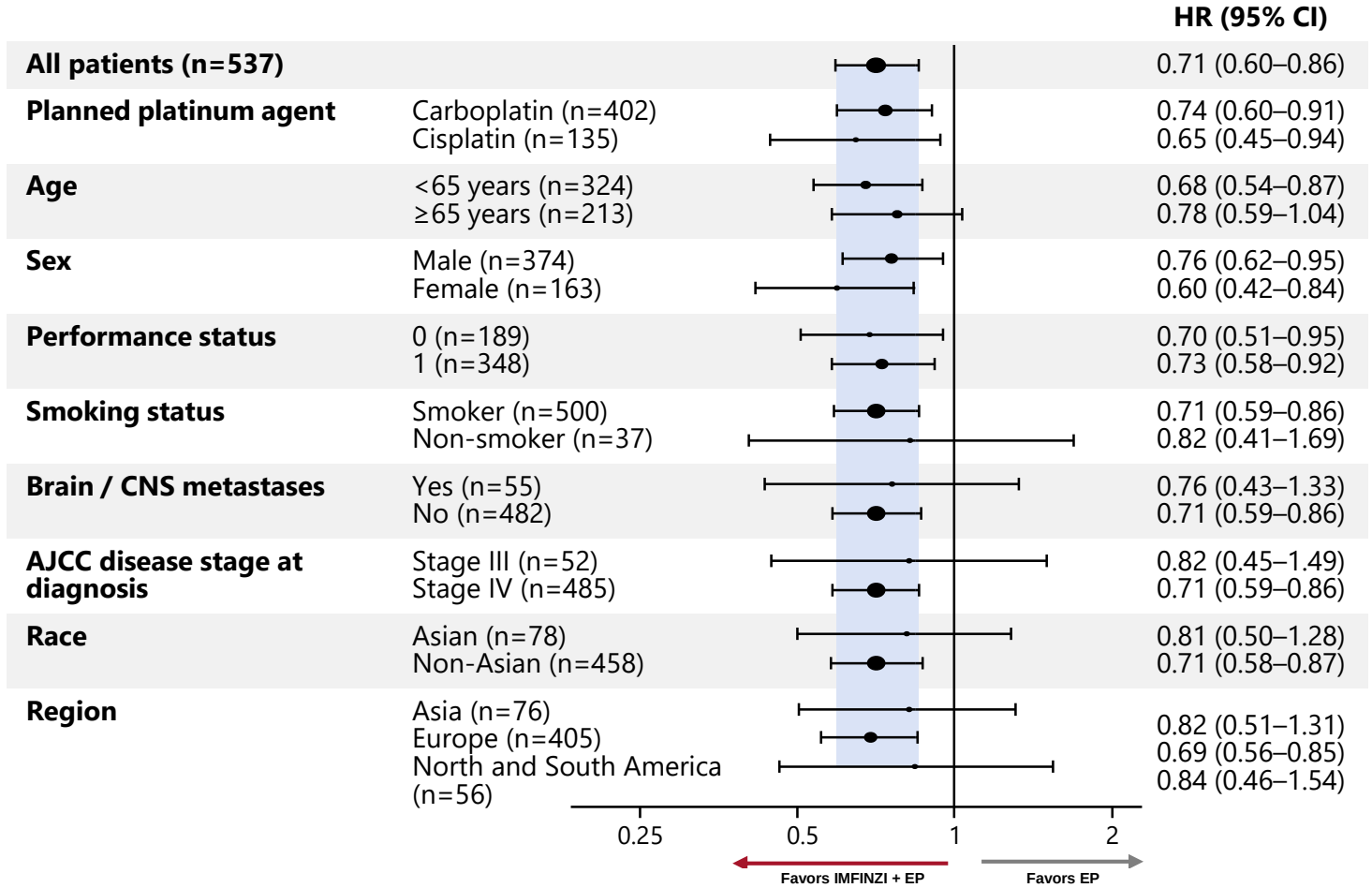
Luis Paz-Ares et al. Lancet 2019; 394: 1929-39 Horn L et al. N Engl J Med 2018; 379: 2220-9 Luis Paz-Ares et al. 3 years CASPIAN update Presented at ESMO 2021

For internal reference purposes only; direct cross-trial comparison not appropriate

18. Horn et al. N Engl J Med 2018; 41: Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the Phase 3 CASPIAN study. Presented at Virtual ESMO 2021, 16–21 September 2021: Abstract LBA61; 53: Genentech. “Efficacy in Extensive-Stage Small Cell Lung Cancer (Es-SCLC): TECENTRIQ® (Atezolizumab).”

At 3-yrs, OS benefit consistently favored IMFINZI + EP across pre-specified subgroups that are reflective of clinical practice in ES-SCLC

3-yr Overall Survival Analysis by Pre-specified Subgroups in the CASPIAN Trial[41]



IMFINZI + EP was evaluated in key patient subgroups reflective of clinical practice in ES-SCLC

