IO Combinations In First Line NSCLC: Exploring New Treatment Avenues

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Unmet Need

≈80% of lung cancer patients are diagnosed with metastatic (stage IV) NSCLC and the 5-year survival rate prior to treatment of this stage is 6.3%[1]

Clinical outcomes remain poor in first-line advanced/metastatic NSCLC and disease progresses an average of 4-6 months after discontinuing chemotherapy

There have been **marked improvements in care with the introduction of IO based treatments**.[2]

Several Phase I, II, and III **trials have demonstrated efficacy and safety of IO + chemotherapy** in stage IV NSCLC.[4]

NSCLC = non-small cell lung cancer; IO = immuno-oncology.

1. Cancer Stat Facts: Lung and Bronchus Cancer. https://seer.cancer.gov/statfacts/html/lungb.html. 2. Sculier JP et al. *Eur Respir J.* 2009; 33:915–930. 3. Study NCT03164616. ClinicalTrials.gov website. 4. Pabani A et al. *Curr Oncol*. 2018; 25(suppl 1):S94–S102.

Rationale for Immunotherapy and Chemotherapy Combination

Chemotherapy provides rapid disease control in mNSCLC

- Four cycles of chemotherapy provide rapid and strong disease control in patients with advanced NSCLC; long-term evidence to support fewer than four chemotherapy cycles is currently lacking.[1]

- Chemotherapy causes cancer cell death and reduces tumor burden, which releases antigens that can prime an immune response; the subsequent immune response requires the presence and activation of T-cells that recognize these neoantigens.[2–4]

Both anti-CTLA-4 and anti-PD-L1 antibodies compliment chemotherapy

- Anti-CTLA-4 and anti-PD-L1 antibodies promote effective anti-tumor T-cell responses that can persist, even in the absence of continued therapy; this can complement the short-term control of tumor growth achieved by chemotherapy and lead to prolonged survival benefit.[5-7]

- PD-L1 blockade primarily strengthens pre-existing anti-tumor T-cell responses,[5,8,9] which in a subset of patients leads to prolonged survival benefit.[9] CTLA-4 blockade primarily promotes new anti-tumor T-cell responses, which can be further strengthened by PD-L1 blockade.[8,9] Combining CTLA-4 and PD-L1 blockade therefore increases the proportion of patients with active anti-tumor T-cell responses and long-term benefit.[11-13]

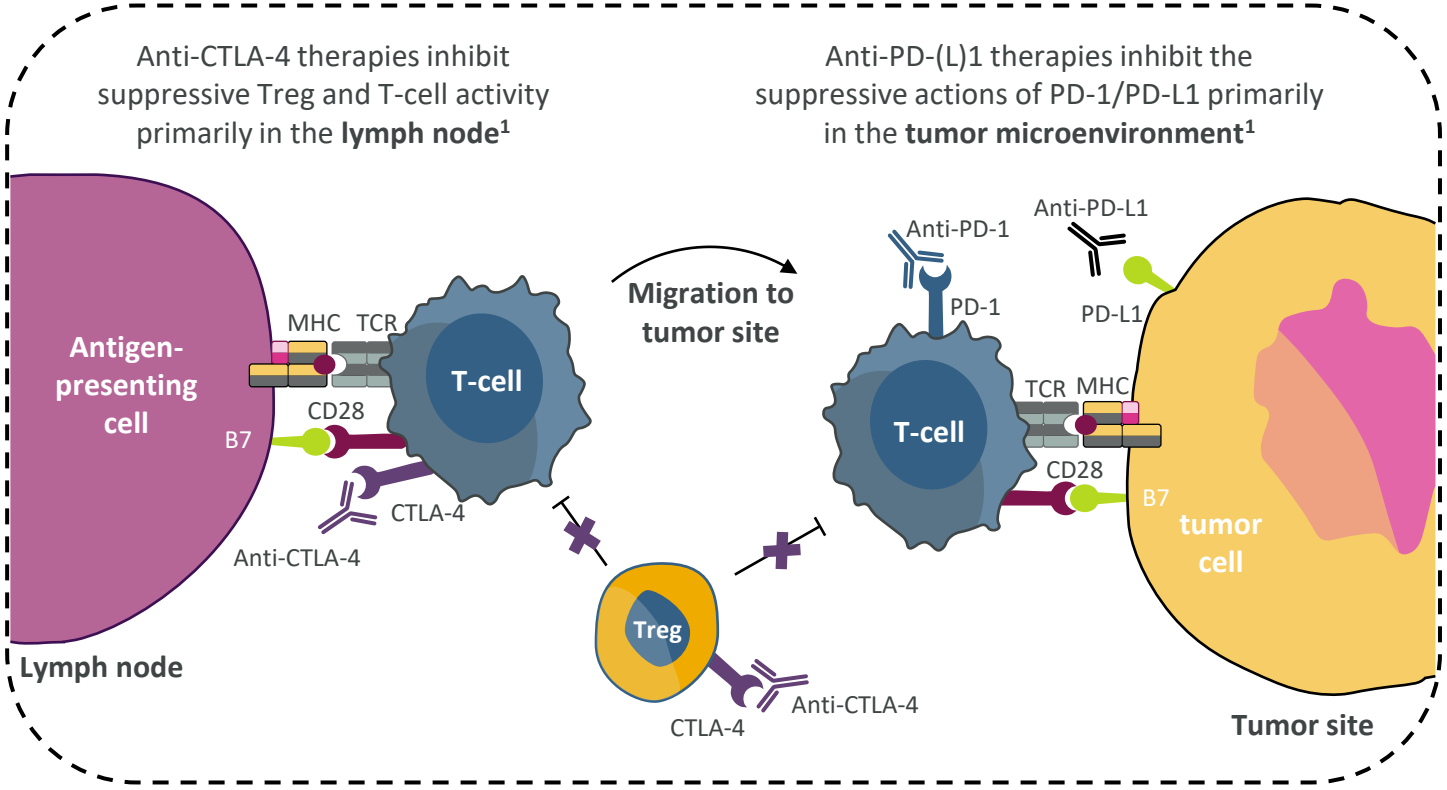
- Preclinical data show that anti-CTLA-4 and chemotherapy potentiates the induction of a potent anti-tumor immune response, with an important role for both CD4+ and CD8+ T-cells for optimal therapeutic effect; this anti-tumor effect was only observed when both drugs were given concomitantly.[14]

CD = cluster of differentiation; CTLA-4 = cytotoxic T lymphocyte-associated antigen-4; mNSCLC = metastatic non-small cell lung cancer; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand-1.

1. Rossi A et l. *Lancet Oncol* 2014;15:1254-62. 2. Emens LA et al. *Front Biosci* 2008;13:249–57. 3. Gulley JL et al. *J Natl Cancer Inst* 2017;109:djw261. 4. Apetoh L et al. *Nat Med* 2007;13:1050–9. 5. Buchbinder EI et al. *Am J Clin Oncol* 2016;39:98–106. 6. Sharma P et al. *Science* 2015;348:56–61. 7. Boutros C et al. *Nat Rev Clin Oncol* 2016;13:473–86. 8. Sharma P et al. *Nat Rev Immunol* 2020;20:75–6. 9. Wei SC et al. *Cell* 2017;170:1120–33. 10. Spigel DR et al. *J Clin Oncol* 2021;39:8511. 11. Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021. 12. Kelley RK et al. *J Clin Oncol* 2021;39:2991–3001. 13. Powles T et al. *Lancet Oncol* 2020;21:1574–88. 14. Lesterhuis WJ et al. *PLoS One* 2013;8:e61895.

Anti-CTLA-4 and anti-PD-L1 together

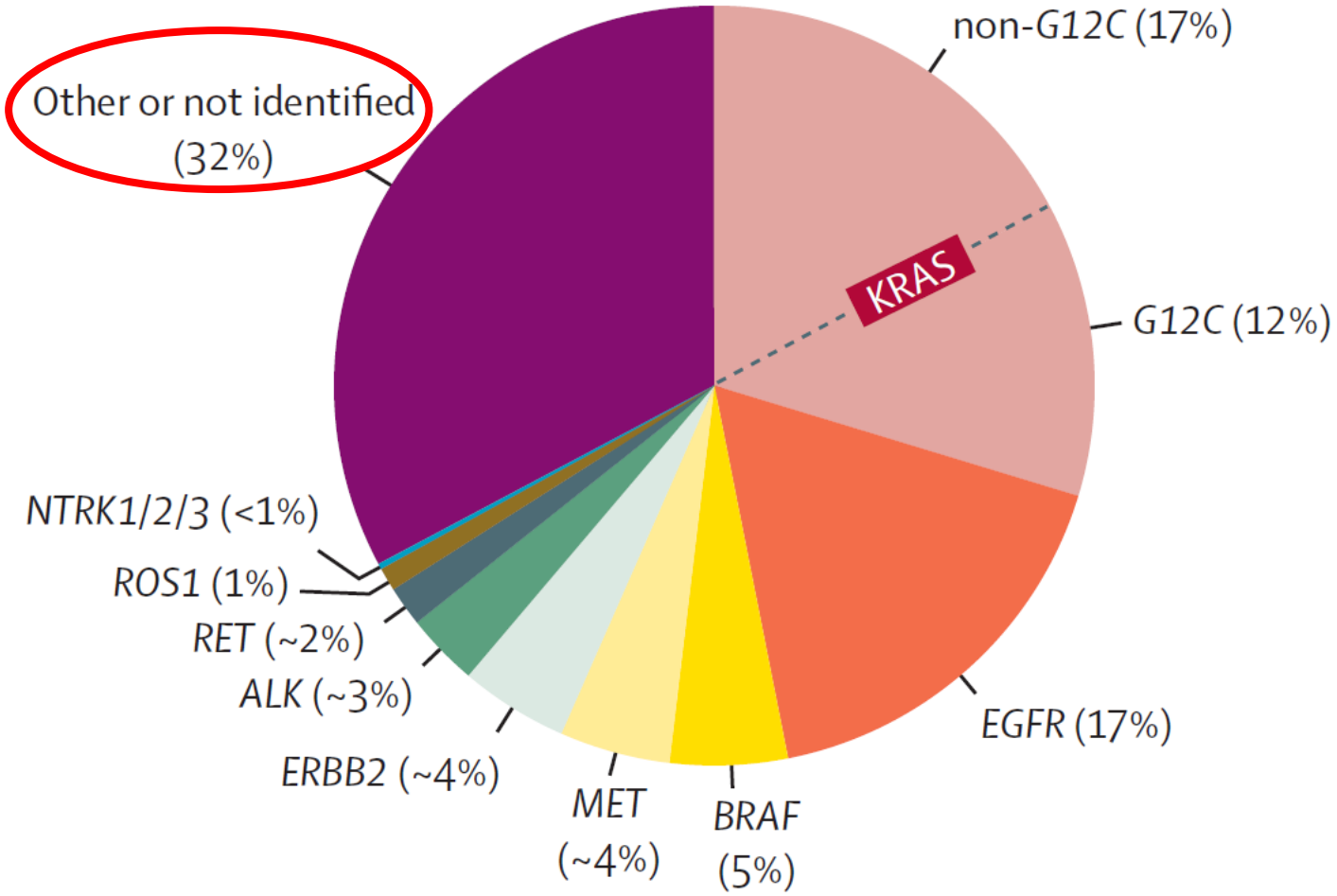
- **Targeting PD-L1 and CTLA-4**, respectively, to simultaneously block multiple pathways that act to limit T-cell activation and effector function[1]
- Anti-CTLA-4 and anti-PD-L1 antibodies promote ***effective anti-tumor T-cell responses*** that can persist, **even in the absence of continued therapy**; this can complement the short-term control of tumor growth achieved by chemotherapy and lead to prolonged survival benefit[1–3]



CTLA-4 = cytotoxic T lymphocyte-associated antigen-4; MHC = major histocompatibility complex; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1; TCR = T-cell receptor.

