Lung Cancer UPDATES
IASLC HIGHLIGTHS
06-09 AGOSTO 2022
Viena, Austria

Iniciativa científica de:
GECP
lung cancer research

OTROS TUMORES TORÁCICOS
CMP, Mesotelioma, Tumores tímicos

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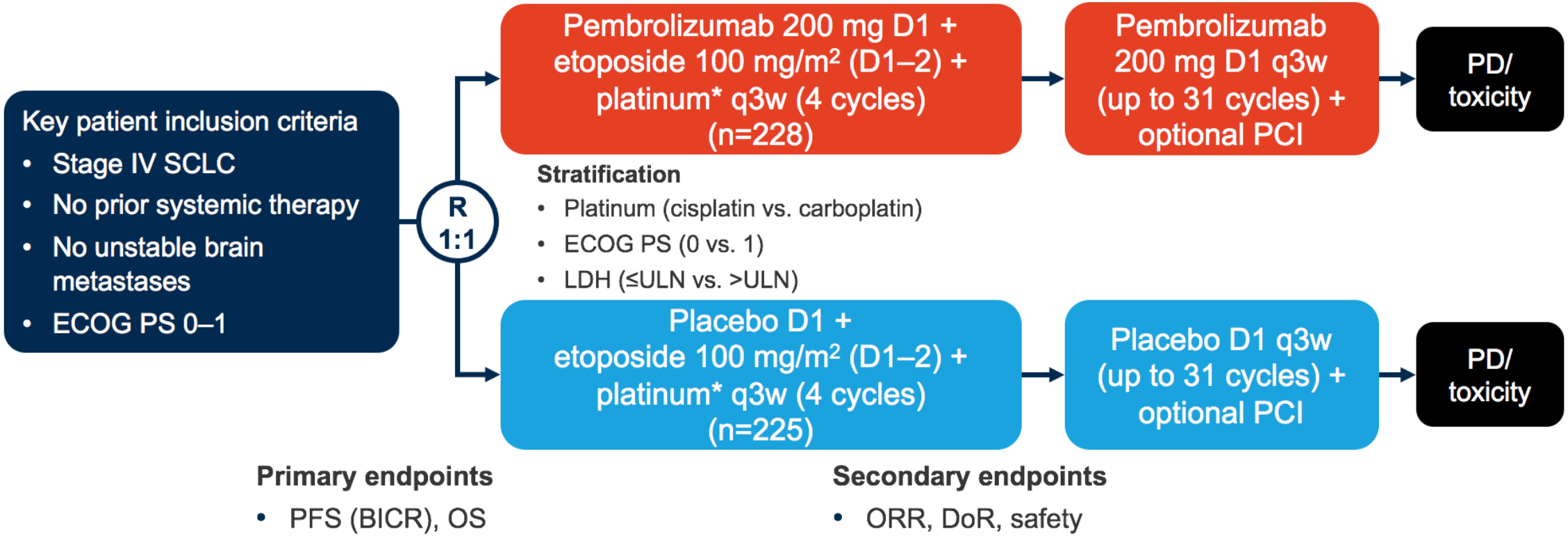
Carcinoma Microcítico Pulmón (CMP)

OA12.06: First-Line Pembrolizumab or Placebo Combined With Etoposide and Platinum for ES-SCLC: KEYNOTE-604 Long-Term Follow-Up Results - Rudin CM, et al

- *Study objective*
  - To evaluate the long-term efficacy and safety of 1L pembrolizumab + etoposide + platinum in patients with extensive-stage SCLC in the KEYNOTE-604 study



*Carboplatin AUC5 D1 or cisplatin 75 mg/m² D1

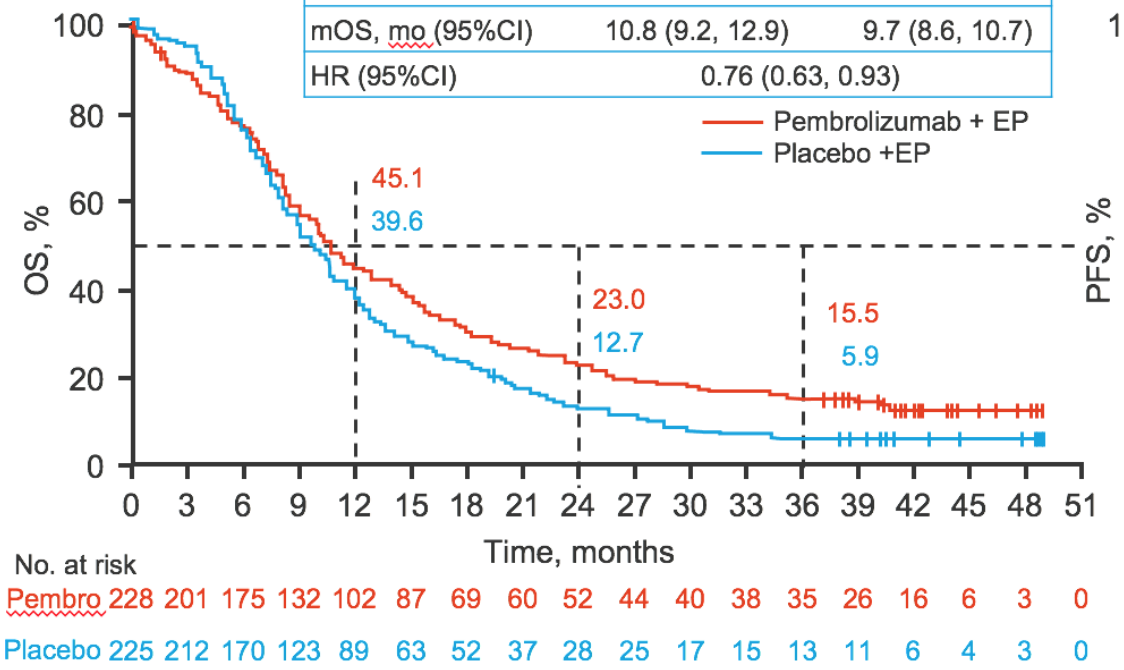
Rudin CM, et al. J Thorac Oncol 2022;17(suppl):Abstr OA12.06

OA12.06: First-Line Pembrolizumab or Placebo Combined With Etoposide and Platinum for ES-SCLC: KEYNOTE-604 Long-Term Follow-Up Results - Rudin CM, et al

Co-primary objectives

Overall survival

	Pembrolizumab + EP (n=228)	Placebo + EP (n=225)
Events, n (%)	197 (86.4)	211 (93.8)
mOS, mo (95%CI)	10.8 (9.2, 12.9)	9.7 (8.6, 10.7)
HR (95%CI)	0.76 (0.63, 0.93)	

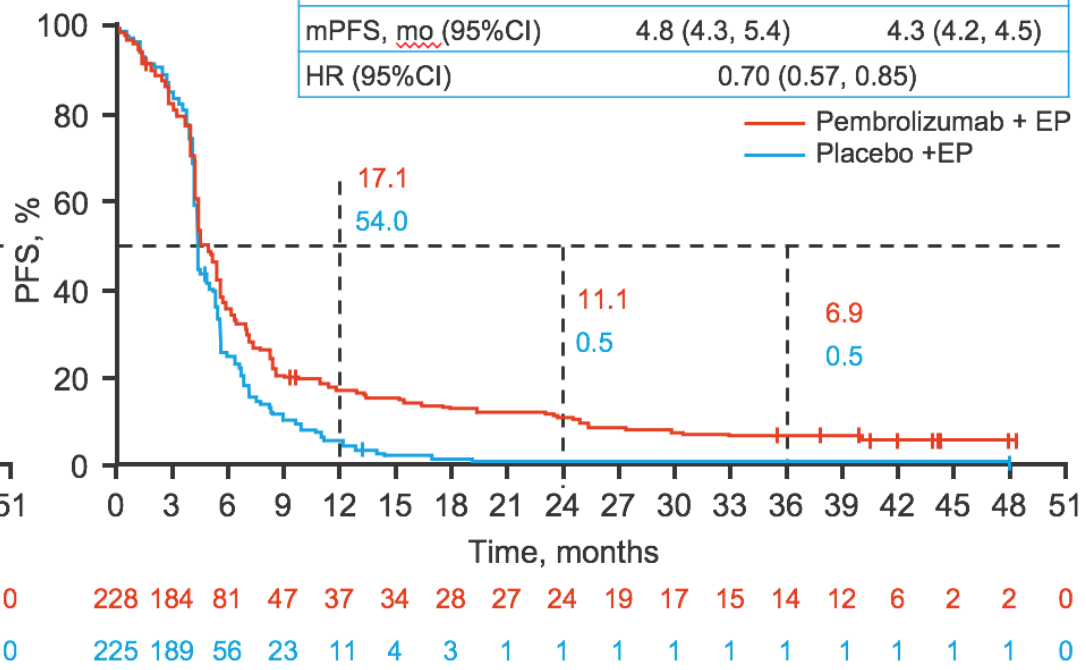


No. at risk

Pembro	228	201	175	132	102	87	69	60	52	44	40	38	35	26	16	6	3	0
Placebo	225	212	170	123	89	63	52	37	28	25	17	15	13	11	6	4	3	0

Progression-free survival

	Pembrolizumab + EP (n=228)	Placebo + EP (n=225)
Events, n (%)	210 (92.1)	221 (98.2)
mPFS, mo (95%CI)	4.8 (4.3, 5.4)	4.3 (4.2, 4.5)
HR (95%CI)	0.70 (0.57, 0.85)	



	228	184	81	47	37	34	28	27	24	19	17	15	14	12	6	2	2	0
	225	189	56	23	11	4	3	1	1	1	1	1	1	1	1	1	1	0