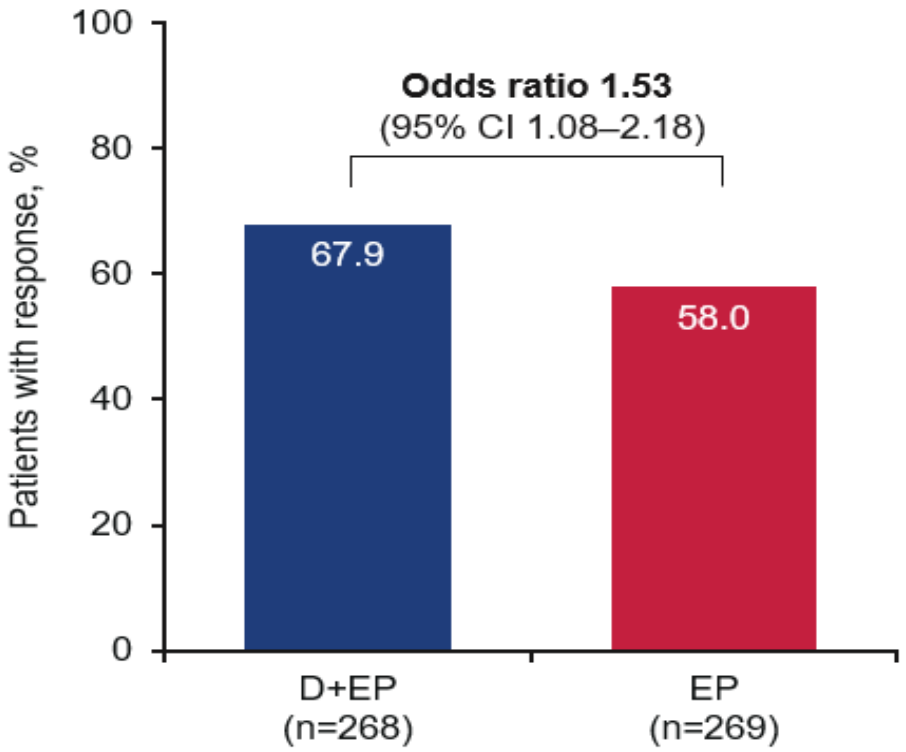
- Cisplatin- and carboplatin-eligible patients
- Patients over 65
- Former and active smokers
- Patients with brain/CNS metastases

Size of circle is proportional to the number of events across both treatment groups. *Post hoc analysis; other subgroups were pre-specified
Outcomes for patients with liver metastases was not reported at the 3 year planned exploratory analysis (DCO March 22,2021) as this was not a pre-specified subgroup.[41]
AJCC: American Joint Committee on Cancer; CI: confidence interval; CNS: central nervous system; EP: platinum-etoposide; OS: overall survival

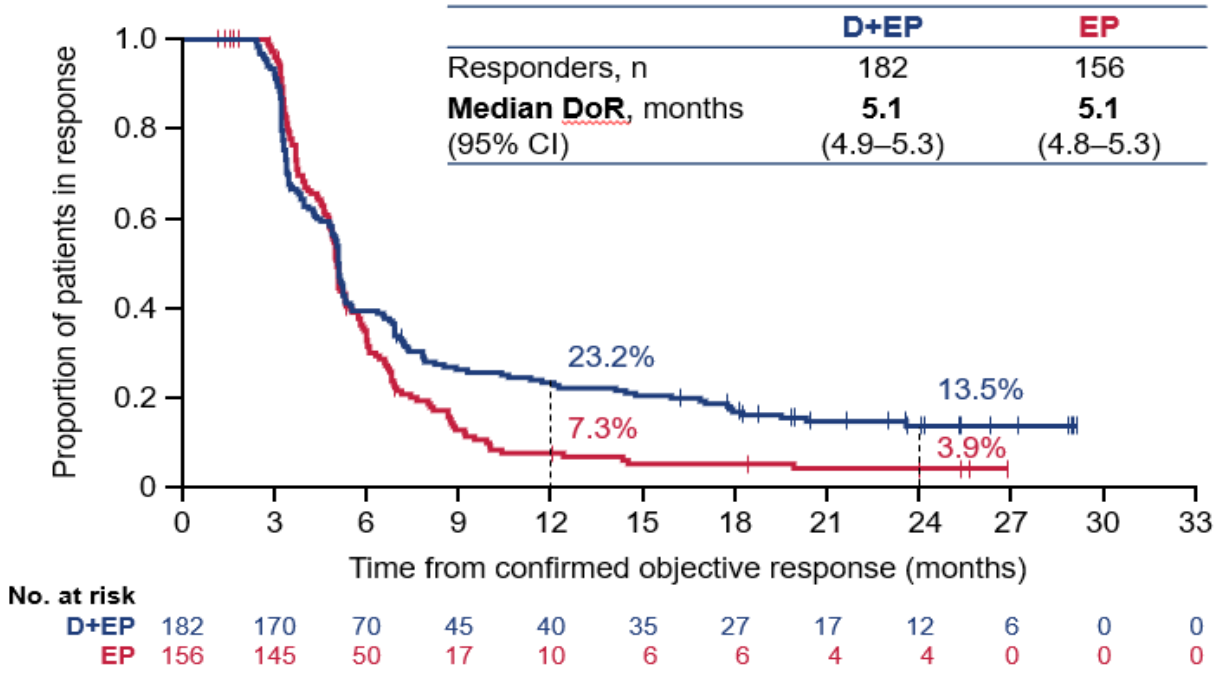
41. Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the Phase 3 CASPIAN study. Presented at Virtual ESMO 2021, 16–21 September 2021: Abstract LBA61

IMFINZI is the first approved IO to improve both response rate (68% vs. 58%) and durability of response at 24 months (13.5% vs. 3.9%) in ES-SCLC

24 month Confirmed ORR Analysis in the Caspian Trial[27]



24 month Duration of Response Analysis in the CASPIAN Trial[27]



>3x more patients remaining in response at 24 months with IMFINZI + EP vs EP alone