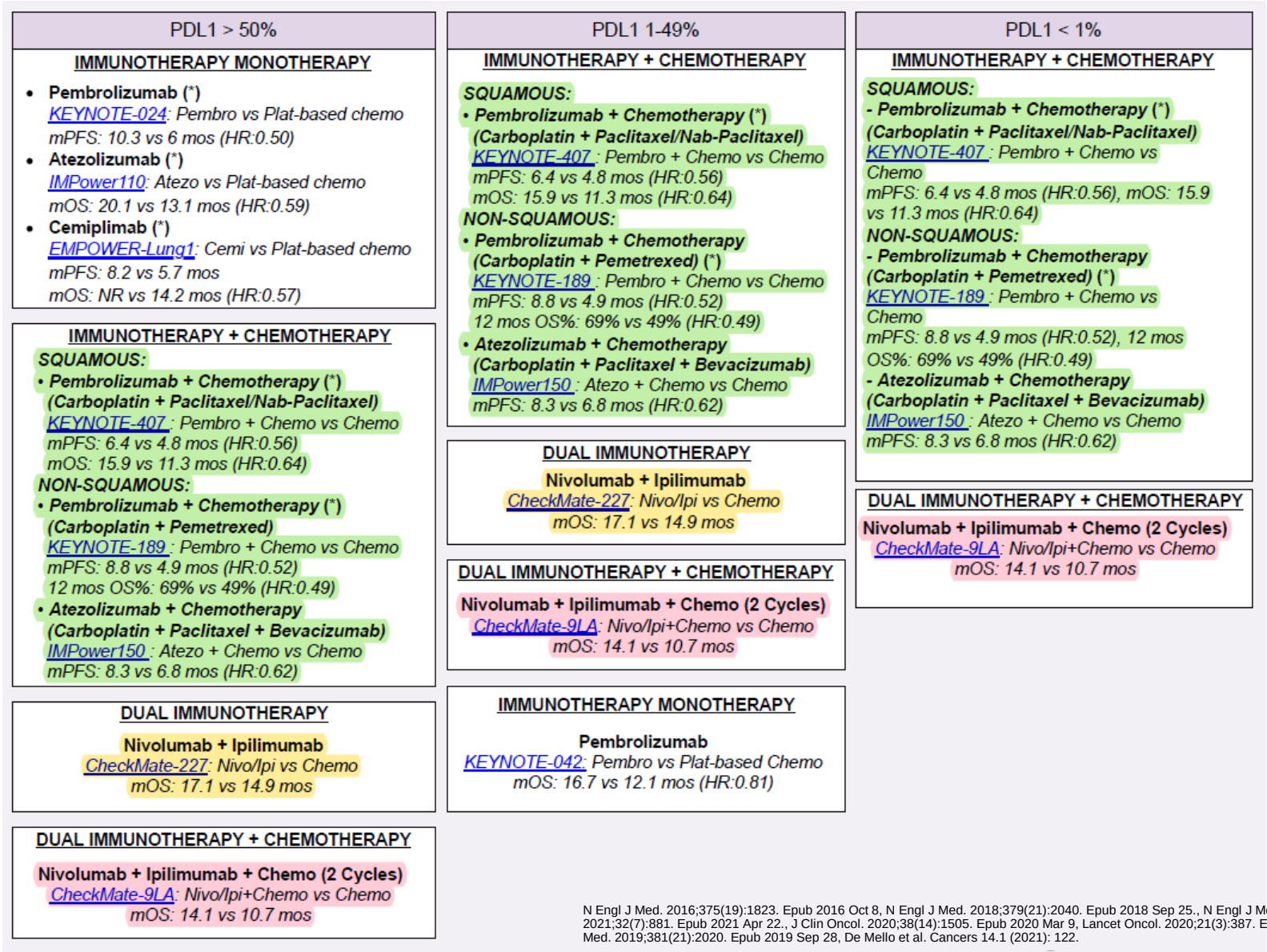
1. Buchbinder EI et al. *Am J Clin Oncol* 2016;39:98–106. 2. Sharma P et al. *Science* 2015;348:56–61. 3. Boutros C et al. *Nat Rev Clin Oncol* 2016;13:473–86.