OA12.06: First-Line Pembrolizumab or Placebo Combined With Etoposide and Platinum for ES-SCLC: KEYNOTE-604 Long-Term Follow-Up Results - Rudin CM, et al

Response Rate and DoR

Responses	Pembrolizumab + EP (n=228)	Placebo + EP (n=225)
ORR, % (95%CI)	70.6 (64.2, 76.4)	61.8 (55.1, 68.2)
BOR, n (%)		
CR	2 (2.2)	2 (0.9)
PR	156 (68.4)	137 (60.9)
SD	40 (17.5)	56 (24.9)
PD	8 (3.5)	12 (5.3)
NE	5 (2.6)	5 (2.2)
NA	13 (5.7)	13 (5.8)
mDoR, mo (range)	4.2 (1.0+ to 47.2+)	3.7 (1.4+ to 46.8+)

Summary patients completed 35 cycles

	Completed 35 cycles n = 18
Median OS (95% CI),[c] mo	NR (16.6–NR)
2-year OS rate after completing 35 cycles (95% CI),[d] %	72.2 (39.5–89.2)
ORR (95% CI),[e] %	100.0 (81.5–100.0)
Best overall response,[e] n (%)	
CR	2 (11.1)
PR	16 (88.9)
DOR, median (range),[c,e] mo	NR (14.1 to 46.8+)
DOR ≥12 mo, %	100.0
DOR ≥24 mo, %	83.3

- 14 patients (77.8% of 18 and 6.1% of 228) were alive as of last assessment before data cutoff
- 2/225 (0.9%) patients in the placebo + EP arm completed 35 cycles and were alive as of data cutoff

- **Conclusions**

  - In patients with extensive-stage SCLC, 1L pembrolizumab + etoposide + platinum continued to demonstrate clinically meaningful improvements in survival. Patients who completed 35 cycles of pembrolizumab had durable response and a majority were alive 2 years after completing the treatment (4 years after randomization)

First line chemo-inmunotherapy in SCLC

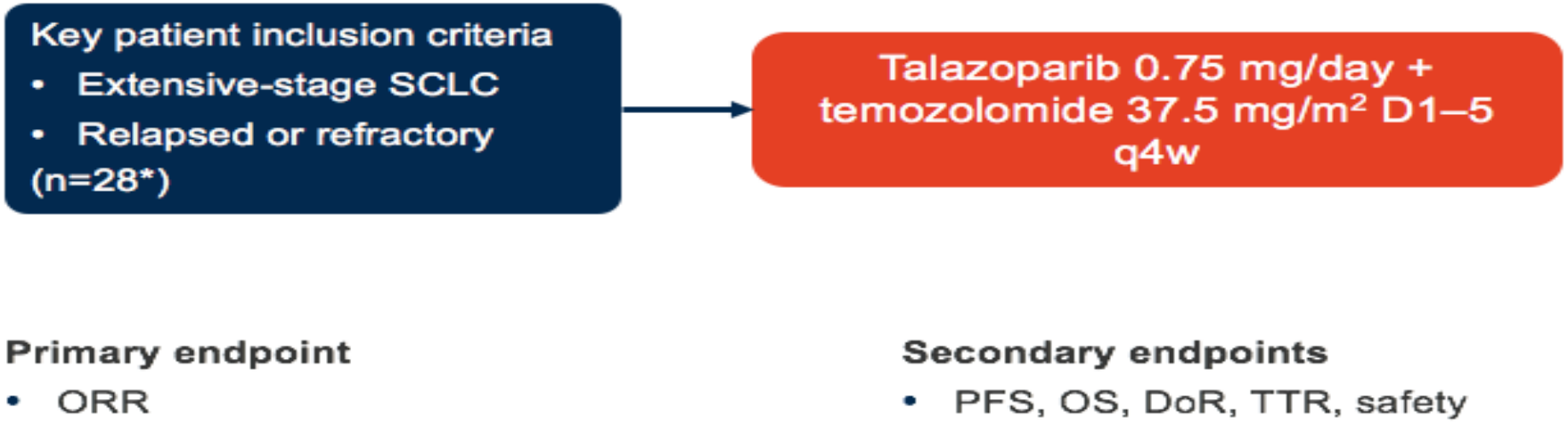
Phase III Trials of Chemotherapy + anti(PD-1/L1) combinations

	Impower133 Atezolizumab (PD-L1)	CASPIAN Durvalumab (PD-L1)	Capstone-1 Adebrelimab (PD-L1)	KN604 Pembrolizumab (PD-1)	ASTRUM-005 Serplulimab (PD-1)
n	403	805	462	453	585
OS Median (Ch-IO / Ch+/-PCB) HR (95% CI) 36-month	12.3 / 10.3 mo 0.76 (0.60-0.95) ND	12.9 / 10.5 mo 0.71 (0.60-0.86) 17.6% / 5.8%	15.3 / 12.8 mo 0.72 (0.58-0.90) ND	**10.8 / 9.7 mo** 0.76 (0.63-0.93) **15.5% / 5.9%**	15.4 / 10.9 mo 0.63 (0.49-0.82) ND
PFS HR (95% CI)	0.77 (0.63-0.95)	0.80 (0.66-0.96)	0.67 (0.54-0.83)	**0.70 (0.57-0.85)**	0.48 (0.38-0.59)
ORR DOR, median	60.2 / 64.4% 4.2 / 3.9 mo	68% / 58% 5.1 / 5.1 mo	70.4 / 65.9% 5.6 / 4.6	70.6% / 61.8% 4.2 / 3.7 mo	80.2 / 70.4 5.6 / 3.2

S.V. Liu, J Clin Oncol 2021 (Impower133), L. Paz-Ares, ESMO Open 2022 & J.W. Goldman, Lancet Oncol 2021 (CASPIAN);
J. Wang, Lancet Oncol 2022; Y. Cheng, ASCO 2022 Abstract 8505 (ASTRUM-005)

OA12.03: Phase 2 Study Analysis of Talazoparib (TALA) Plus Temozolomide (TMZ) for Extensive-Stage Small Cell Lung Cancer (ES-SCLC) - Goldman J, et al

- **Study objective**
  - To evaluate the efficacy and safety of talazoparib + temozolomide in patients with extensive-stage SCLC



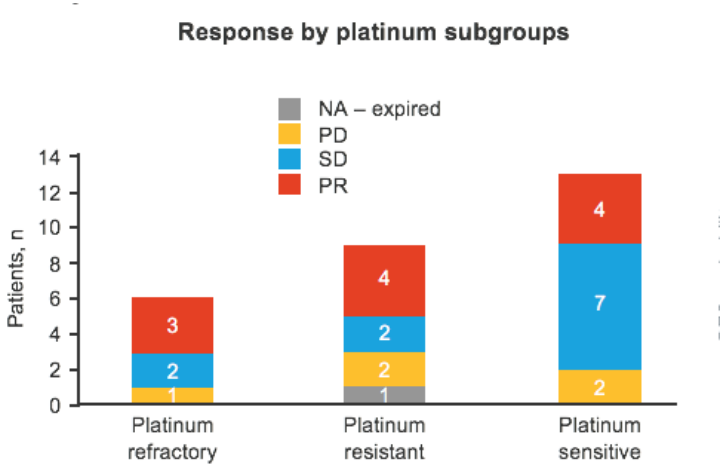
*15 patients were initially enrolled and 13 additional patients added as ORR ≥3/15

Goldman J, et al. J Thorac Oncol 2022;17(suppl):Abstr OA12.03

OA12.03: Phase 2 Study Analysis of Talazoparib (TALA) Plus Temozolomide (TMZ) for Extensive-Stage Small Cell Lung Cancer (ES-SCLC) - Goldman J, et al

Response Rate and AEs

Response	Talazoparib + temozolomide (n=28)
PR, n (%)	11 (39.3)
mTTR, mo	1.8
mDoR, mo	4.3
mPFS, mo	4.3
mOS, mo	11.9



Grade 3–4 AEs, %	Talazoparib + temozolomide (n=28)
Platelet count decreased	60.7
Anemia	53.6
Neutrophil count decreased	32.1
WBC count decreased	17.9
Atypical pneumonia	3.6

- **Conclusions**
  - In patients with extensive-stage SCLC, talazoparib + temozolomide demonstrated promising clinical activity with significtive hematological toxicity

Refractory or Relapsed SCLC

Second-line PARPi-Temozolomide combinations

	Topotecan	Talazoparib + TMZ **37.5 mg/m² D1-5 28-day cycles**	Olaparib + TMZ 75 mg/m² D1-7 21-day cycles	Veliparib or PCB +TMZ 150-200 mg/m² D1-5 28-day cycles
n	444 All 2nd line, refractory 52%	28 **2nd line 93%** 3rd line 3%	50 2nd line 46%, 3rd line 34%, 4+ 20%	104 2nd line 67%, 3rd line 33% Refractory 59%
ORR All Plat-refractory Plat-resistant Plat-sensitive	21% ND ND ND	11/28 (**39.3%**) **3/6** **4/9** 4/13	41.7% 28.6% 47.1%	39%/14% 37%/15% 41%/11%
Median DOR	4.9 mo	4.3 mo	4.3 mo	4.6/3.7 mo
Median PFS	4.3 mo	4.3 mo	4.2 mo	3.8/2
Median OS	8.6 mo	**11.9 mo**	8.5 mo	8.2/7

Blackhall F, J Thorac Oncol 2021; Farago, Cancer Discovery 2019 (olaparib); Pietanza, J Clin Oncol 2018 (veliparib)