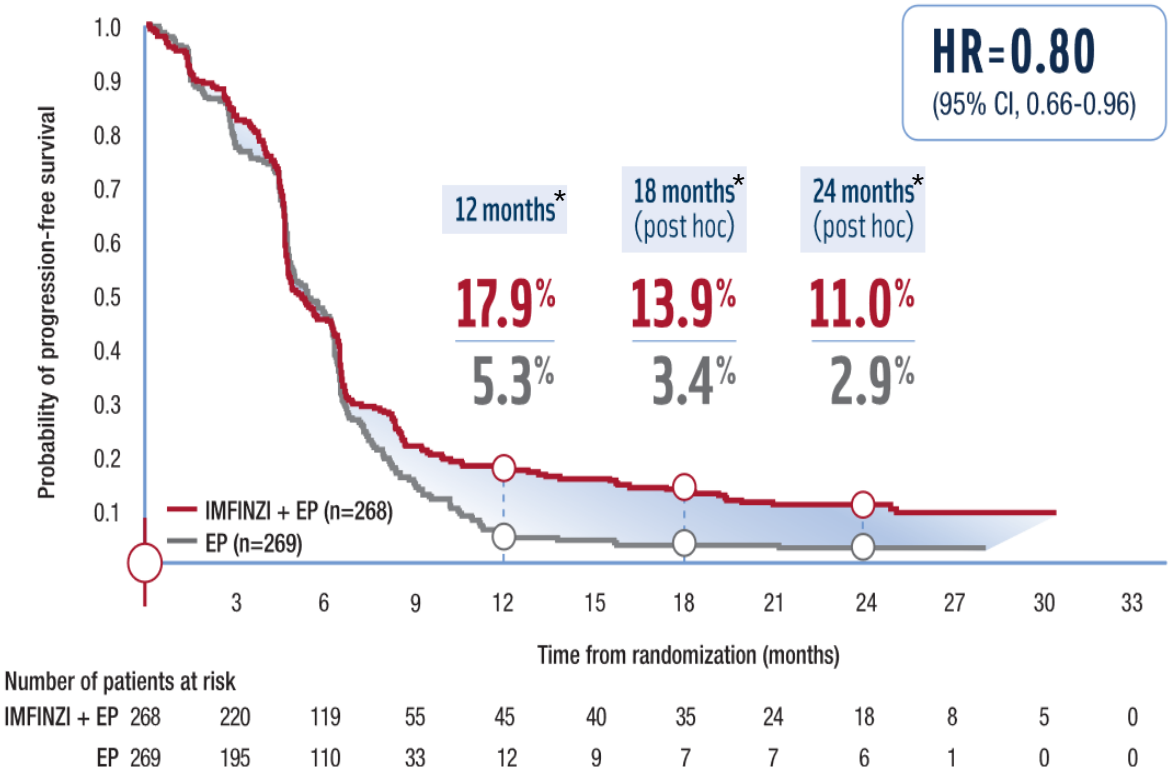
DoR: duration of response; EP: platinum-etoposide; ES-SCLC: extensive-stage small-cell lung cancer; IO: immuno-oncology; ORR: objective response rate

27. Paz-Ares LG, Dvorkin M, Chen Y, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC: updated results from the phase III CASPIAN study. *J Clin Oncol*. 2020;38(15 suppl). Presented at ASCO 2020; published online May 25, 2020. doi:10.1200/JCO.2020.38.15_suppl.9002.

IMFINZI + EP demonstrated a sustained improvement in PFS with nearly 4x the number of patients progression-free at 24 months vs EP and ~10.1% of patients with ongoing treatment at 3 yrs

24 mo Progression-free survival with IMFINZI + EP and EP alone[26,27,41]

(median duration of follow-up 25.1 months)**



	IMFINZI + EP	EP
Events, n/N (%)	234/268 (87.3)	236/269 (87.7)
Median PFS (months)	**5.1**	**5.4**
95% CI	4.7-6.2	4.8–6.2
HR	**0.80**	
95% CI	0.66–0.96	

- >3x the number of patients were progression-free at 12 months, and nearly 4x the number of patients were progression-free at 24 months with IMFINZI + EP vs EP alone[27]
- **9.1% of patients have been on IMFINZI for ≥3 years[41]**
- **10.1% of patients were continuing treatment with IMFINZI at the 3-year data cut-off[41]**

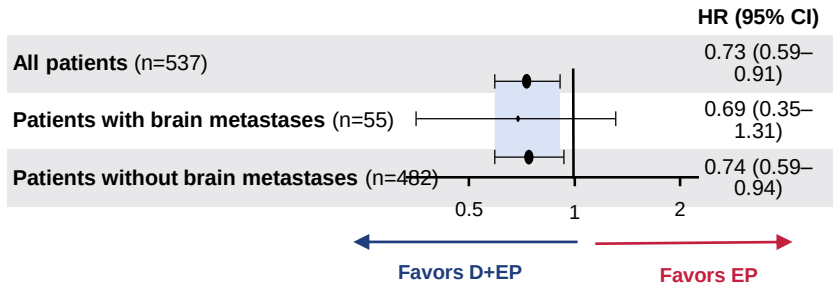
*PFS rates at 12, 18, and 24 months are the estimated proportion of patients alive and progression free based on the updated analysis.
**CASPIAN was designed as a treat to progression trial; ~57% of patients received 6 cycles of EP in the control arm[26]
CI: confidence interval; EP: platinum-etoposide; HR: hazard ratio; PFS: progression-free survival