NSCLC lacking a driver mutation



Lancet 2021; 398: 535–54

Management of advanced NSCLC lacking a driver mutation



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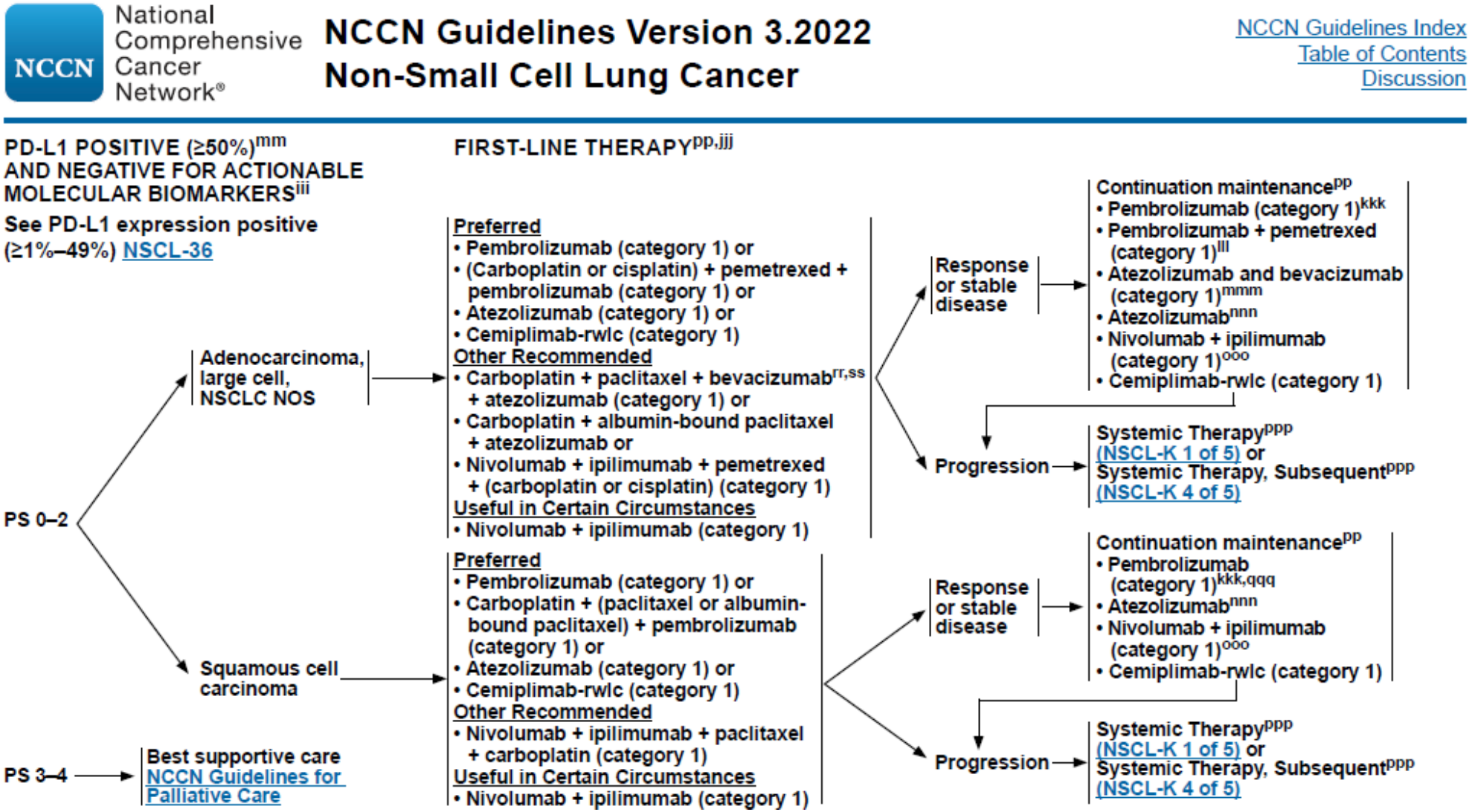
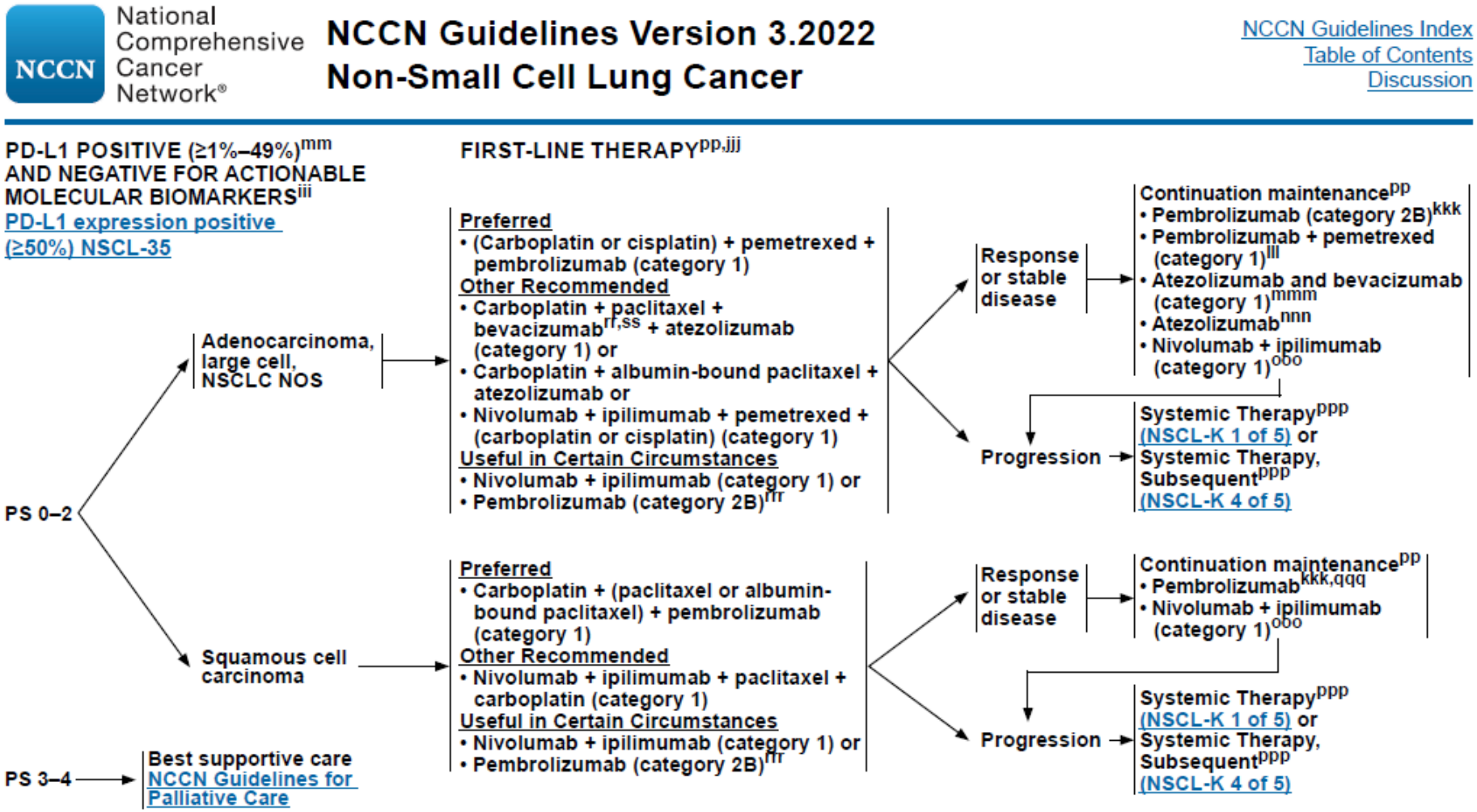
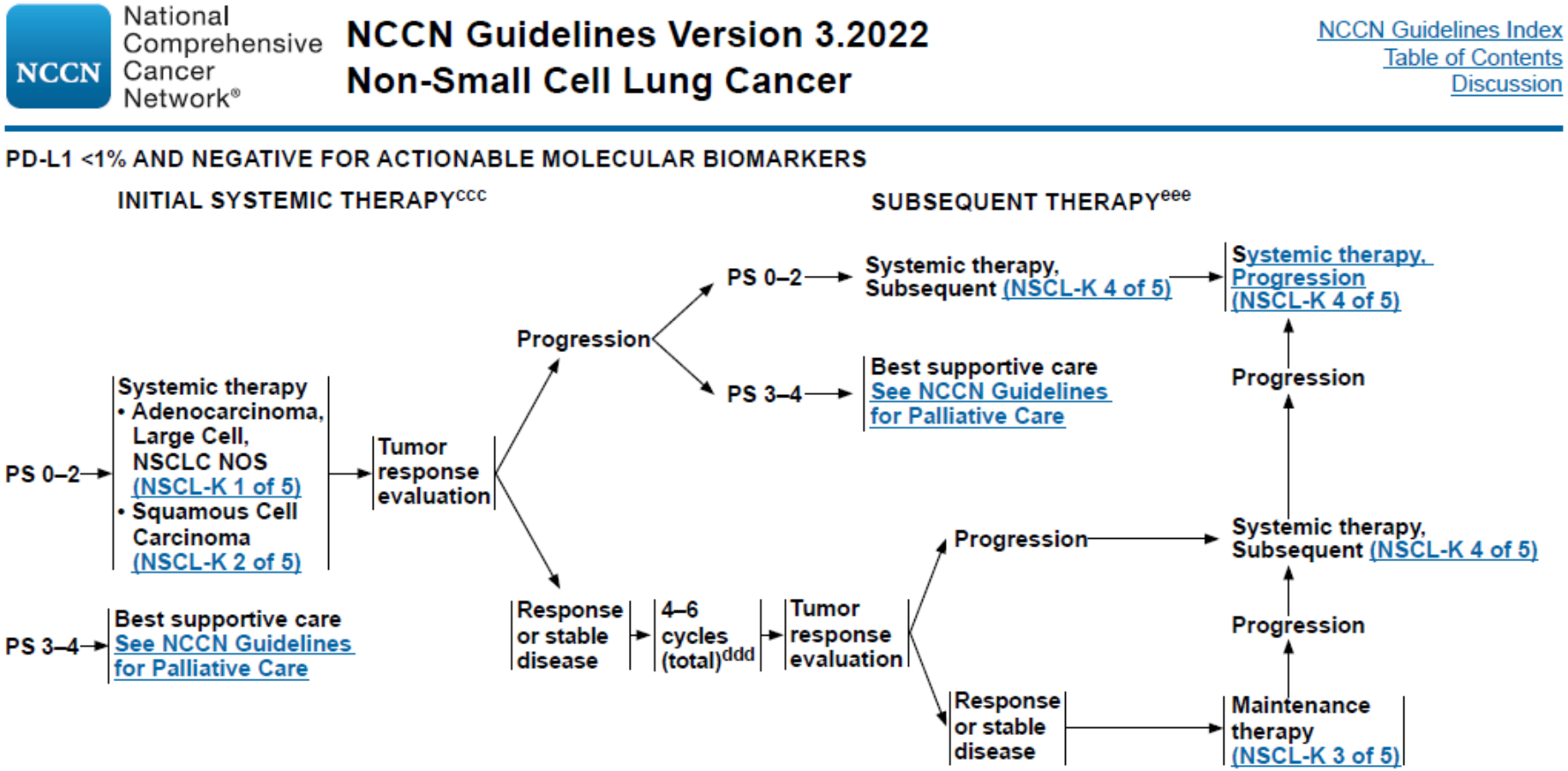
NCCN Guidelines: NSCLC negative for actionable markers (PD-L1≥50%)



NCCN Guidelines: NSCLC negative for actionable markers (PD-L1≥1%-49%)



NCCN Guidelines: NSCLC negative for actionable markers (PD-L1≤1%)



POSEIDON: Study Design[1,2]

Phase III, randomized, open-label, multicenter, global study

First-line treatment of patients with metastatic NSCLC that lack activating EGFR mutations and ALK fusions

N=1013

R 1:1:1

Stratification factors:
- PD-L1 expression (TC ≥50% vs <50%)[e]
- Disease stage (IVA vs IVB)
- Histology (non-squamous vs squamous)

	Maintenance phase
Durvalumab 1500 mg IV Q3W + Tremelimumab 75 mg IV Q3W + Chemotherapy[a] (4 cycles)	**Durvalumab 1500 mg IV Q4W** until disease progression **+ Tremelimumab 75 mg IV (Week 16 only)[b] + Pemetrexed[c]** until disease progression
Durvalumab 1500 mg IV Q3W + Chemotherapy[a] Q3W (4 cycles)	**Durvalumab 1500 mg IV Q4W + Pemetrexed[c]** until disease progression
Platinum-based chemotherapy[a] Q3W (up to 6 cycles)	**Pemetrexed[c]** until disease progression

Primary endpoints

- PFS (BICR)[d] and OS in D+CT vs CT

Secondary endpoints

- PFS (BICR)[d] and OS in D+T+CT vs CT
- OS in patients with bTMB ≥20 mut/Mb (D+T+CT vs CT)
- Objective response rate[d]
- Duration of response[d]
- PFS at 12 months
- Best objective response[d]
- HRQoL
- Safety and tolerability

[a]Includes nab-paclitaxel + carboplatin for squamous and non-squamous patients, gemcitabine + cisplatin/carboplatin for squamous patients only, and pemetrexed + carboplatin/cisplatin for non-squamous patients only; [b]Patients received an additional dose of tremelimumab post chemotherapy (5th dose); [c]Pemetrexed maintenance was allowed in all arms in patients with non-squamous disease who initially received pemetrexed during first-line treatment only (if eligible); **[d]Assessed using Blinded Independent Central Review (BICR) per RECIST version 1.1.** [e]PD-L1 expression status (defined by the Ventana SP263 PD-L1 IHC assay)
Disclaimer: Tremelimumab is not available/approved in India

1. Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021. 2. Study NCT03164616. ClinicalTrials.gov website.

POSEIDON: Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥18 years	Mixed small cell lung cancer and NSCLC histology, sarcomatoid variant
Histologically or cytologically documented stage IV NSCLC	Active or prior documented autoimmune or inflammatory disorders
No prior chemotherapy or any other systemic therapy for stage IV NSCLC	Brain metastases or spinal cord compression unless the patient's condition is stable and off steroids
Tumors without activating EGFR mutations and ALK fusions	Prior exposure to immune-mediated therapy, excluding therapeutic anticancer vaccines
Confirmed tumor PD-L1 expression level prior to randomization	Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus
WHO/ECOG performance status of 0 or 1	

ALK = anaplastic lymphoma kinase; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death ligand-1; WHO = World Health Organization.

Study NCT03164616. ClinicalTrials.gov website.

POSEIDON: Patient Baseline Characteristics

Characteristic	D+CT (n=338)	D+T+CT (n=338)	CT (n=337)
Median age (range), years	64.5 (32–87)	63.0 (27–87)	64.0 (32–84)
Male, %	74.9	79.6	73.6
White / Asian / Other, %	53.8 / 36.4 / 9.8	60.7 / 29.3 / 10.1	53.1 / 38.0 / 8.9
Eastern Europe / Asia / North America / Western Europe / Other, %	30.5 / 35.5 / 13.6 / 7.7 / 12.7	36.1 / 28.4 / 13.0 / 8.6 / 13.9	28.2 / 36.8 / 11.9 / 8.3 / 14.8
ECOG PS 0 / 1, %	32.2 / 67.8	32.5 / 67.5	35.3 / 64.4
Squamous / Non-squamous histology[a], %	37.9 / 61.8	36.7 / 63.3	36.2 / 63.5
AJCC disease stage IVA / IVB[a], %	50.3 / 49.4	50.6 / 48.8	49.3 / 50.4
Current or former / Never smoker, %	75.1 / 24.9	82.5 / 17.5	76.3 / 23.4
PD-L1 TC ≥50%[a] / TC ≥1%, %	27.8 / 66.3	29.9 / 63.0	28.8 / 61.4
CNS metastases, %	8.3	9.8	13.4
Liver metastases, %	18.3	20.4	23.7

[a]Stratification factors.