Refractory or Relapsed SCLC

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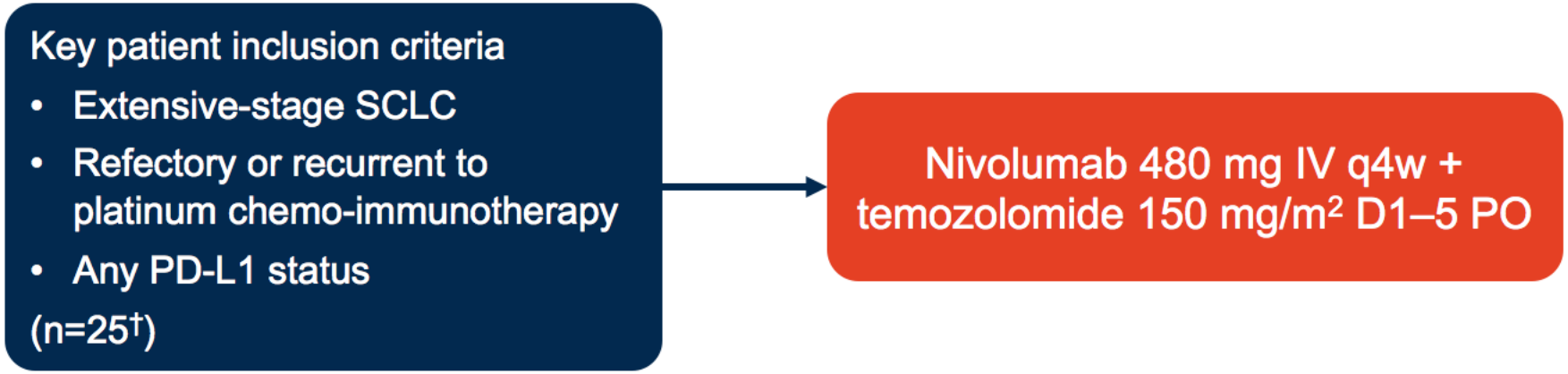
n	**AEs**		**Grade 3/4**	104 2nd line 67%, 3rd line 33% Refractory 59%
	Anemia		53.6%	
	Neutrophil count decreased		32.1%	
	Platelet count decreased		60.7%	
ORR All				39%/14%
Plat-refractory	ND	**4/9**	28.6%	37%/15%
Plat-resistant	ND	4/13	47.1%	41%/11%
Median DOR	4.9 mo	4.3 mo	4.3 mo	4.6/3.7 mo
Median PFS	4.3 mo	4.3 mo	4.2 mo	3.8/2
Median OS	8.6 mo	**11.9 mo**	8.5 mo	8.2/7

Blackhall F, J Thorac Oncol 2021; Farago, Cancer Discovery 2019 (olaparib); Pietanza, J Clin Oncol 2018 (veliparib)

OA12.04: Efficacy of Nivolumab and Temozolomide in Extensive Stage Small Cell Lung Cancer after Chemo-Immunotherapy: A Phase 2 Trial - Owen DH, et al

- **Study objective**
  - To evaluate the efficacy and safety of nivolumab + temozolomide in a cohort of patients with extensive-stage SCLC*



Primary endpoint

- ORR (RECIST v1.1)

Secondary endpoints

- PFS, OS, safety

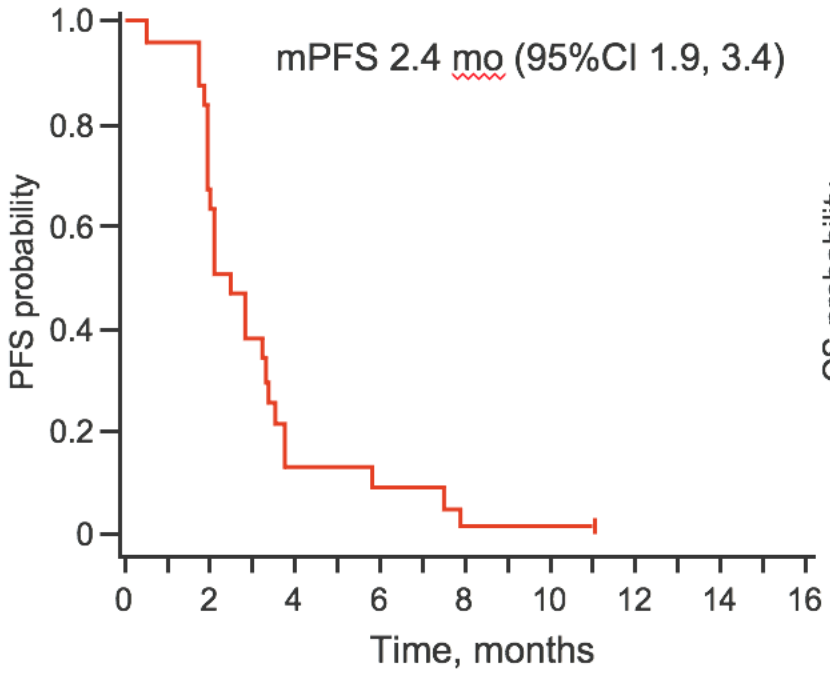
*A second cohort of patients with metastatic neuroendocrine carcinoma was also assessed;
†15 patients were initially enrolled and a total of 25 patients enrolled if ≥2 responses were observed

Owen DH, et al. J Thorac Oncol 2022;17(suppl):Abstr OA12.04

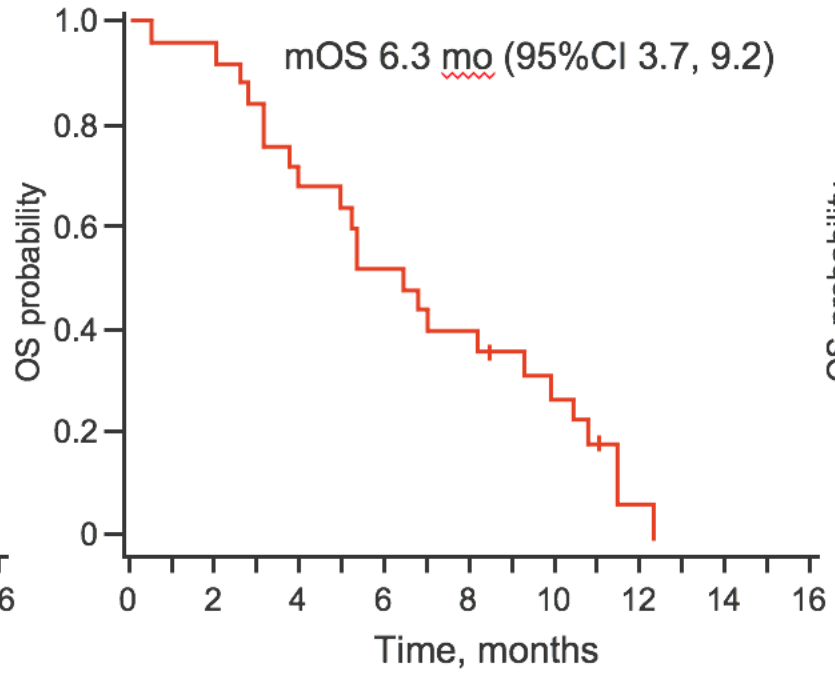
OA12.04: Efficacy of Nivolumab and Temozolomide in Extensive Stage Small Cell Lung Cancer after Chemo-Immunotherapy: A Phase 2 Trial - Owen DH, et al

Results

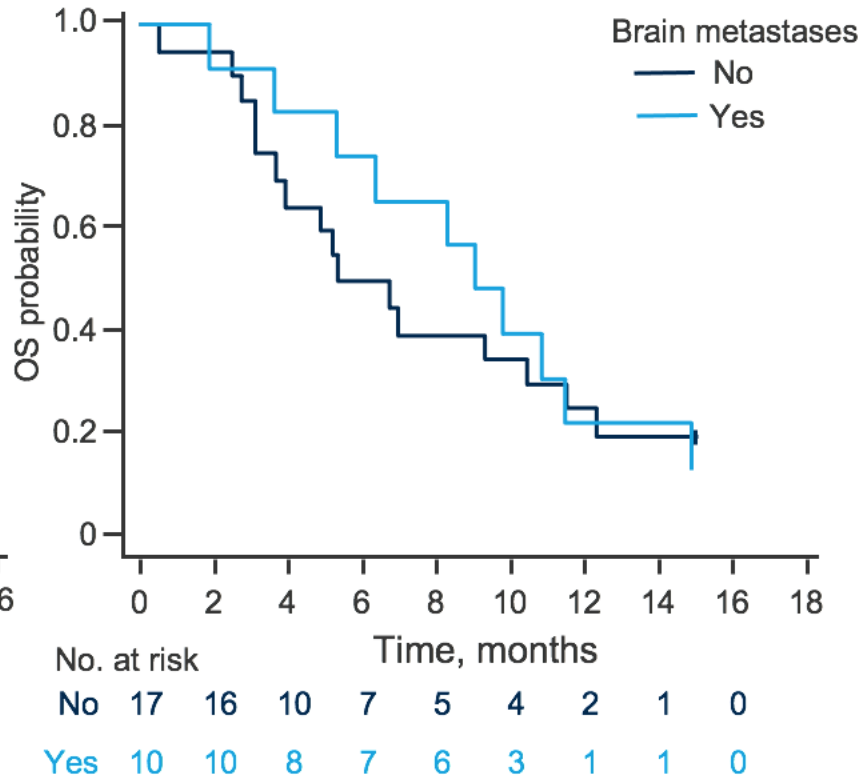
Progression-free survival



Overall survival



Overall survival according to brain metastases



OA12.04: Efficacy of Nivolumab and Temozolomide in Extensive Stage Small Cell Lung Cancer after Chemo-Immunotherapy: A Phase 2 Trial - Owen DH, et al