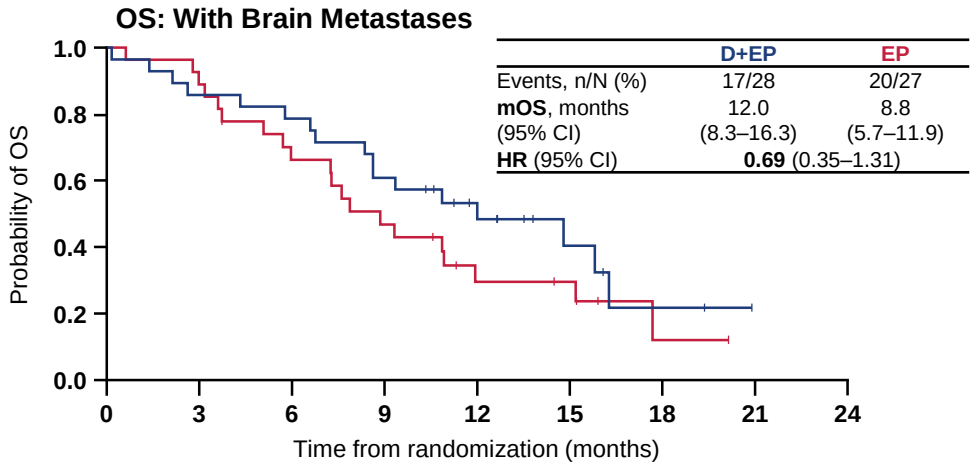
26. Paz-Ares et al. Lancet 2019; 27. Paz-Ares LG, Dvorkin M, Chen Y, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC: updated results from the phase III CASPIAN study. *J Clin Oncol*. 2020;38(15 suppl). Published online May 25, 2020. doi:10.1200/JCO.2020.38.15_suppl.9002. ; 41: Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the Phase 3 CASPIAN study. Presented at Virtual ESMO 2021, 16–21 September 2021: Abstract LBA61

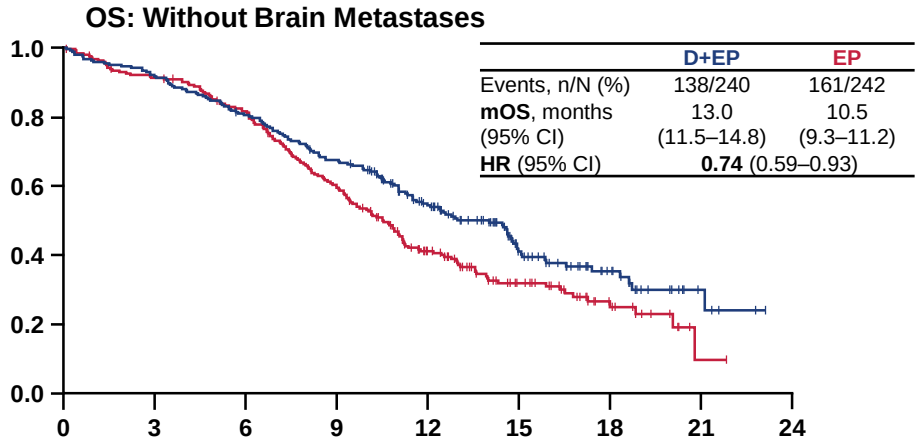
CASPIAN Study: OS Based on Baseline Brain Metastases

Durvalumab + EP consistently improved OS versus EP in patients regardless of the presence of baseline brain metastases

- With brain metastases: HR 0.69 [0.35–1.31]
- Without brain metastases: 0.74 [0.59–0.93]







At 24 months, the overall safety profile, including discontinuation rates, were comparable for IMFINZI + EP vs. EP and consistent with the known safety profiles of each component

Updated Analysis Safety Profile	IMFINZI + EP[27] N = 265, n (%)	EP[27] N = 266, n (%)
Any Grade all cause AEs	260 (98.1%)	258 (97.0%)
Grade 3,4 AEs	165 (62.3%)	167 (62.8%)
Serious AEs	85 (32.1%)	97 (36.5%)
AEs leading to treatment discontinuation*	27 (10.2%)	25 (9.4%)
imAEs†	53 (20.0%)	7 (2.6%)
AEs leading to death	13 (4.9%)	15 (5.6%)
Treatment-related AEs leading to death‡	6 (2.3%)	2 (0.8%)

- **Rates of grade 3,4 AEs and serious AEs were numerically lower in the IMFINZI + EP arm, relative to EP[27]**
- **There are nominal differences in discontinuation rates due to AEs in either arm[27]**
- **imAEs were higher with IMFINZI + EP, relative to EP, driven by thyroid events[27]**
- **The majority of imAEs were low grade and managed in line with standard treatment guidelines[27,28]**

* Includes patients who permanently discontinued at least one study drug. †An event that is associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate aetiology and the event required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy; majority of imAEs were low grade and thyroid related. ‡AEs assessed by the investigator as possibly related to any study treatment. Causes of death were death, febrile neutropenia, and pulmonary embolism (two patients each), and enterocolitis, general physical health deterioration/multiple organ dysfunction syndrome, pneumonia, pneumonitis/hepatitis, respiratory failure, and sudden death (one patient each) in the durvalumab + tremelimumab + EP arm; cardiac arrest, dehydration, hepatotoxicity, interstitial lung disease, pancytopenia, and sepsis (one patient each) in the durvalumab + EP arm; pancytopenia and thrombocytopenia/haemorrhage (one patient each) in the EP arm