AJCC = American Joint Committee on Cancer; CNS = central nervous system; CT = chemotherapy; D = durvalumab; ECOG = Eastern Cooperative Oncology Group; PD-L1 = programmed cell death ligand-1; PS = performance status; T = tremelimumab; TC = tumor cell.

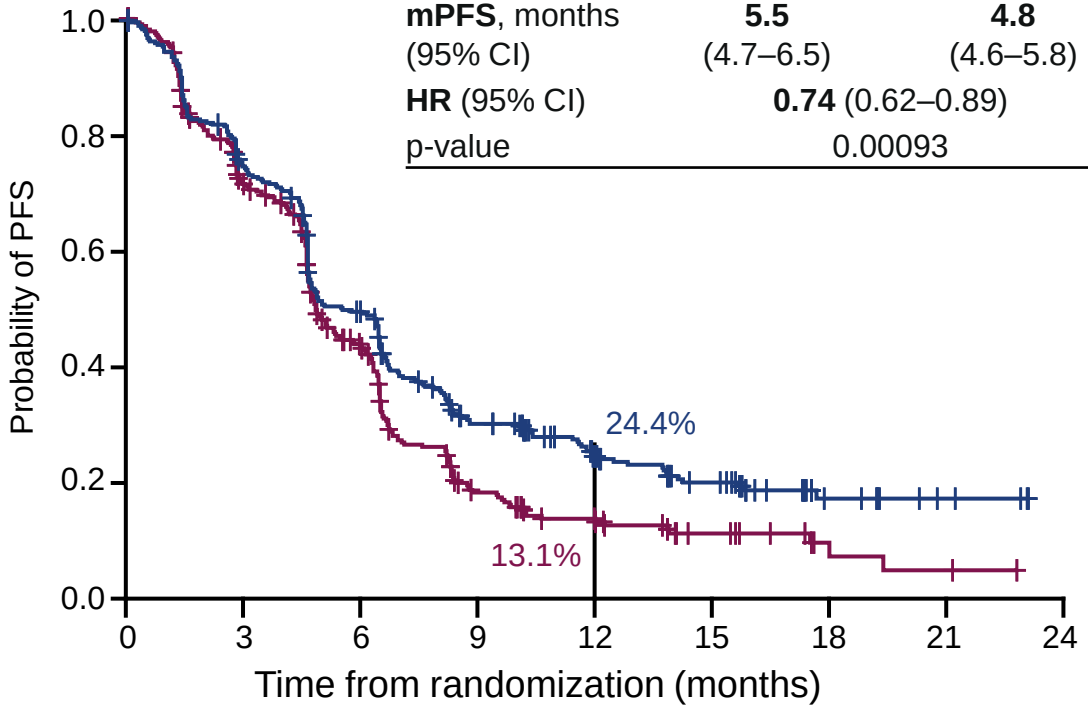
Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.

POSEIDON: Results

POSEIDON: Efficacy Results - D+CT vs CT (Primary endpoints)

PFS[a]

	D+CT	CT
Events, n/N (%)	253/338 (74.9)	258/337 (76.6)
mPFS, months (95% CI)	**5.5** (4.7–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.74** (0.62–0.89)	
p-value	0.00093	

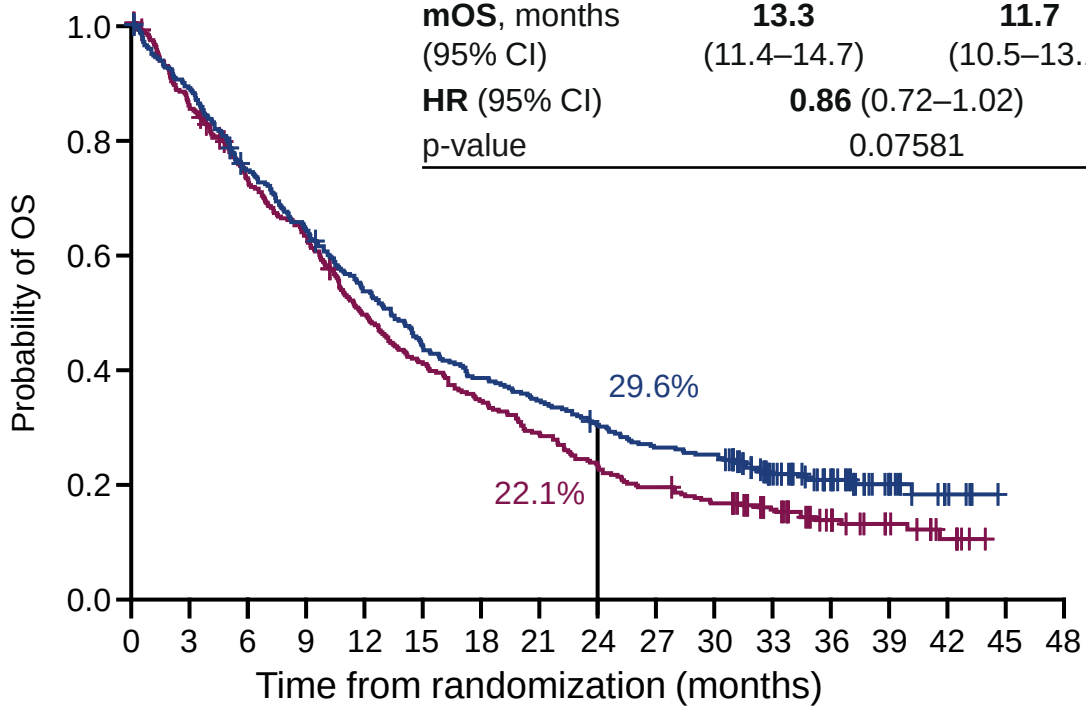


No. at risk									
D+CT	338	246	158	88	53	35	11	4	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS[b]

	D+CT	CT
Events, n/N (%)	264/338 (78.1)	285/337 (84.6)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR (95% CI)	**0.86** (0.72–1.02)	
p-value	0.07581	



No. at risk																	
D+CT	338	296	247	212	176	142	126	112	97	85	81	51	33	15	5	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

[a]DCO PFS FA: July 24, 2019; [b]DCO OS FA: March 12, 2021

CI = confidence interval; CT = chemotherapy; D = durvalumab; DCO = data cutoff; FA = final analysis; HR = hazard ratio; mOS = median overall survival; mPFS = median progression-free survival; OS = overall survival; PFS = progression-free survival.

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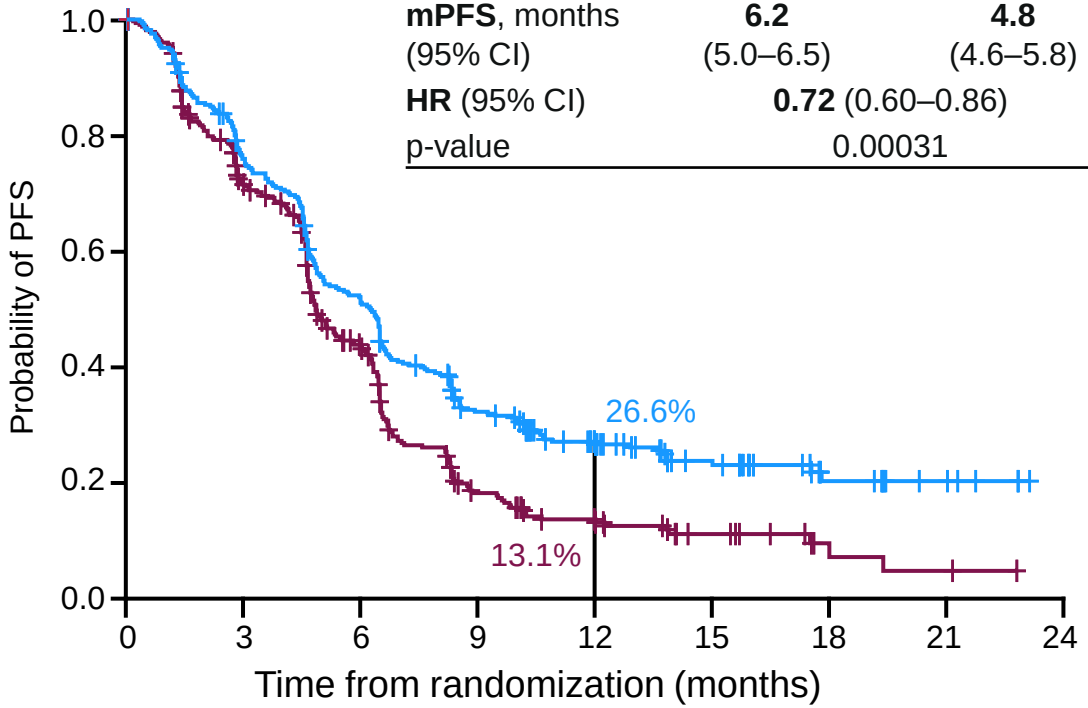
POSEIDON: Efficacy Results - D+T+CT vs CT (Secondary endpoints)

PFS[a]