Response Rate and AEs

Response Rate

		ORR	95% CI	p-value
All patients		7/25 (28%)	12% - 49%	
Platinum resistant	Y	0/10 (0 %)	0 – 31%	0.057
	N	7/15 (47%)	21 – 73%	
Brain metastases	Y	2/10 (20%)	3% - 56%	0.659
	N	5/15 (33%)	12% - 62%	

Grade ≥3 TRAEs, n (%)	Nivolumab + temozolomide (n=28)
Any	19 (70)
Lymphocyte count decreased	10 (37)
Fatigue	5 (19)
Platelet count decreased	3 (11)
Anemia	2 (7)
Vomiting	2 (7)
Generalized muscle weakness	2 (7)
Nausea	1 (4)
Diarrhea	1 (4)
Anorexia	1 (4)
Constipation	1 (4)

- **Conclusions**
  - In patients with extensive-stage SCLC, nivolumab + temozolomide demonstrated clinical activity particularly in those with platinum-sensitive disease with manageable toxicity

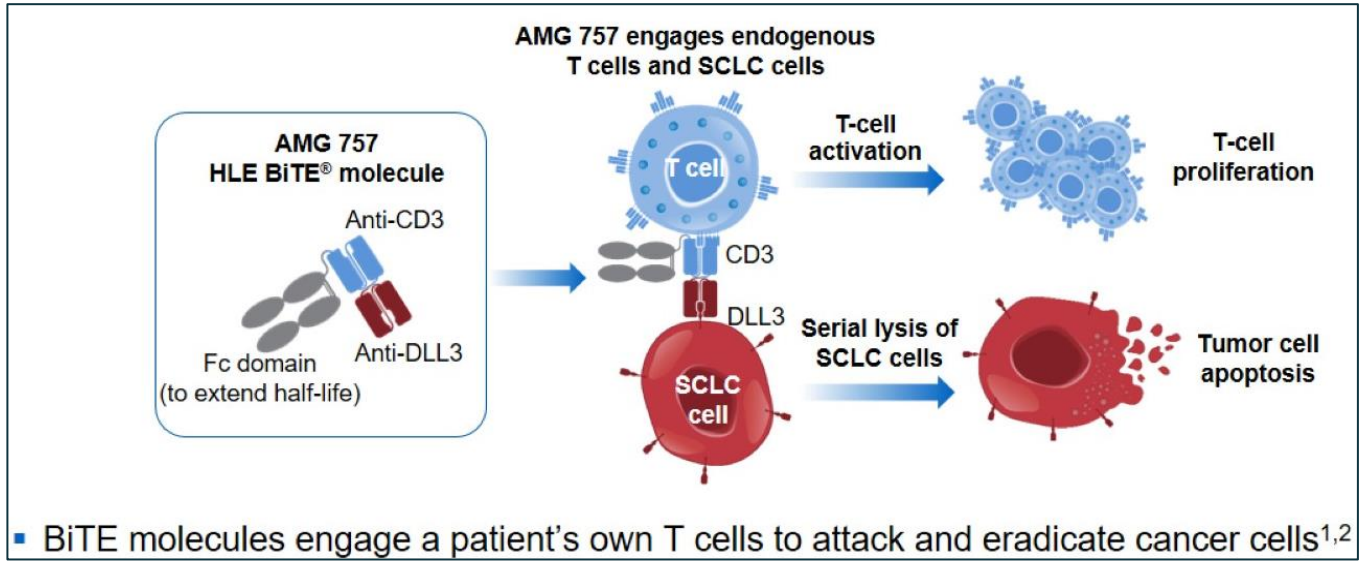
Refractory or Relapsed SCLC

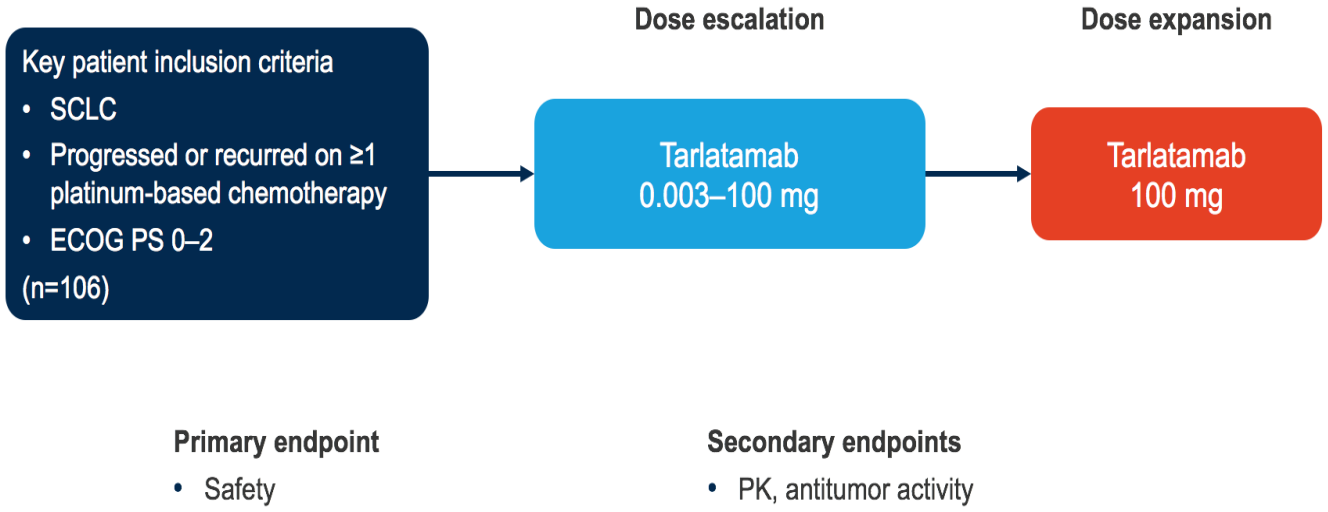
Second-line Nivolumab-TMZ after chemo-immunotherapy

	Topotecan or amrubicin CM331	Nivolumab CM331	Nivolumab + TMZ 150 mg/m^2 D1-5 28-day cycles
N Plat sensitive 2nd/3rd line/4+	285 56.1% All 2nd line	284 57.4% All 2nd line	25 59% 3rd line 75%
ORR All Plat-refractory Plat-resistant Plat-sensitive	16.5%	13.7%	7/25 (**28%**) 0 7/15 (47%)
Median DOR	4.5 mo	8.3 mo	ND
Median PFS	3.8	1.4	2.4
Median OS	8.4	7.5	6.3

Spigel DR, Ann Oncol 2021

OA12.05: Phase 1 Updated Exploration and First Expansion Data for DLL3-targeted T-cell Engager Tarlatamab in Small Cell Lung Cancer - Borghaei H, et al