AE: Adverse event; EP: platinum-etoposide; imAE: immune-mediated adverse event

27. Paz-Ares LG, Dvorkin M, Chen Y, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC: updated results from the phase III CASPIAN study. J Clin Oncol. 2020;38(15 suppl). Published online May 25, 2020. doi:10.1200/JCO.2020.38.15_suppl.9002; 28. ESMO Clinical Practice Guideline 2018

At 36 months, there were no new safety signals identified or significant changes in the safety profile for IMFINZI + EP vs EP, demonstrating consistency in patient tolerability

Safety Profile	IMFINZI + EP[27,41] N = 265, n (%)		EP[27,41] N = 266, n (%)	
	24 months	36 months	24 months	36 months
Serious AEs (all cause), n (%)[a]	85 (32.1)	86 (32.5)	97 (36.5)	97 (36.5)
Febrile neutropenia		12 (4.5)		12 (4.5)
Pneumonia		6 (2.3)		11 (4.1)
Anaemia		5 (1.9)		12 (4.5)
Thrombocytopenia		1 (0.4)		9 (3.4)
Hyponatraemia		2 (0.8)		4 (1.5)
Neutropenia		2 (0.8)		7 (2.6)
Diarrhoea		2 (0.8)		4 (1.5)
Pulmonary embolism		1 (0.4)		0
AEs leading to death (all cause), n (%)[b]	13 (4.9)	14 (5.3)	15 (5.6)	16 (6.0)
Treatment-related AEs leading to death	6 (2.3)	6 (2.3)	2 (0.8)	2 (0.8)

- **Rates of grade 3,4 AEs and serious AEs were numerically lower in the IMFINZI + EP arm, relative to EP[41]**
- **The safety and tolerability for each combination in the trial was consistent with the known safety profiles of these agents[41]**
- **9.1% of patients have been on IMFINZI for ≥3 years and 10.1% of patients have ongoing treatment with IMFINZI at the 3 year data cut-off[41]**

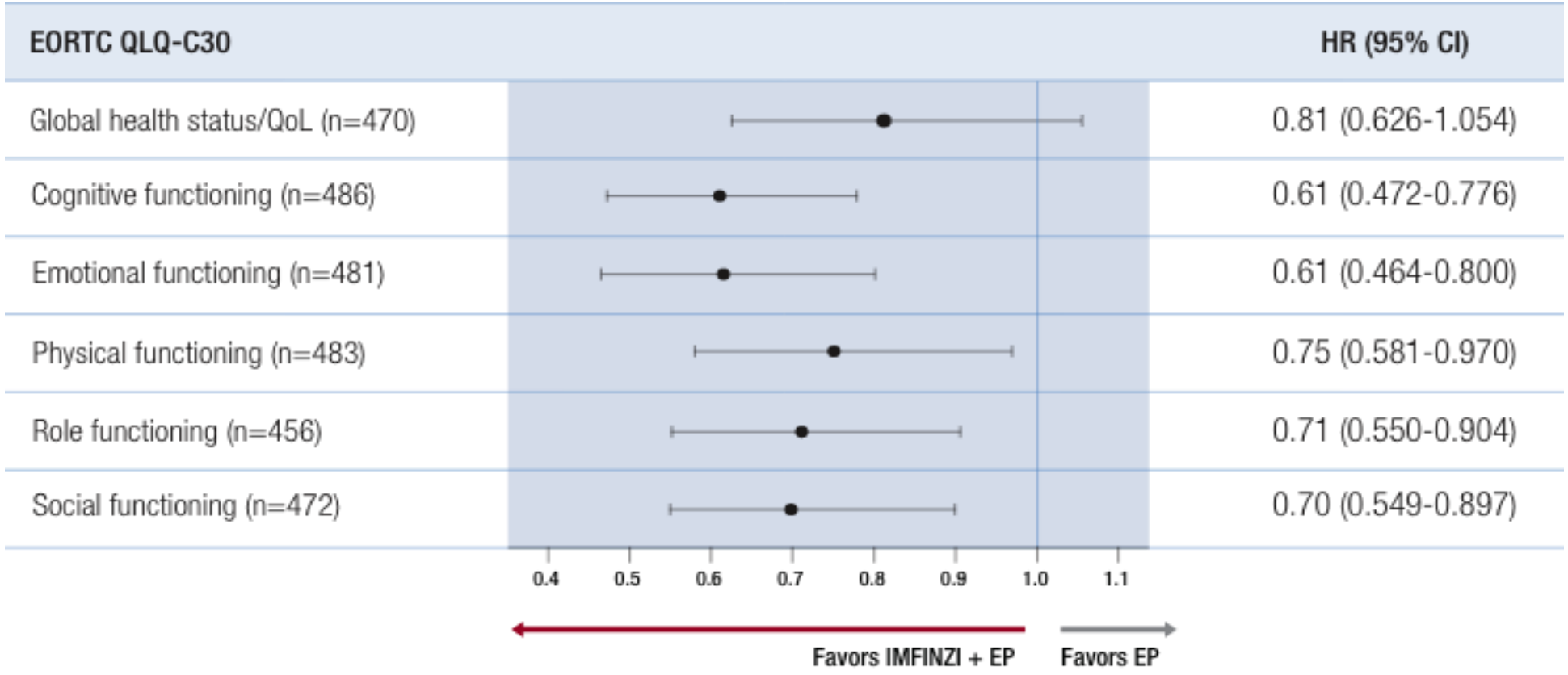
aSerious AEs occurring in ≥2% patients in any treatment arm are shown; bFour additional deaths were reported since the previous analysis (none considered treatment related): one in the D+EP arm (aspiration), two in the D+T+EP arm (drowning and pneumocystis jirovecii pneumonia) and one in the EP arm (small intestine leiomyosarcoma)