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	

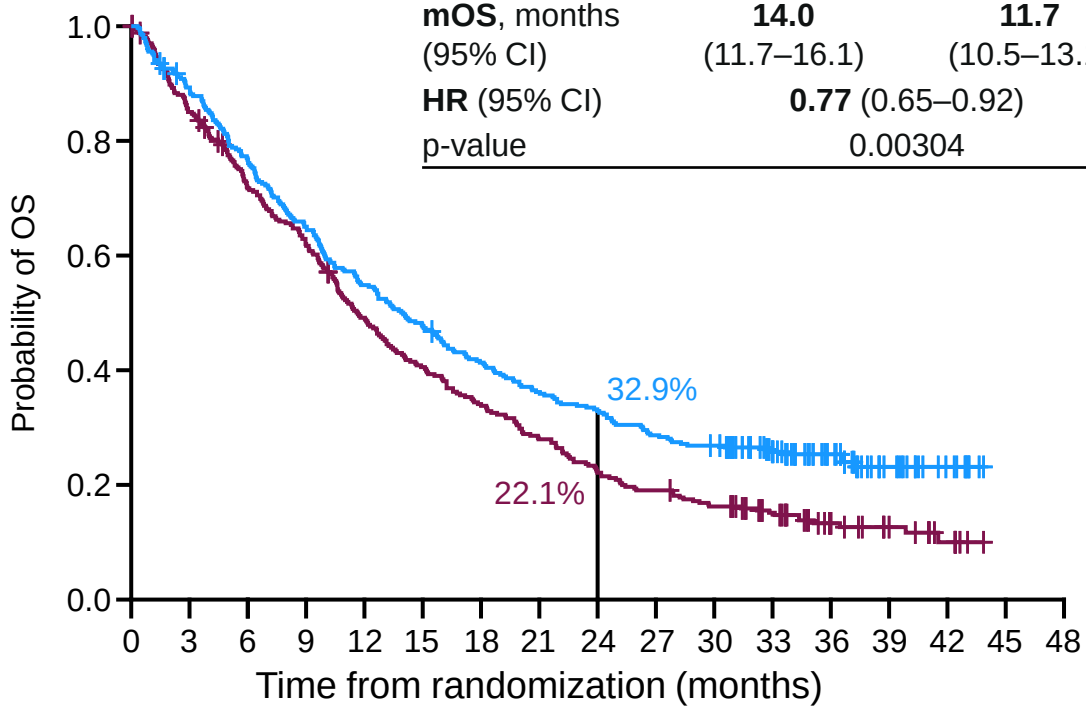


No. at risk									
D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS[b]

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



No. at risk																	
D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

[a]DCO PFS FA: July 24, 2019; [b]DCO OS FA: March 12, 2021

CI = confidence interval; CT = chemotherapy; D = durvalumab; DCO = data cutoff; FA = final analysis; HR = hazard ratio; mOS = median overall survival; mPFS = median progression-free survival; OS = overall survival; PFS = progression-free survival; T = tremelimumab.

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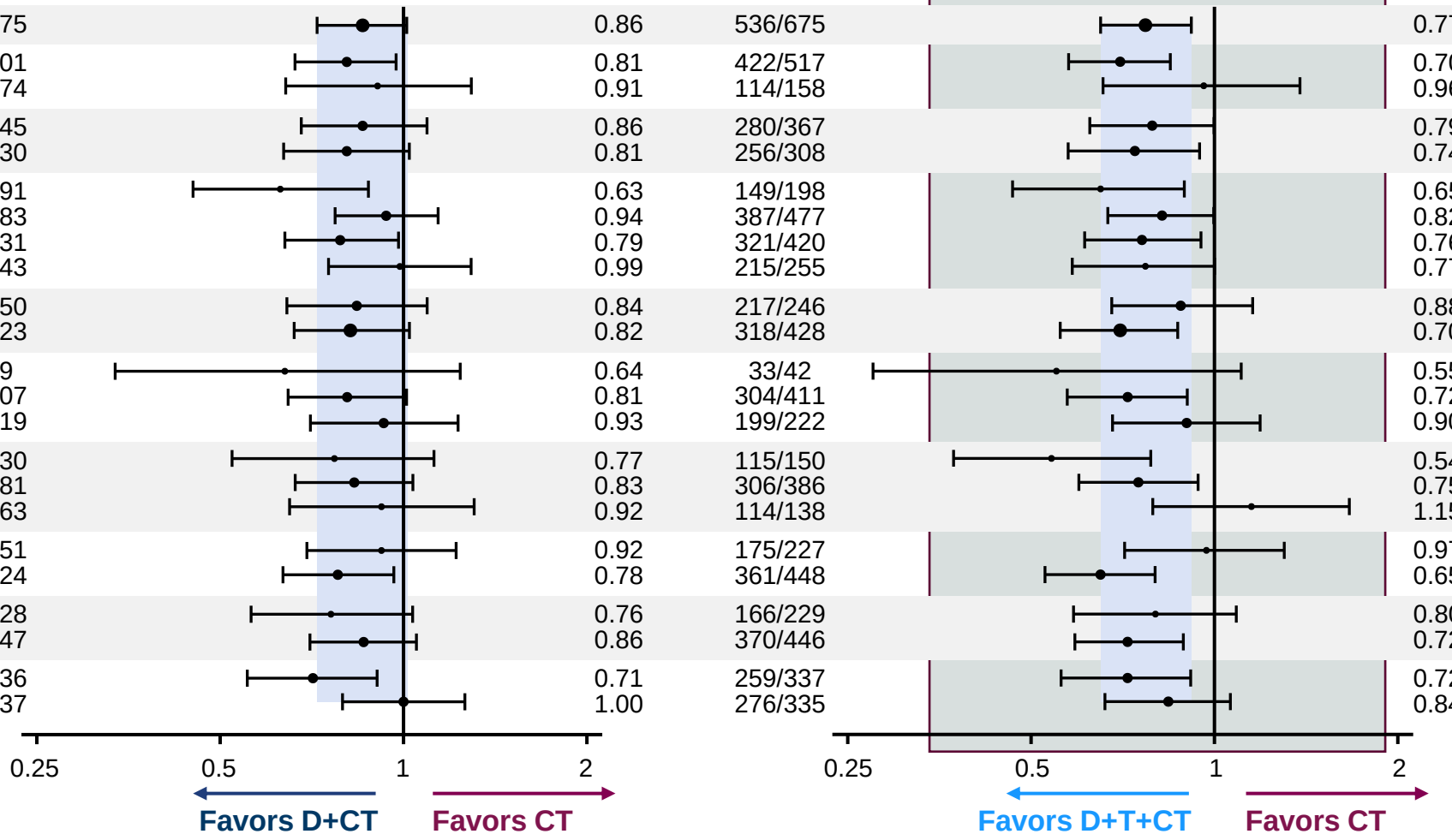
POSEIDON: Overall Survival[a] (Subgroup Analysis)

		Events/ patients, n/N	D+CT vs CT HR	Events/ patients, n/N	D+T+CT vs CT HR
All patients		549/675	0.86	536/675	0.77
Sex	Male	423/501	0.81	422/517	0.70
	Female	126/174	0.91	114/158	0.96
Age	<65 years	273/345	0.86	280/367	0.79
	≥65 years	276/330	0.81	256/308	0.74
Tumor PD-L1 expression	TC ≥50%	144/191	0.63	149/198	0.65
	TC <50%	405/483	0.94	387/477	0.82
	TC ≥1%	335/431	0.79	321/420	0.76
	TC <1%	214/243	0.99	215/255	0.77
Histology	Squamous	220/250	0.84	217/246	0.88
	Non-squamous	327/423	0.82	318/428	0.70
Planned CT	Nab-paclitaxel doublet	40/49	0.64	33/42	0.55
	Pemetrexed doublet	311/407	0.81	304/411	0.72
	Gemcitabine doublet	198/219	0.93	199/222	0.90
Smoking history	Current	107/130	0.77	115/150	0.54
	Former	314/381	0.83	306/386	0.75
	Never	127/163	0.92	114/138	1.15
Race	Asian	195/251	0.92	175/227	0.97
	Non-Asian	354/424	0.78	361/448	0.65
ECOG PS	0	168/228	0.76	166/229	0.80
	1	381/447	0.86	370/446	0.72
AJCC disease stage	IVA	259/336	0.71	259/337	0.72
	IVB	288/337	1.00	276/335	0.84



[a]DCO OS FA: March 12, 2021.

AJCC = American Joint Committee on Cancer; CT = chemotherapy; D = durvalumab; DCO = data cutoff; ECOG = Eastern Cooperative Oncology Group; FA = final analysis; HR = hazard ratio; PD-L1 = programmed cell death ligand-1; PS = performance status; T = tremelimumab; TC = tumor cell.

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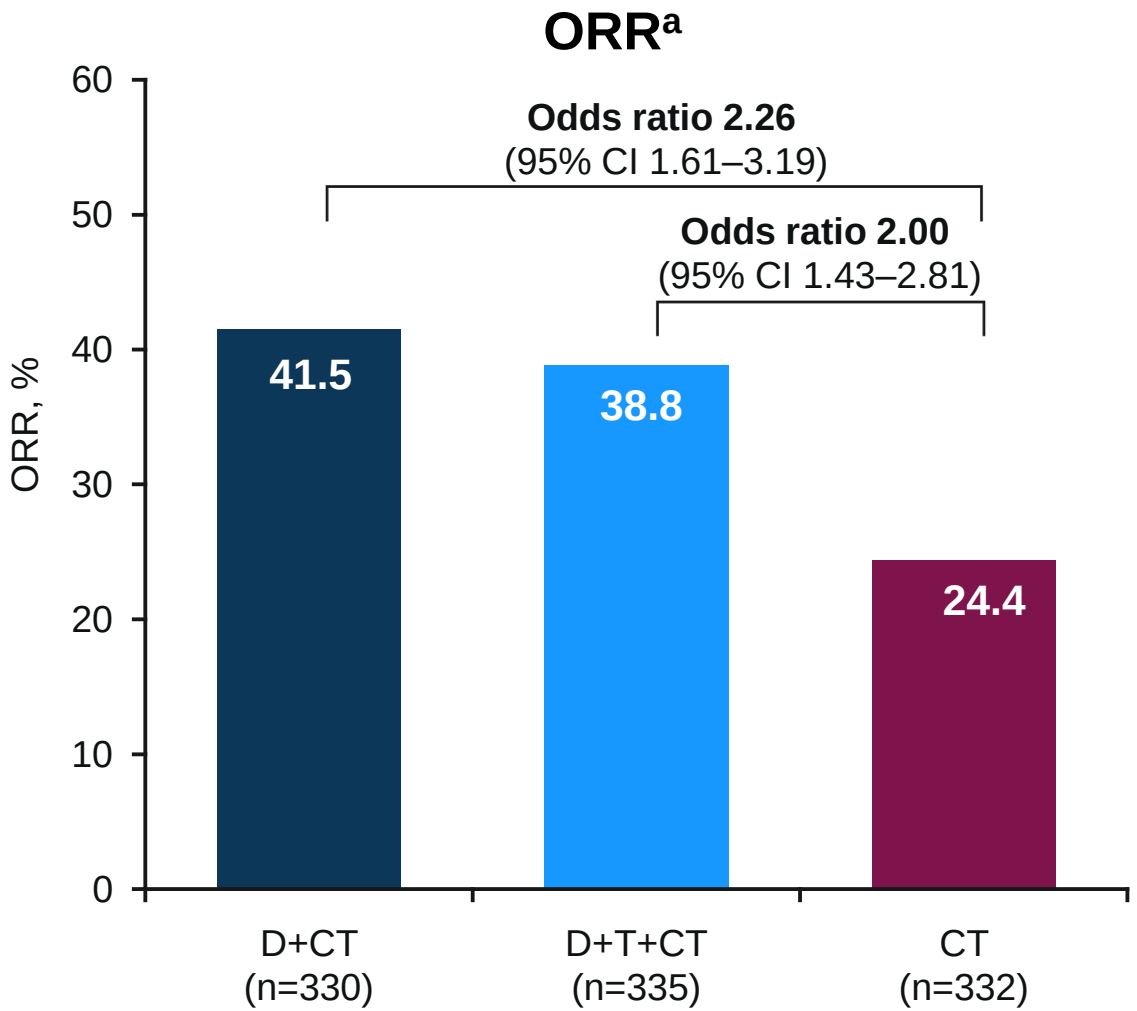
POSEIDON: Confirmed ORR and Duration of Response