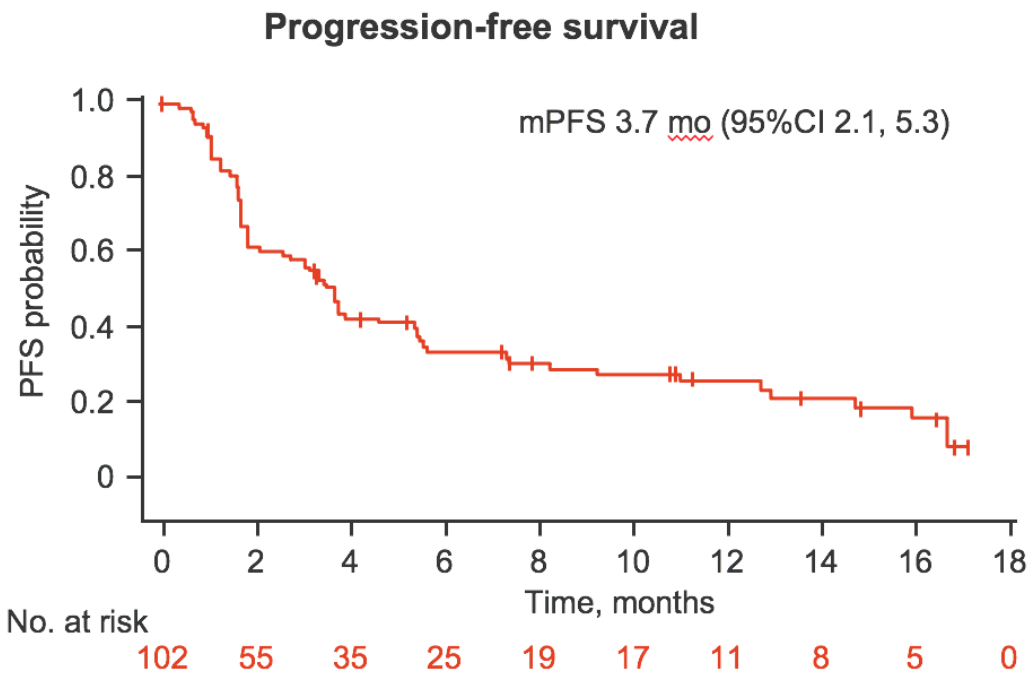


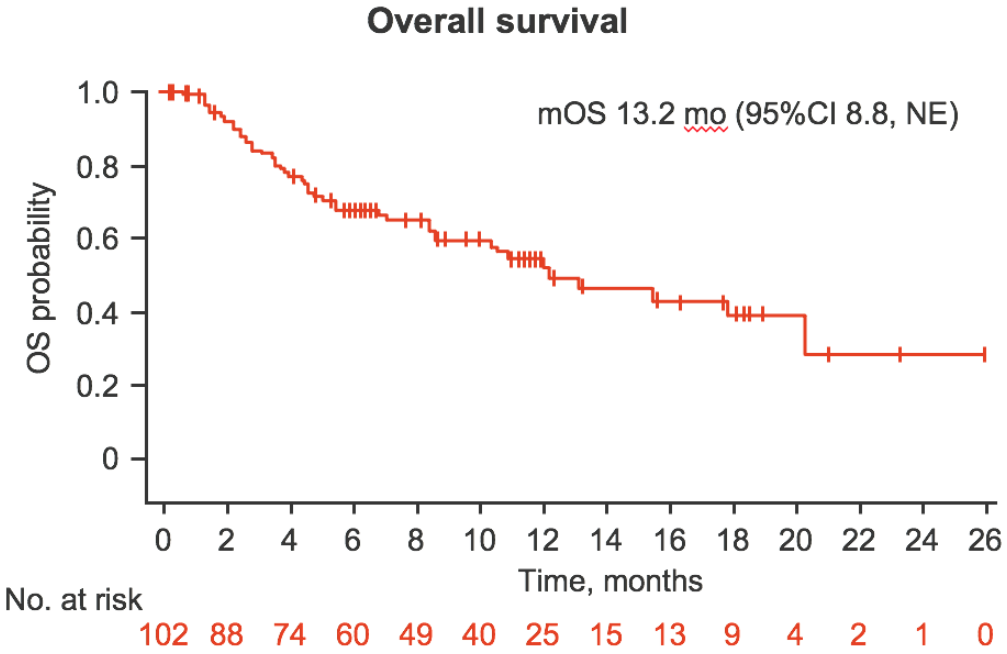
Prior lines of therapy, n (%)	
1	30 (28)
2	44 (42)
≥ 3	32 (30)
Median (range)	2 (1–6)
Prior anti-PD-(L)1 treatment, n (%)	52 (49)

Borghaei H, et al. J Thorac Oncol 2022;17(suppl):Abstr OA12.05

OA12.05: Phase 1 Updated Exploration and First Expansion Data for DLL3-targeted T-cell Engager Tarlatamab in Small Cell Lung Cancer - Borghaei H, et al

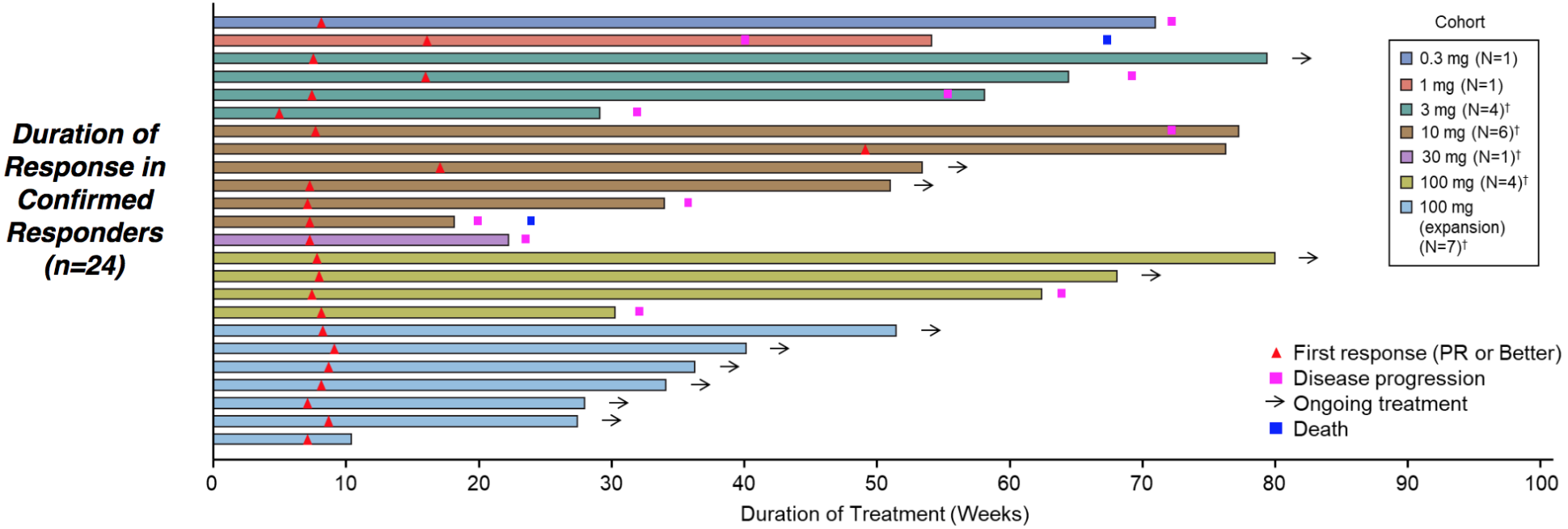
PFS and OS





OA12.05: Phase 1 Updated Exploration and First Expansion Data for DLL3-targeted T-cell Engager Tarlatamab in Small Cell Lung Cancer - Borghaei H, et al

Tarlatamab Delivers Durable Responses in Previously Treated SCLC



- **Median duration of response was <u>13.0 months</u> (95% CI: 6.2, 14.9)***
  - 11 responders had treatment ongoing as of data cutoff, including 2 complete responders
  - Median time to response was 1.8 months (range: 1.2–7.4)

Bar graph includes all patients with confirmed response (n = 24), with each bar representing 1 patient. *The interim time to event analysis set used in the duration of response analysis includes subjects whose data cut-off date is at least 6 months after first dose date (N=23). † Indicates step dosing with 1 mg run-in dose.

OA12.05: Phase 1 Updated Exploration and First Expansion Data for DLL3-targeted T-cell Engager Tarlatamab in Small Cell Lung Cancer - Borghaei H, et al

Confirmed responses, n (%)	Tarlatamab (n=105)
ORR	24 (23)
BOR	
CR	2 (2)
PR	22 (21)
SD	31 (3)
PD	8 (8)
NE	35 (33)
NA	7 (7)
DCR	55 (52)

Grade ≥3 TRAEs, n (%)	Tarlatamab (n=106)
Any	33 (31)
Led to discontinuation	4 (4)
Cytokine release syndrome	1 (1)
Pyrexia	2 (2)
Fatigue	3 (3)
AESI	
Neurologic events	7 (7)
Neutropenia	10 (9)

- **Conclusions**
  - In previously treated patients with SCLC, tarlatamab demonstrated encouraging antitumor activity with a manageable safety profile

MA01.04: Molecular Subtypes of Surgically Resected Small Cell Lung Cancer: Expression Pattern and Prognostic Relevance - Megyesfalvi Z, et al

Study objective

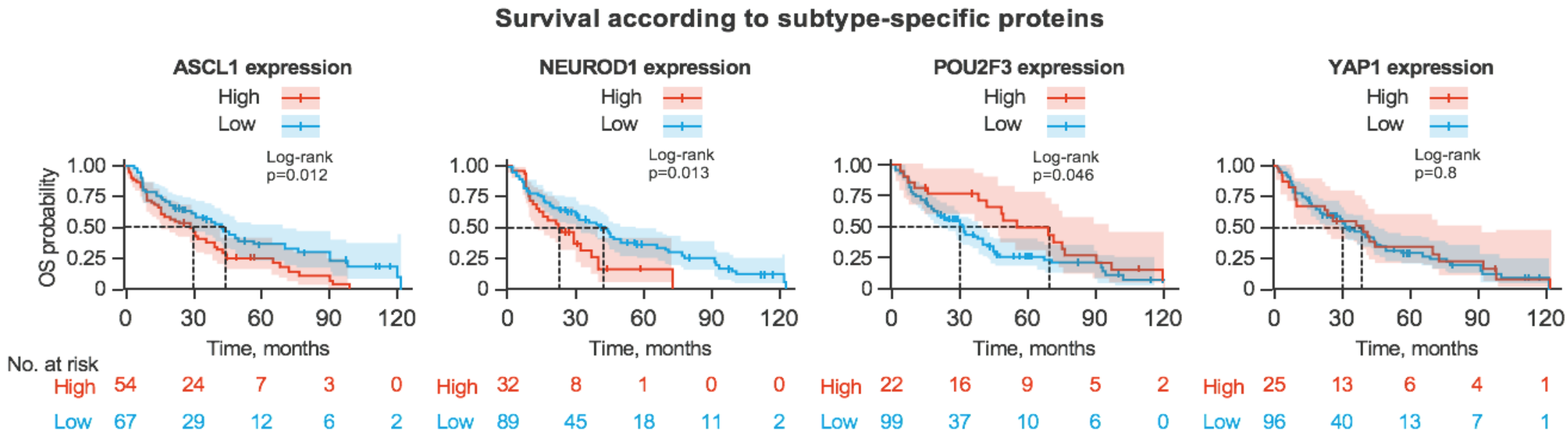
- To evaluate the molecular subtypes of surgically resected SCLC and their impact on survival

Methods

- IHC analysis was performed on 386 surgically resected SCLC samples to determine expression of subtype-specific transcription factors as well as P53 and RB1 proteins

Megyesfalvi Z, et al. J Thorac Oncol 2022;17(suppl):Abstr MA01.04

MA01.04: Molecular Subtypes of Surgically Resected Small Cell Lung Cancer: Expression Pattern and Prognostic Relevance - Megyesfalvi Z, et al