AE: Adverse event; EP: platinum-etoposide; imAE: immune-mediated adverse event

27. Paz-Ares LG, Dvorkin M, Chen Y, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC: updated results from the phase III CASPIAN study. J Clin Oncol. 2020;38(15 suppl). Published online May 25, 2020. doi:10.1200/JCO.2020.38.15_suppl.9002; 28. ESMO Clinical Practice Guideline 2018; 41: Paz-Ares L, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the Phase 3 CASPIAN study. Presented at Virtual ESMO 2021, 16–21 September 2021: Abstract LBA61

IMFINZI + EP delayed patients' time to deterioration in functioning and QoL

Time to Deterioration in EORTC QLQ-C30 Functioning and HRQoL Scales[29]

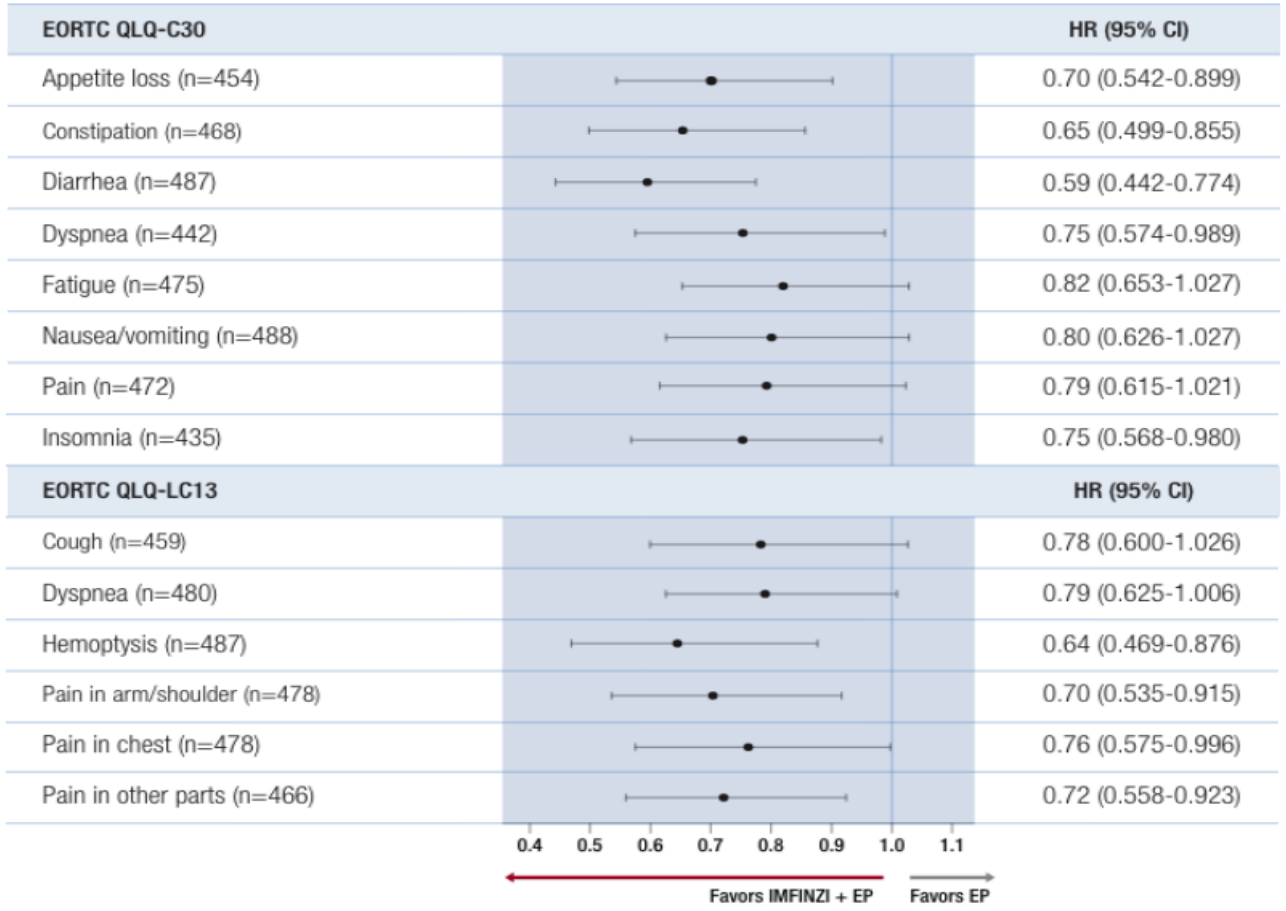


EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EP: platinum-etoposide; HRQoL: health-related quality of life; QoL: quality of life

29. Paz-Ares et al. ESMO 2019

IMFINZI + EP delayed time to deterioration in symptoms including dyspnea, appetite loss, pain, fatigue and cough

Time to symptom deterioration from baseline[29]