Duration of Response

	D+CT	D+T+CT	CT
Responders[a], n	137	130	81
Median DoR, months (95% CI)	7.0 (5.7–9.9)	**9.5** (7.2–NE)	5.1 (4.4–6.0)
Remaining in response at 12 months, %	38.9	**49.7**	21.4

DCO PFS FA: July 24, 2019. [a]Confirmed objective response by BICR assessed in patients with measurable disease at baseline; confirmation was not required per protocol (post-hoc analysis).

BICR = blinded independent central review; CI = confidence interval; CT = chemotherapy; D = durvalumab; DCO = data cutoff; DoR = duration of response; FA = final analysis; NE = not estimable; ORR = objective response rate; T = tremelimumab.

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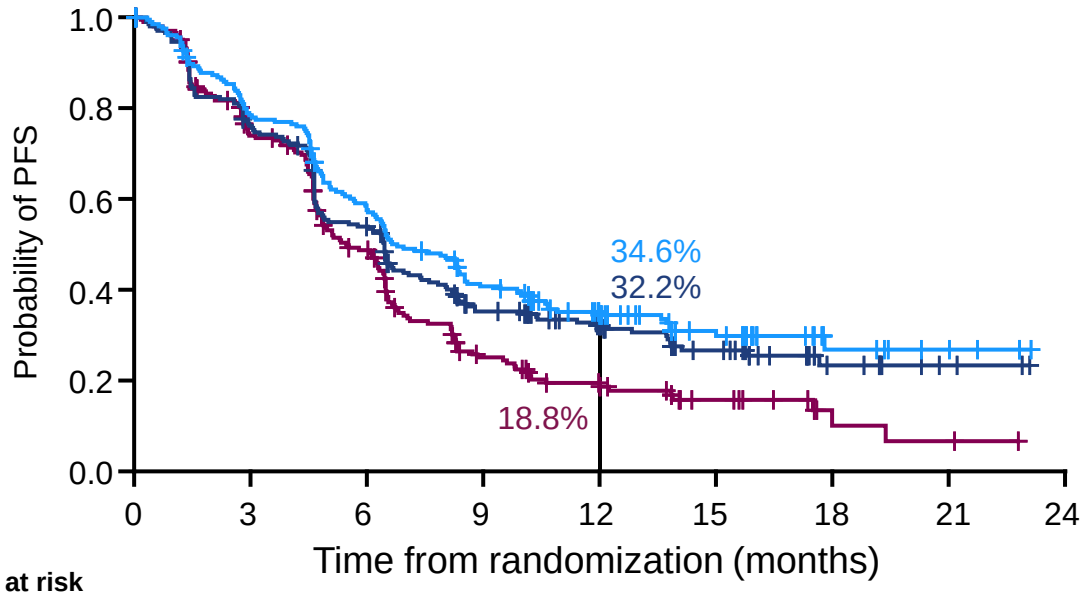
POSEIDON: Outcomes in Patients with Non-Squamous Histology[a]

PFS and ORR

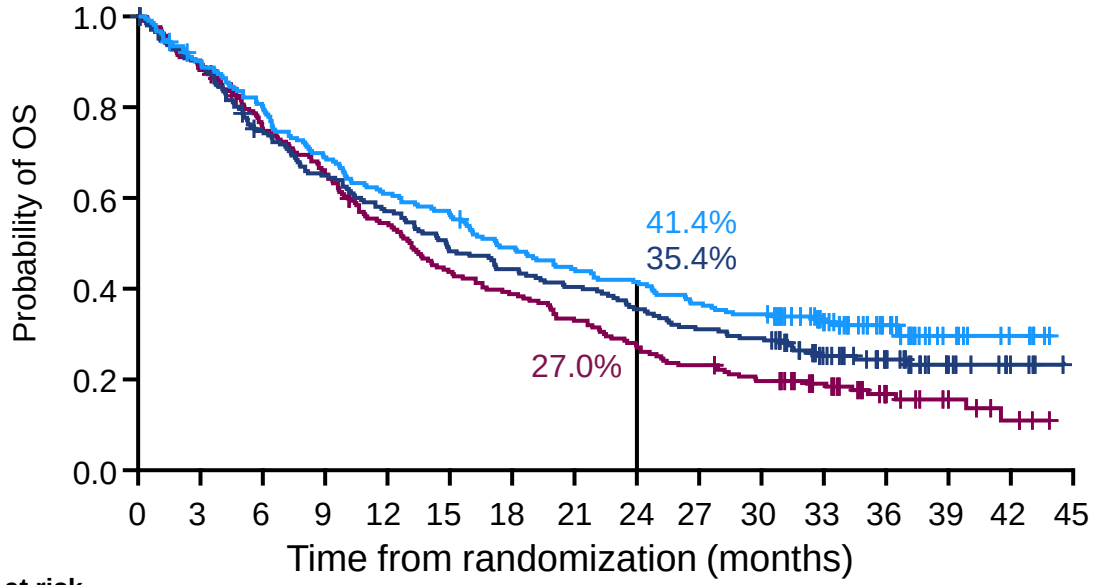
	D+CT	D+T+CT	CT
Events, n/N (%)	144/209 (68.9)	136/214 (63.6)	154/214 (72.0)
mPFS, months (95% CI)	**6.4** (4.7–7.4)	**6.8** (6.1–8.5)	**5.5** (4.8–6.4)
HR[b] (95% CI)	**0.77** (0.61–0.96)	**0.66** (0.52–0.84)	–
Confirmed ORR[c], % (n/N)	**44.3** (90/203)	**45.5** (96/211)	**23.7** (50/211)
mDoR[c], months (95% CI)	**10.6** (6.6–NE)	**16.4** (9.3–NE)	**6.0** (4.4–8.7)



No. at risk									
D+CT	209	156	108	64	45	29	10	3	0
D+T+CT	214	160	115	78	48	27	9	4	0
CT	214	142	88	38	22	12	3	2	0

OS

	D+CT	D+T+CT	CT
Events, n/N (%)	154/209 (73.7)	145/214 (67.8)	173/214 (80.8)
mOS, months (95% CI)	**14.8** (11.8–18.3)	**17.2** (14.9–21.8)	**13.1** (10.6–15.1)
HR[b] (95% CI)	**0.82** (0.66–1.03)	**0.70** (0.56–0.87)	–



No. at risk																
D+CT	209	185	152	132	116	98	90	82	72	63	59	38	25	11	4	0
D+T+CT	214	191	169	146	129	119	103	93	87	77	72	50	31	12	6	0
CT	214	187	155	135	111	89	79	67	55	47	39	29	15	8	4	0

Note: DCO PFS FA: July 24, 2019; DCO OS FA: March 12, 2021. [a]95.5% of patients with non-squamous histology receiving CT had pemetrexed + platinum; [b]HR <1 favors D (±T) + CT versus CT; [c]Analysis of ORR and DoR by histology was post hoc.

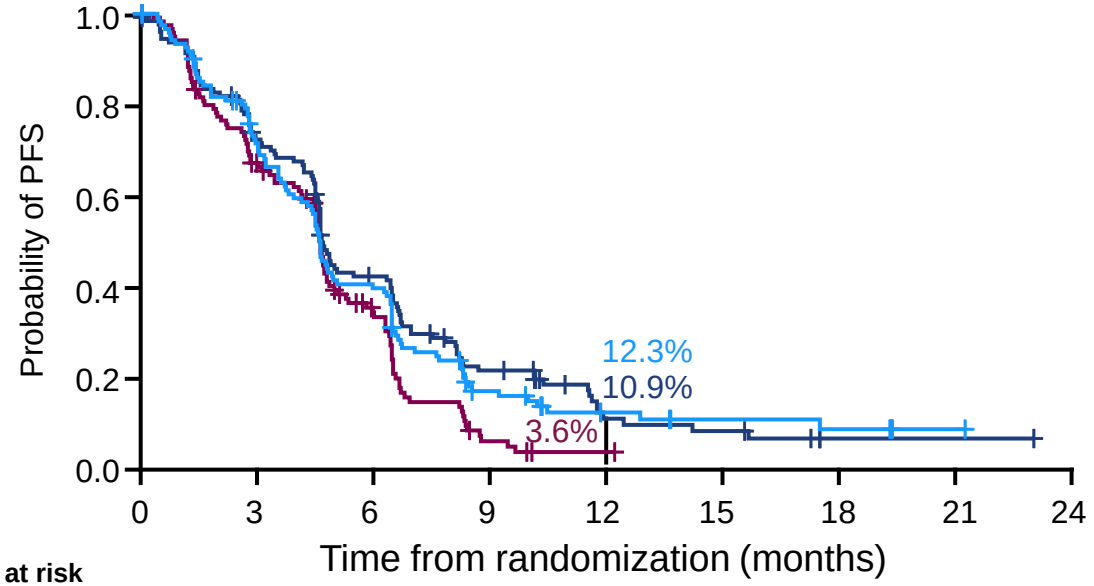
CI = confidence interval; CT = chemotherapy; D = durvalumab; DCO = data cutoff; FA = final analysis; HR = hazard ratio; mDoR = median duration of response; mOS = median overall survival; mPFS = median progression-free survival; NE = not estimable; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; T = tremelimumab.

Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.