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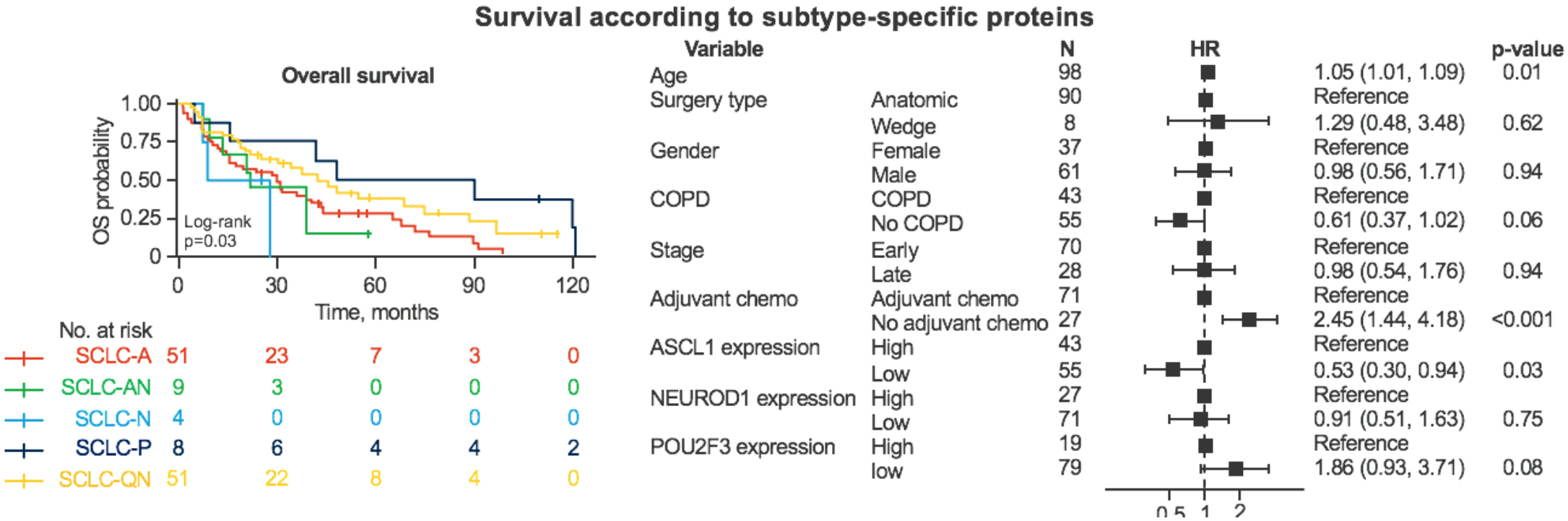

- **Conclusions**
  - In patients with SCLC, differential expression of ASCL1, NEUROD1 and POU2F3 can distinguish different subtypes with high POU2F3 expression being associated with better survival outcomes and ASCL1 and NEUROD1 expression being associated with poorer survival outcomes

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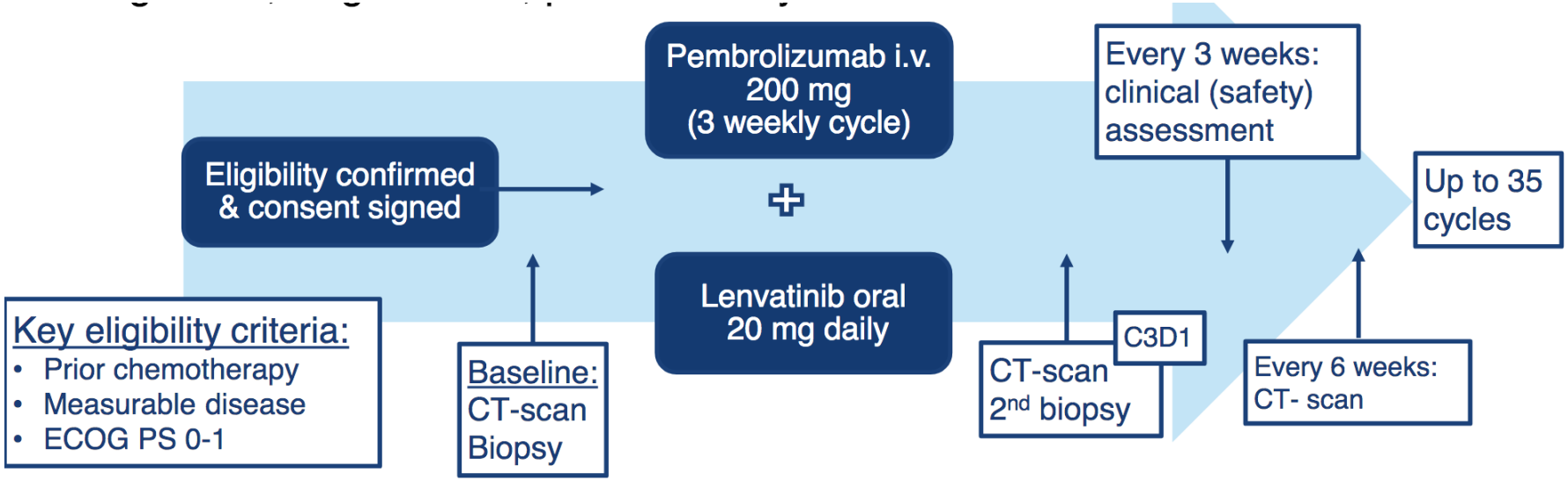
Mesotelioma

OA04.06: PEMbrolizumab Plus Lenvatinib In Second And Third Line Malignant Pleural MEsotheLiomA Patients: A Single Arm Phase II Study (PEMMELA)

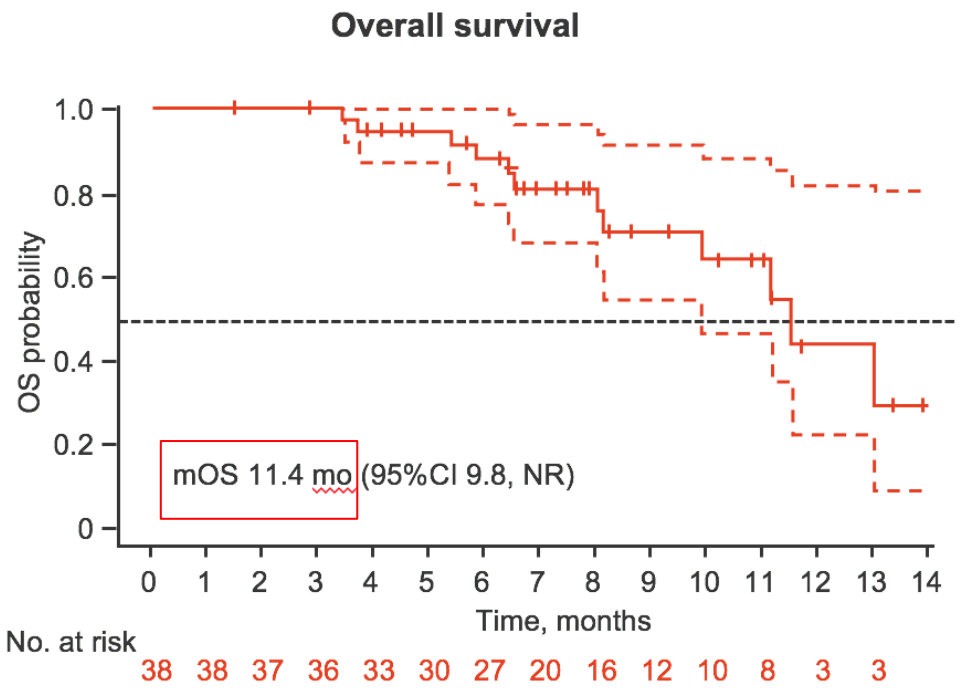


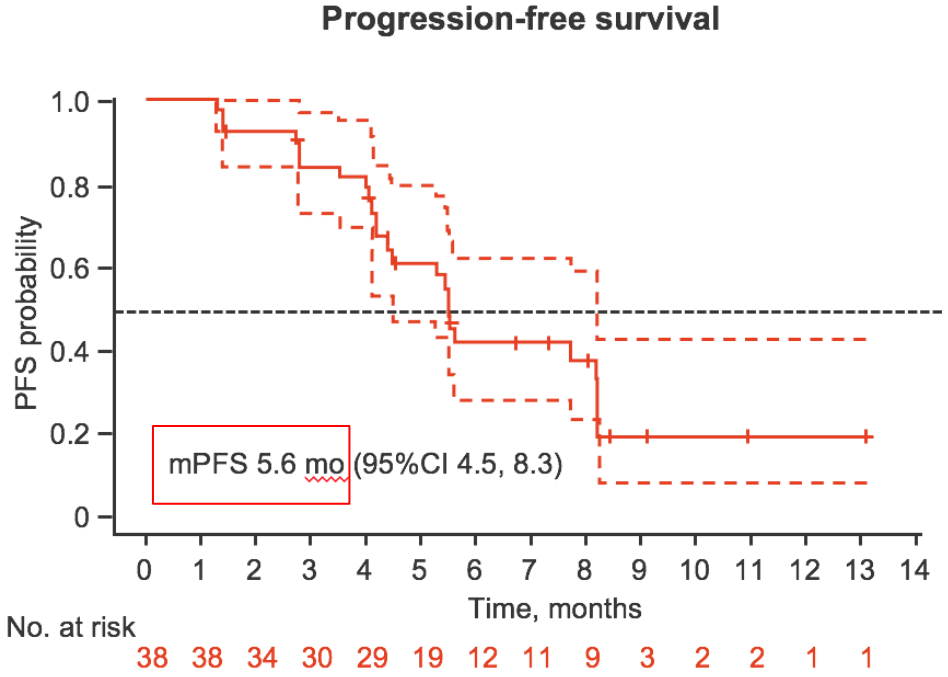
Primary endpoint
- ORR assessed by local investigator (mRECIST)

Secondary endpoints
- ORR (independent central review)
- PFS, OS
- Toxicity

Douma L-A, et al. J Thorac Oncol 2022;17(suppl):Abstr OA04.06

OA04.06: PEMbrolizumab Plus Lenvatinib In Second And Third Line Malignant Pleural MEsotheLiomA Patients: A Single Arm Phase II Study (PEMMELA)