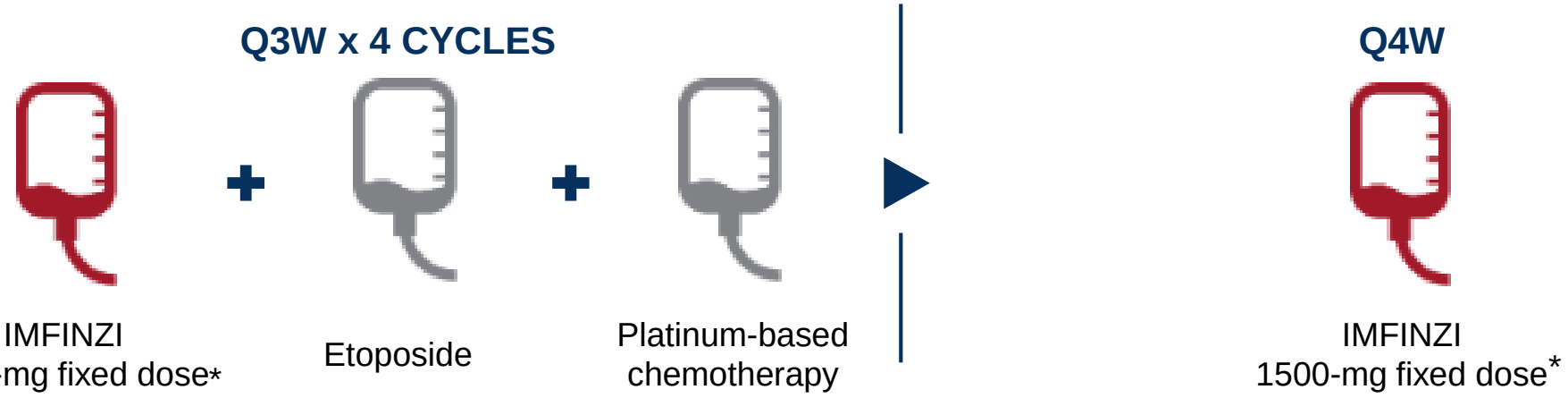
CI: confidence interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-LC13: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13; EP: platinum-etoposide; HR: hazard ratio

29. Paz-Ares et al. ESMO 2019

IMFINZI is the only IO with clinical trial data supporting a Q4W maintenance dose administration schedule for ES-SCLC patients

CASPIAN Administration Schedule[26,37]

Induction*	Maintenance* until disease progression or unacceptable toxicity



CASPIAN demonstrated that IMFINZI can be administered Q3W with EP and Q4W as a maintenance treatment

*Patients with a body weight of ≤30 kg must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg according to the same dosing schedule as above; IMFINZI may be given as 1500-mg fixed dose once body weight increases to >30 kg; EP consists of etoposide 80 mg/m^2 to 100 mg/m^2 with either carboplatin AUC 5 mg/mL/min or 6 mg/mL/min or cisplatin 75 mg/m^2 to 80 mg/m^2; for more information please refer to the prescribing information for each treatment

26. Paz-Ares et al. Lancet 2019; 37. Paz-Ares, L et al. Clinical Study Report 2019

Study Design differentiators – CASPIAN vs IMP133

	IMP133	CASPIAN
All comers (no biomarker selection)	Included	Included
Untreated brain metastasis	Excluded	Included
PCI allowed in control arm	Included (~10%)	Included
PCI allowed in experimental arm	**Included (~10%)**	**Excluded**
Up to 6 cycles of chemo in control arm	**Not Allowed**	**Allowed**
Cisplatin	**Excluded**	**Allowed**
Carboplatin	Allowed	Allowed

CASPIAN study inclusion criteria is reflective of real-world clinical practice

- Allowed treatment with either cis- or carboplatin
- Included patients with either asymptomatic/untreated or treated brain metastases
- Compared against up to 6 cycles of chemotherapy* with optional PCI

26

Luis Paz-Ares et al. Lancet 2019; 394: 1929-39 Horn L et al. N Engl J Med 2018; 379: 2220-9

PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC:

Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimen

- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg day 1, every 21 days (category 1, for all)[b,5]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]

Other Recommended Regimens

- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[7]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[9]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[10]

Useful In Certain Circumstances

- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[11]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[12]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[13]

See Evidence Blocks on SCL-E (EB-1)

[a] Cisplatin contraindicated or not tolerated.
[b] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.

Subsequent Systemic Therapy (SCL-E 2 of 4)
Response Assessment (SCL-E 3 of 4)
References
(SCL-E 4 of 4)

CONCLUSION

- First line Durvalumab + EP has shown sustained improvement in OS compared with a robust control arm that is reflective of a real world scenario by allowing up to 6 cycles of EP and the use of PCI as compared to the results from the atezolizumab + carboplatin-etoposide study of IMPower133
- Durvalumab is the only IO that provides flexibility of choosing Cisplatin/Carboplatin along with etoposide
- Benefit with Durvalumab + EP was observed across all subgroups include brain metastasis subgroup
- More than 17% patients on Durvalumab+ EP arm are surviving even after 3 years showing prolonged survival benefit.
- IMFINZI + EP provided a high response rate and demonstrated ongoing responses at 2 year in 3X more patients than EP arm.
- Durvalumab offers convenient once monthly dosing regimen in the maintenance phase
- Safety findings remains consistent with the known safety profile of Durvalumab and EP.