POSEIDON: Outcomes in Patients with Squamous Histology[a]

PFS and ORR

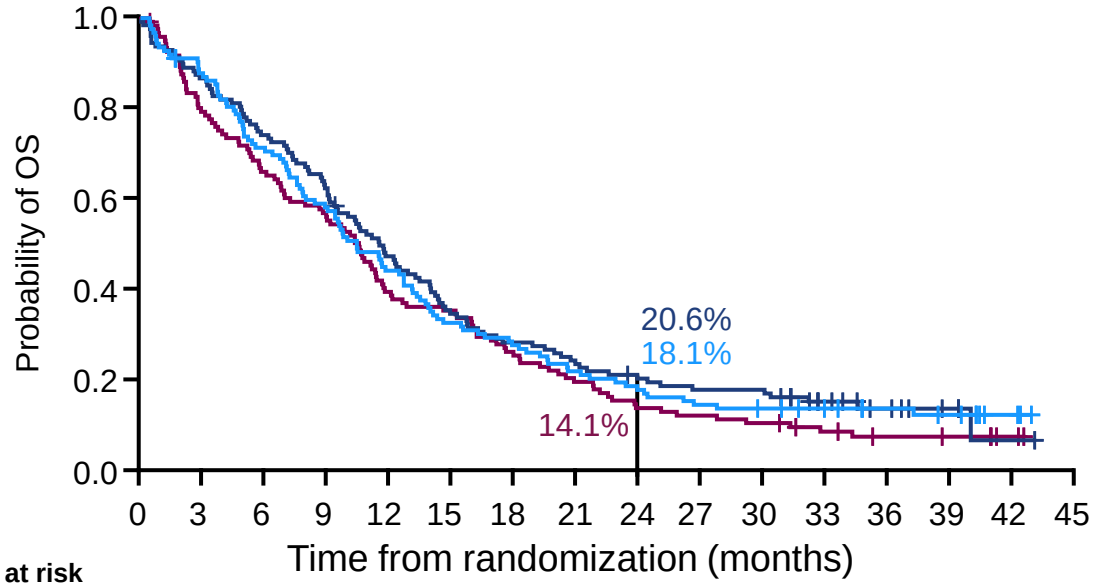
	D+CT	D+T+CT	CT
Events, n/N (%)	108/128 (84.4)	102/124 (82.3)	104/122 (85.2)
mPFS, months (95% CI)	**4.7** (4.6–6.3)	**4.6** (3.9–5.1)	**4.6** (4.2–4.8)
HR[b] (95% CI)	**0.68** (0.52–0.90)	**0.77** (0.58–1.01)	–
Confirmed ORR[c], % (n/N)	**37.3** (47/126)	**27.4** (34/124)	**25.6** (31/121)
mDoR[c], months (95% CI)	**5.5** (4.9–6.7)	**5.6** (4.3–7.2)	**4.8** (3.7–5.2)



No. at risk									
D+CT	128	90	50	24	8	6	1	1	0
D+T+CT	124	83	46	16	8	5	4	1	0
CT	122	77	33	5	1	0	0	0	0

OS

	D+CT	D+T+CT	CT
Events, n/N (%)	109/128 (85.2)	106/124 (85.5)	111/122 (91.0)
mOS, months (95% CI)	**11.5** (9.4–14.0)	**10.4** (8.4–12.7)	**10.5** (8.0–11.7)
HR[b] (95% CI)	**0.84** (0.64–1.10)	**0.88** (0.68–1.16)	–



No. at risk																
D+CT	128	111	95	80	60	44	36	30	25	22	22	13	8	4	1	0
D+T+CT	124	107	87	71	54	40	34	27	22	18	16	14	10	8	3	0
CT	122	96	80	68	48	43	32	24	17	15	13	9	6	5	2	0

Note: DCO PFS FA: July 24, 2019; DCO OS FA: March 12, 2021. [a]88.3% of patients with squamous histology receiving CT had gemcitabine + platinum; [b]HR <1 favors D (±T) + CT versus CT; [c]Analysis of ORR and DoR by histology was post hoc.

CI = confidence interval; CT = chemotherapy; D = durvalumab; DCO = data cutoff; FA = final analysis; HR = hazard ratio; mDoR = median duration of response; mOS = median overall survival; mPFS = median progression-free survival; NE = not estimable; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; T = tremelimumab.

Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.

POSEIDON: Safety Results

POSEIDON: Safety Summary

Characteristic, n (%)	D+CT (n=334)	D+T+CT (n=330)	CT (n=333)
Any grade all-causality AEs	321 (96.1)	321 (97.3)	320 (96.1)
Grade 3 or 4 AEs[a]	183 (54.8)	176 (53.3)	172 (51.7)
Serious AEs	134 (40.1)	146 (44.2)	117 (35.1)
AEs leading to treatment discontinuation[b]	68 (20.4)	73 (22.1)	51 (15.3)
AEs leading to death	34 (10.2)	41 (12.4)	30 (9.0)
Any grade treatment-related AEs[c]	296 (88.6)	306 (92.7)	298 (89.5)
Grade 3 or 4 AEs[a]	149 (44.6)	171 (51.8)	148 (44.4)
Serious AEs	65 (19.5)	91 (27.6)	59 (17.7)
AEs leading to treatment discontinuation[b]	47 (14.1)	51 (15.5)	33 (9.9)
AEs leading to death	7 (2.1)	11 (3.3)	8 (2.4)

Note: DCO OS FA: March 12, 2021. [a]Maximum reported CTCAE grade; [b]Includes patients who permanently discontinued at least one study drug; [c]AEs assessed by the investigator as possibly related to any study treatment.

AE = adverse event; CT = chemotherapy; CTCAE = Common Terminology Criteria for Adverse Events; D = durvalumab; DCO = data cutoff; FA = final analysis; OS = overall survival; T = tremelimumab.

Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.

POSEIDON: Treatment-related Adverse Events

	D+CT (n=334)	T+D+CT (n=330)	CT (n=333)
Any maximum grade 3/4 TRAE, n (%)[a]	149 (44.6)	171 (51.8)	148 (44.4)
Anemia	51 (15.3)	57 (17.3)	68 (20.4)
Neutropenia	42 (12.6)	53 (16.1)	40 (12.0)
Neutrophil count decreased	24 (7.2)	24 (7.3)	25 (7.5)
Thrombocytopenia	15 (4.5)	18 (5.5)	17 (5.1)
Platelet count decreased	9 (2.7)	8 (2.4)	15 (4.5)
Leukopenia	8 (2.4)	9 (2.7)	12 (3.6)
White blood cell count decreased	10 (3.0)	9 (2.7)	9 (2.7)

[a]Events occurring in ≥3% of patients in any treatment arm are shown. CT = chemotherapy; D = durvalumab; T = tremelimumab; TRAE = treatment-related adverse event.

Cho BC et al. Poster presented at: ASCO Annual meeting; June 3-7, 2022; Chicago, IL. Poster 9305.

POSEIDON: Summary of Immune-mediated AEs

	D+CT (n=334)	T+D+CT (n=330)	CT (n=333)
Any imAE, n (%)	64 (19.2)	111 (33.6)	17 (5.1)
Maximum grade 3/4	23 (6.9)	33 (10.0)	5 (1.5)
Serious	20 (6.0)	32 (9.7)	4 (1.2)
Leading to treatment discontinuation[a]	14 (4.2)	19 (5.8)	2 (0.6)
Leading to death[b]	1 (0.3)	2 (0.6)	0

[a]Includes imAEs leading to permanent discontinuation of at least one study drug; [b]imAEs leading to death were hepatic, renal, and pancreatic events and myocarditis, all in the same patient, and pneumonitis in 1 patient in the T+D+CT arm, and myocarditis in 1 patient in the D+CT arm. AE = adverse event; CT = chemotherapy; D = durvalumab; imAE = immune-mediated adverse event; T = tremelimumab.

Cho BC et al. Poster presented at: ASCO Annual meeting; June 3-7, 2022; Chicago, IL. Poster 9305.

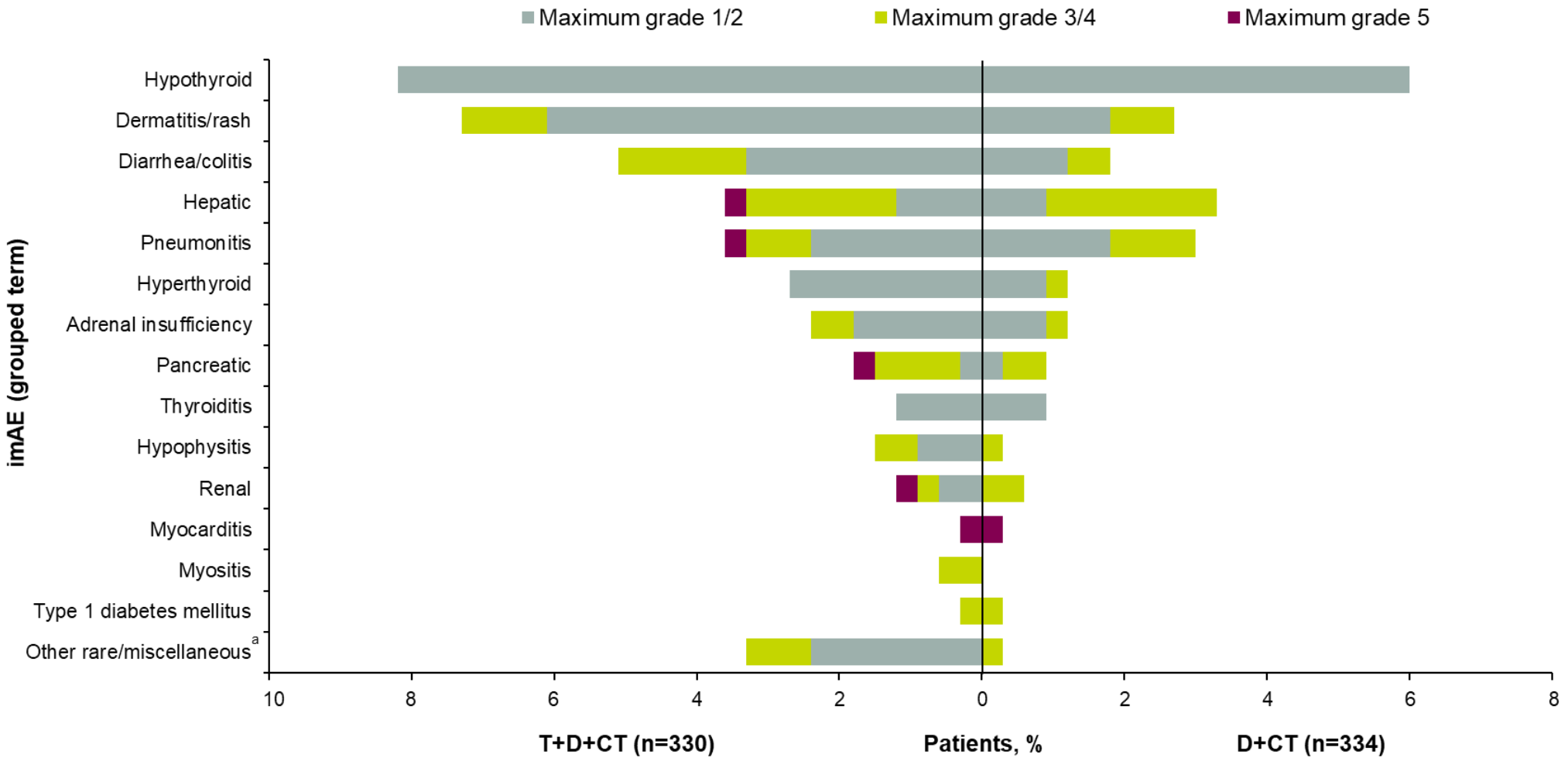
POSEIDON: Incidence of Immune-mediated AEs[a]