OA04.06: PEMbrolizumab Plus Lenvatinib In Second And Third Line Malignant Pleural MEsotheLiomA Patients: A Single Arm Phase II Study (PEMMELA)

Response Rate and TRAEs

	Pembrolizumab + lenvatinib (n=38)	
Response	**Investigator assessed**	**ICR**
ORR, % (95%CI)	58 (41, 74)	42 (26, 59)
BOR, n (%)		
CR	0	0
PR	22 (58)	16 (42)
SD	16 (42)	22 (58)
PD	0	0

	Pembrolizumab + lenvatinib (n=38)		
TRAEs	**Grade 1–2**	**Grade 3**	**Grade 4**
Fatigue	21	0	0
Hoarseness	21	0	0
Anorexia	13	3	0
Diarrhea	13	2	0
Hypertension	5	8	0
ALT/AST increased	5	2	0
Stroke	0	2	0
Myositis	0	0	2

- **Conclusions**
  - In patients with recurrent malignant pleural mesothelioma, pembrolizumab + lenvatinib demonstrated encouraging clinical activity with a high ORR (58%) and remarkable but manageable safety profile with dose reductions of 76%

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Tumores tímicos

MA10.09: Outcomes of Induction Therapy Followed by Surgical Resection for Advanced Thymic Tumor - Shin S, et al

Study objective

- To evaluate the efficacy and safety of induction therapy before surgical resection in patients with advanced thymic epithelial tumours

Endpoints

- Clinicopathologic, surgical and oncologic outcomes

Induction treatment

Chemotherapy	**65 (93)**
CCRT	**3 (4)**

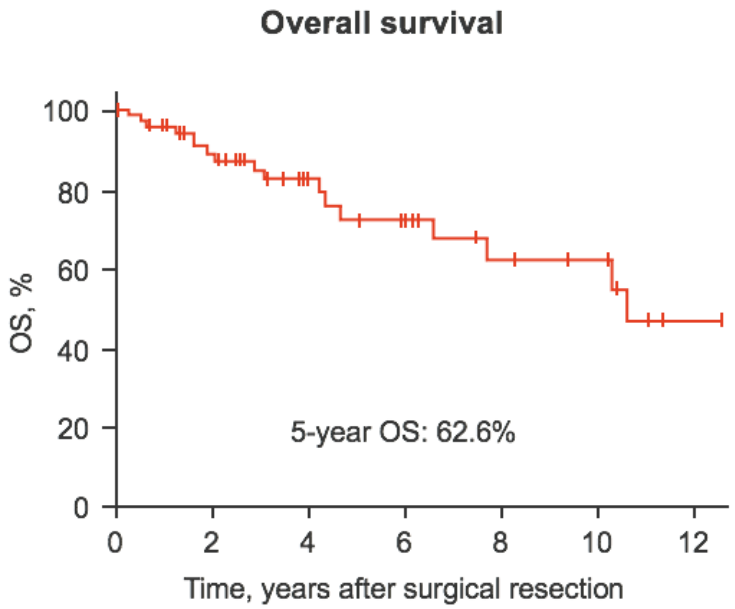
m/c regimen : CAP (n=24)

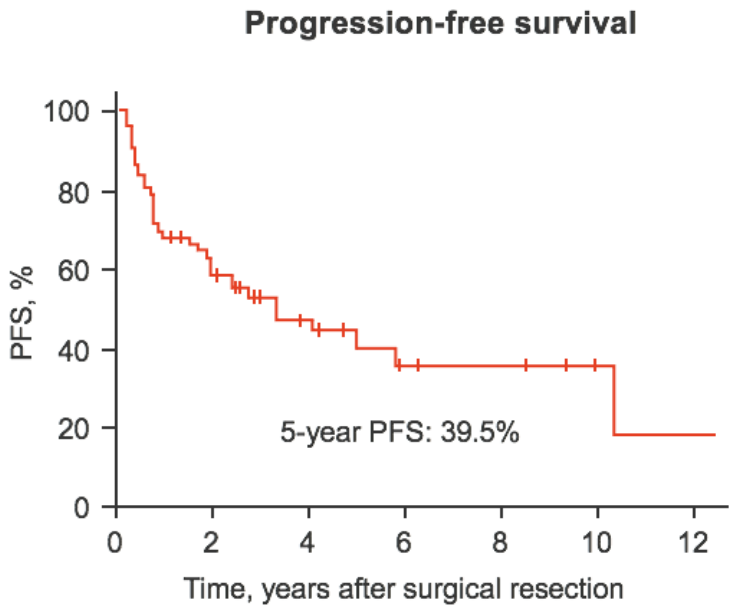
DP + pembrolizumb (n=5)
(MK3475-971 trial)

*Included chemotherapy, chemotherapy with concurrent chemoradiotherapy, capecitabine or pembrolizumab + docetaxel

Shin S, et al. J Thorac Oncol 2022;17(suppl):Abstr MA10.09

MA10.09: Outcomes of Induction Therapy Followed by Surgical Resection for Advanced Thymic Tumor - Shin S, et al





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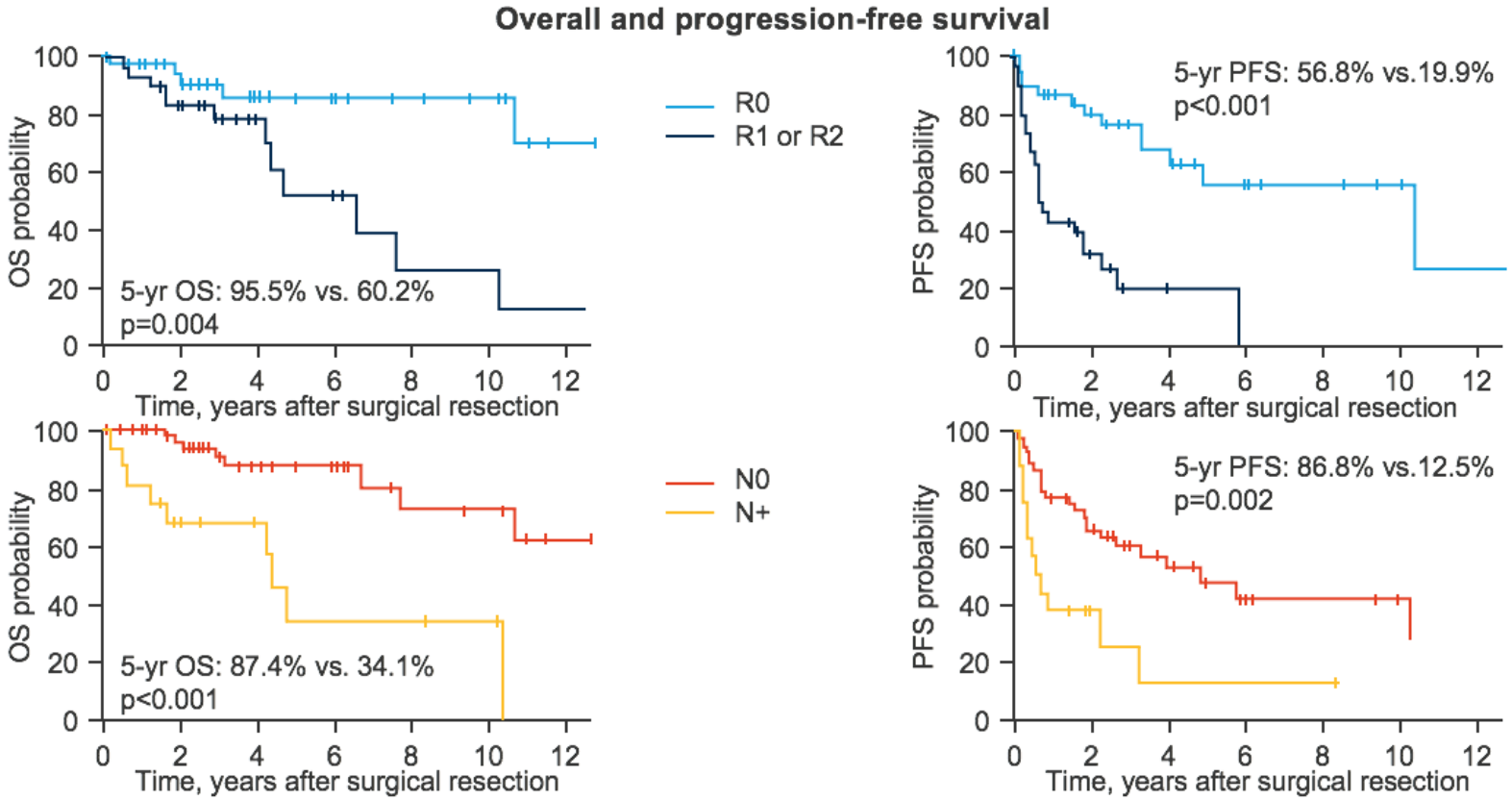


MA10.09: Outcomes of Induction Therapy Followed by Surgical Resection for Advanced Thymic Tumor - Shin S, et al

Response, n (%)	Induction therapy
PR	44 (60)
SD	16 (23)
PD	5 (7)
Unknown	1 (1)

Surgical approaches, n (%)	
Sternotomy	57 (81)
Thoracotomy	7 (10)
VATS	4 (6)
Sternotomy + thoracotomy	2 (3)

Risk factors for survival, n (%)	OS Adjusted* HR (95%CI)	PFS Adjusted* HR (95%CI)
R0 resection	2.744 (0.855, 8.811)	**4.283 (1.892, 9.693)**
Node positive	**5.680 (1.791, 18.014)**	**2.280 (1.045, 4.975)**

Surgical outcomes, n (%)	
R0 resection	39 (56)