Abbreviated Prescribing Information
Durvalumab intravenous solution

- For the use of a registered oncologist only. DURVALUMAB INTRAVENOUS INFUSION: -IMFINZI™ Vial 500 mg (500mg/10mL) and 120 mg (120 mg/2.4mL) in 10 mL Abbreviated Prescribing Information: QUALITATIVE AND QUANTITATIVE COMPOSITION-Each mL contains 50 mg of IMFINZI. Each vial of 2.4 mL contains 120 mg of durvalumab. Each vial of 10 mL contains 500 mg of durvalumab. IMFINZI is a human immunoglobulin (IgG1κ) monoclonal antibody. THERAPEUTIC INDICATIONS: Urothelial Carcinoma IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has progressed during or after platinum-based chemotherapy. Locally Advanced Non-Small Cell Lung Cancer (NSCLC) IMFINZI is indicated for the treatment of patients with locally advanced, unresectable non-small cell lung cancer whose disease has not progressed following platinum-based chemoradiation therapy and Small Cell Lung Cancer. SCLC- IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC). POSOLOGY AND METHOD OF ADMINISTRATION: Urothelial Carcinoma The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, as long as clinical benefit is observed or until unacceptable toxicity. Locally Advanced NSCLC-The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity. Small Cell Lung Cancer SCLC - 1500 mg[a] in combination with chemotherapy[b,c] every 3 weeks (21 days) for 4 cycles,followed by 1500 mg every 4 weeks as monotherapy; until disease progression or unacceptable toxicity. a - Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.. b - Administer IMFINZI prior to chemotherapy when given on the same day. c - When IMFINZI is administered in combination with chemotherapy, refer to the Prescribing Information for etoposide and carboplatin or cisplatin for dosing information. Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability. CONTRAINDICATIONS: None. WARNINGS & PRECAUTIONS-Given the mechanism of action of IMFINZI®, potential immune-mediated adverse reactions may occur. Patients should be monitored for signs and symptoms and managed as recommended in full prescribing information. For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. Withholding of IMFINZI should be considered for Grade 3 immune-mediated adverse reactions, unless clinical judgment indicates discontinuation. Systemic corticosteroids should be considered. Special patient populations-Paediatric and adolescents. The safety and effectiveness of IMFINZI have not been established in children and adolescents aged less than 18 years. Elderly (≥65 years)-No dose adjustment is required for elderly patients (≥65 years of age). Renal Impairment-Based on a population pharmacokinetic analysis, no dose adjustment of IMFINZI is recommended in patients with renal impairment. Hepatic Impairment-Based on a population pharmacokinetic analysis, no dose adjustment of IMFINZI is recommended for patients with mild hepatic impairment. IMFINZI has not been studied in patients with moderate or severe hepatic impairment. Fertility, Pregnancy and Lactation. Pregnancy-Durvalumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception during treatment and for at least 3 months after the last dose.Breast-feeding-Because of the potential for adverse reactions in breastfed infants from durvalumab, advise lactating women not to breastfeed during treatment and for at least 3 months after the last dose. Fertility- There are no data on the potential effects of durvalumab on fertility in humans. In repeat-dose toxicology studies with durvalumab in sexually mature cynomolgus monkeys of up to 3 months duration, there were no notable effects on the male and female reproductive organs. Interaction with other medicinal products and other forms of interaction-Durvalumab is an immunoglobulin, therefore no formal pharmacokinetic drug-drug interaction studies have been conducted with durvalumab. PHARMACOLOGICAL PROPERTIES Pharmacodynamic properties-Mechanism of Action. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1) while leaving PD-1/PD-L2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances anti-tumour immune responses. These anti-tumour responses may result in tumour elimination. In preclinical studies, PD-L1 blockade led to increased T-cell activation and decreased tumour size. Pharmacokinetic properties Pharmacokinetic (PK) exposure increased more than dose-proportionally (non-linear PK) at doses <3 mg/kg and dose proportionally (linear PK) at doses ≥ 3 mg/kg. Steady state was achieved at approximately 16 weeks. Based on population PK analysis, the geometric mean steady state volume of distribution (Vss) was 5.64 L. The terminal half-life (t1/2), based on baseline CL, was approximately 18 days. PHARMACEUTICAL PARTICULARS. List of excipients-L-histidine,L-histidine hydrochloride monohydrate,α,α-Trehalose dihydrate,Polysorbate 80,Water for Injection. Incompatibilities-Durvalumab; No incompatibilities between IMFINZI and 9 g/L (0.9%) sodium chloride or 50 g/L (5%) dextrose in polyvinylchloride or polyolefin IV bags have been observed. IMFINZI infusion solution must not be mixed with other drug products. Do not co-administer other drugs through the same intravenous line.Shelf-life-Unopened Vial - 2 years at 2°C–8°C.After preparation of infusion solution- 24 hours at 2°C to 8°C (36°F to 46°F) & 4 hours at room temperature. Nature and contents of container-10 mL of concentrate in a 10 mL Type 1 glass vial with an elastomeric stopper and a white flip-off aluminum seal contains 500 mg durvalumab. Pack size of 1 vial.-2.4 mL of concentrate in a 10 mL Type 1 glass vial with an elastomeric stopper and a gray flip-off aluminum seal contains 120 mg durvalumab. Pack size of 1 vial. Instructions for use, handling and disposal-Preparation of solution-IMFINZI is supplied as a single-dose vial and does not contain any preservatives, aseptic technique must be observed.Visually inspect drug product for particulate matter and discoloration. IMFINZI is clear to opalescent, colorless to slightly yellow solution. Discard the vial if the solution is cloudy, discolored or visible particles are observed. Do not shake the vial. Administration • Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter. For full prescribing information, please contact: AstraZeneca Pharma India Limited; Block N1, 12th Floor; Manyata Embassy Business Park; Rachenahalli, Outer Ring Road; Bangalore – 560045 www.astrazenecaindia.com Based on prescribing information Version 2.0 , dated 13 July 2020