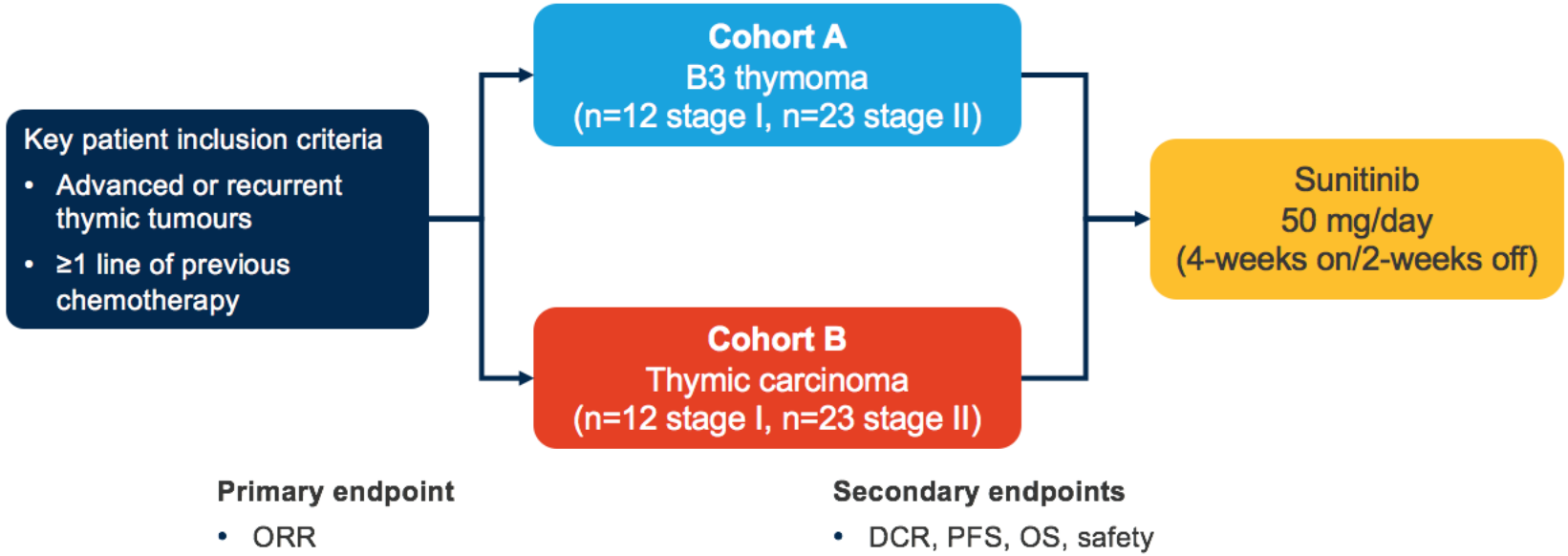
Conclusions

- In patients with advanced thymic epithelial tumours, induction therapy prior to surgery demonstrated favourable long-term survival with completeness of resection and nodal metastasis being significant prognostic factors

MA10.07: Phase II Trial of Sunitinib in Patients with Type B3 Thymoma or Thymic Carcinoma in Second and Further Lines - STYLE Trial (NCT03449173) - Proto C, et al

Study objective

– To evaluate the efficacy and safety of ≥2L sunitinib in patients with type B3 thymoma or thymic carcinoma in the STYLE study



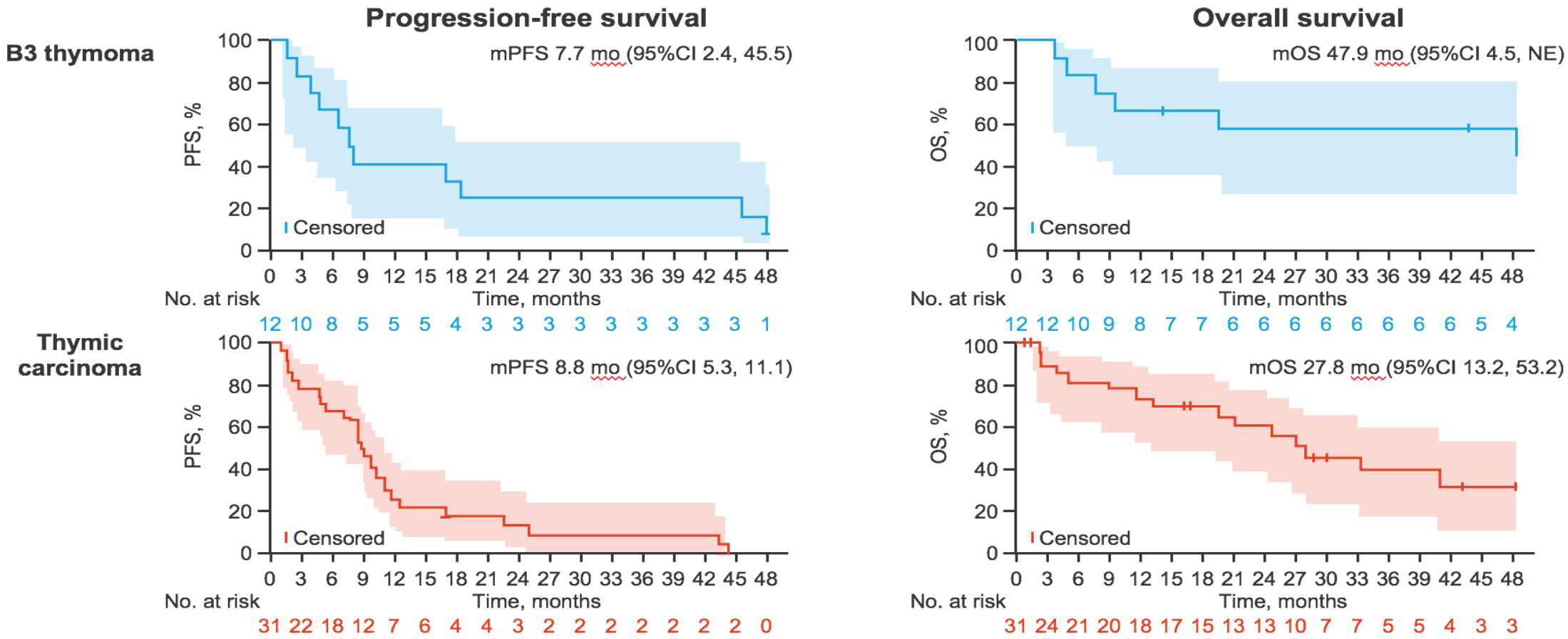
Proto C, et al. J Thorac Oncol 2022;17(suppl):Abstr MA10.07

MA10.07: Phase II Trial of Sunitinib in Patients with Type B3 Thymoma or Thymic Carcinoma in Second and Further Lines - STYLE Trial (NCT03449173) - Proto C, et al

Responses	B3 thymoma (n=12) Interim analysis	Thymic carcinoma (n=23) Efficacy analysis	Thymic carcinoma (n=31) ITT analysis
ORR, n (%) [95%CI]	0 [0, 26.5]	5 (21.7) [7.5, 43.7]	6 (21.4) [8.3, 41.0]
BOR, n (%)			
CR	0	1 (4.3)	1 (3.6)
PR	0	4 (17.4)	5 (17.9)
SD	11 (91.7)	15 (65.2)	19 (67.9)
PD	1 (8.3)	3 (13.0)	3 (10.7)
NE	0	0	3 (9.7)
DCR, n (%) [95%CI]	11 (91.7) [61.5, 99.8]	20 (87.0) [66.4, 97.2]	25 (89.3) [71.8, 97.7]

- **Conclusions**
  - In previously treated patients with thymic carcinoma, sunitinib demonstrated clinical activity but accrual in the B3 thymoma cohort was stopped owing to futility

MA10.07: Phase II Trial of Sunitinib in Patients with Type B3 Thymoma or Thymic Carcinoma in Second and Further Lines - STYLE Trial (NCT03449173) - Proto C, et al



Sunitinib for Thymoma and Thymic carcinoma

	Thymic carcinoma (n=23)		Thymoma (n=16)	
	Patients (%)	95% CI	Patients (%)	95% CI
Objective response*	6 (26%)	10·2–48·4†	1 (6%)	0·2–30·2
Stable disease	15 (65%)	42·7–83·6	12 (75%)	47·6–92·7
Progressive disease	2 (9%)	1·1–28·0	3 (19%)	4·1–45·7
Disease control	21 (91%)	72·0–98·9	13 (81%)	54·4–96·0

A. Thomas Lancet Oncol 2015

Resumen

- El tratamiento estándar de primera línea del CMP-EE continua siendo la combinación de platino-etoposido + anti PD1/L1, todos los estudios muestran un beneficio de esta estrategia.

- La mayoría de los pacientes que completan 35 ciclos de pembrolizumab están vivos a los 2 años de completar el tratamiento (4 años tras la randomización).

- En segundas líneas y sucesivas:
  - Talazoparib + temozolamida ha mostrado una alta eficacia con una toxicidad hematológica importante
  - Nivolumab + temozolamida ha mostrado eficacia fundamentalmente en pacientes sensibles
  - Tarlatamab muestra resultados prometedores con 21% RR, DoR 13 meses con toxicidad muy manejable

- Falta de biomarcadores para mejorar los resultados: Esperanza en el diseño de estudios basados en subtipos moleculares

- Mesotelioma: en segunda y tercera línea la combinación pembrolizumab + levantinib muestra resuestas muy altas con toxicidad hematológica importante

- Tumores tímicos:
  - El tratamiento de inducción previo a la cirugía consigue largos suoervivientes, la resección R0 y NO son factores pronóstico muy importantes
  - En pacientes pretratados sunitinib ha mostrado eficacia en carcinoma tímico y futilidad en timomas B3

MUCHAS GRACIAS