	D+CT (n=334)			T+D+CT (n=330)			CT (n=333)		
	Any grade	Maximum grade 3/4	Maximum grade 5	Any grade	Maximum grade 3/4	Maximum grade 5	Any grade	Maximum grade 3/4	Maximum grade 5
Any imAE, n (%)	64 (19.2)	23 (6.9)	1 (0.3)	111 (33.6)	33 (10.0)	2 (0.6)	17 (5.1)	5 (1.5)	0
Hypothyroid events	20 (6.0)	0	0	27 (8.2)	0	0	3 (0.9)	0	0
Dermatitis/rash	9 (2.7)	3 (0.9)	0	24 (7.3)	4 (1.2)	0	7 (2.1)	2 (0.6)	0
Diarrhea/colitis	6 (1.8)	2 (0.6)	0	17 (5.2)	6 (1.8)	0	2 (0.6)	0	0
Pneumonitis	10 (3.0)	4 (1.2)	0	12 (3.6)	3 (0.9)	1 (0.3)	2 (0.6)	2 (0.6)	0
Hepatic events	11 (3.3)	8 (2.4)	0	12 (3.6)	7 (2.1)	1 (0.3)	0	0	0
Hyperthyroid events	4 (1.2)	1 (0.3)	0	9 (2.7)	0	0	1 (0.3)	0	0
Adrenal insufficiency	4 (1.2)	1 (0.3)	0	8 (2.4)	2 (0.6)	0	0	0	0
Pancreatic events	3 (0.9)	2 (0.6)	0	6 (1.8)	4 (1.2)	1 (0.3)	0	0	0
Thyroiditis	3 (0.9)	0	0	4 (1.2)	0	0	0	0	0
Hypophysitis	1 (0.3)	1 (0.3)	0	5 (1.5)	2 (0.6)	0	0	0	0
Renal events	2 (0.6)	2 (0.6)	0	4 (1.2)	1 (0.3)	1 (0.3)	0	0	0
Myocarditis	1 (0.3)	0	1 (0.3)	1 (0.3)	0	1 (0.3)	0	0	0
Myositis	0	0	0	2 (0.6)	2 (0.6)	0	0	0	0
Type 1 diabetes mellitus	1 (0.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	0	0	0
Other rare/miscellaneous[b]	1 (0.3)	1 (0.3)	0	11 (3.3)	3 (0.9)	0	2 (0.6)	1 (0.3)	0

[a]Grouped terms by maximum CTCAE grade; [b]Other rare/miscellaneous imAEs were arthralgia and vasculitis in the same patient, arthralgia in 5 patients, autoimmune encephalitis, encephalitis, immune thrombocytopenia, subacute cutaneous lupus erythematosus, and vasculitis in 1 patient each in the T+D+CT arm, arthritis in 1 patient in the D+CT arm, and arthralgia in 2 patients in the CT arm. CT = chemotherapy; CTCAE = Common Terminology Criteria for Adverse Events; D = durvalumab; imAE = immune-mediated adverse event; ITT = intention-to-treat; T = tremelimumab.

Cho BC et al. Poster presented at: ASCO Annual meeting; June 3-7, 2022; Chicago, IL. Poster 9305 [supplementary material].

POSEIDON: Frequency of Immune-mediated Adverse Events[a]



[a]Other rare/miscellaneous imAEs were arthralgia and vasculitis in the same patient, arthralgia in 5 patients, autoimmune encephalitis, encephalitis, immune thrombocytopenia, subacute cutaneous lupus erythematosus, and vasculitis in 1 patient each in the T+D+CT arm, and arthritis in 1 patient in the D+CT arm. CT = chemotherapy; D = durvalumab; imAE = immune-mediated adverse event; T = tremelimumab.

Cho BC et al. Poster presented at: ASCO Annual meeting; June 3-7, 2022; Chicago, IL. Poster 9305.

Putting data into context for IO + IO trials in 1L NSCLC

Different chemotherapy backbones in POSEIDON and CM9LA

	POSEIDON[1]	CM9LA[2]
Design	Open-label	Open-label
CTX regimens	5	3
Total patient number	**1013**	719
Endpoint	PFS (BICR) and OS	OS
Randomisation	**1:1:1**	1:1
Stratification factors	PD-L1 50% Histology Disease stage	PD-L1 <1% vs ≥1% Histology Sex
CTX backbone	Pem / platinum (pem is allowed during **maintenance** across three arms) or nab-paclitaxel / carboplatin (NSQ) Gem / platinum or nab-paclitaxel / carboplatin (SQ)	Pem / platinum (pem **is not allowed** during maintenance in experimental arm, but allowed in the control arm) [NSQ] or paclitaxel / carboplatin (SQ)
CTX cycles	**4 for experimental arm**, 4–6 for control arm	**2 for experimental arm**, 4 for control arm
Histology type	SQ and NSQ	SQ and NSQ
Cross-over	No	No

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

BICR, blinded independent central review; gem, gemcitabine; NSQ, non-squamous; OS, overall survival; pem, pemetrexed; PFS, progression-free survival; SQ, squamous

1. AstraZeneca. Data on file; 2. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198–211

Dosing schedules differed between POSEIDON and CM9LA

SoC 4 cycles CTX

Optional pemetrexed maintenance

Q4W durvalumab maintenance (until PD or toxicity)

Short course tremelimumab (5 doses)

	Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
POSEIDON[1]	Durva	■			■			■			■			■				■				■				■				■				■				■				■		
	Treme	■			■			■			■							■																											
	CTx	■			■			■			■			Pem (optional)				Pem				Pem				Pem				Pem				Pem				Pem				Pem		
CM9LA[2]	Nivo	■			■			■			■			■			■			■			■			■			■			■			■			■			■			■
	Ipi	■						■						■						■						■												■						■
	CTx	■			■																																							

Limited CTX (2 cycles)

Q3W nivolumab maintenance (until PD or toxicity)

Q6W ipilimumab maintenance (until PD or toxicity)

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

durva, durvalumab; ipi, ipilimumab; nivo, nivolumab; PD, progressive disease; QXW, once every X weeks; treme, tremelimumab

1. Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.; 2. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198–211

POSEIDON vs CM9LA (ITT): key efficacy data snapshot

	POSEIDON[1]	CM9LA 2020[2]	CM9LA 2-year follow-up[3]
ICI	**Durvalumab + tremelimumab + CTX vs CTX**	**Nivolumab + ipilimumab + CTX vs CTX**	**Nivolumab + ipilimumab + CTX vs CTX**
PFS HR	**0.72**	0.68	0.67
PFS median, months	**6.2** vs 4.8	6.7 vs 5.0	6.7 vs 5.3
PFS at 12 months, %	**26.6** vs 13.1	33 vs 18	33 vs 19
Confirmed ORR, %	**38.8** vs 24.4	38.2 vs 24.9	38 vs 25.4
Median DoR, months	**9.5** vs 5.1	11.3 vs 5.6	13 vs 5.6
OS HR	**0.77**	0.66	0.72
OS median, months	**14.0** vs 11.7	15.6 vs 10.9	15.8 vs 11
OS at 12 months, %	**54.8** vs 49.1	63 vs 47	63 vs 47
Safety: treatment-related discontinuation rate, %	**15.5** vs 9.9	19 vs 7	22 vs 8

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

CM9LA, CheckMate 9LA; DoR, duration of response; ICI, immune checkpoint inhibitor; ITT, intent-to-treat; ORR, objective response rate

1. AstraZeneca. Data on file , Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.; 2. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198–211; 3. Reck M, et al. Presented at ASCO 2021, 4–8 June 2021; Abstract 9000

POSEIDON vs CM9LA (nonsquamous only)

	POSEIDON[1]	CM9LA[2]
ICI	**Durvalumab + tremelimumab + CTX vs CTX**	**Nivolumab + ipilimumab + CTX vs CTX**
CTX regimen	**Pemetrexed / platinum or nab-paclitaxel / carboplatin**	Pemetrexed / platinum
PFS HR (95% CI)	**0.66 (0.524–0.835)[a]**	0.74 (0.60–0.92)
PFS median, months	**6.8** vs 5.5	7.0 vs 5.6
PFS at 12 months, %	**34.6** vs 18.8	33 vs 21
Confirmed ORR, %	**45.5** vs 23.7	33.3 vs 22.0
Median DoR, months	**16.4** vs 6.0	15.8 vs 8.8
OS HR (95% CI)	**0.70 (0.558–0.870)**	0.69 (0.55–0.87)
OS median, months	**17.2** vs 13.1	17.0 vs 11.9
OS at 12 months, %	**61** vs 54	63 vs 50

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

[a]HR from unstratified analysis

CI, confidence interval; KN189, KEYNOTE-189

1. AstraZeneca. Data on file , Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.; 2. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198–211; 3. Gandhi L, et al. *N Engl J Med* 2018;378:2078–2092; 4. Gray J, et al. *J Thorac Oncol* 2021;16(Suppl):S224; Abstract FP13.02; 5. Gadgeel S, et al. *J Clin Oncol* 2019;37(Suppl 15): Abstract 9013; 6. Rodríguez-Abreu D. *Ann Oncol* 2021;32:881–895

POSEIDON vs CM9LA (squamous only)

	POSEIDON[1]	CM9LA[2]
ICI	**Durvalumab + tremelimumab + CTX vs CTX**	**Nivolumab + ipilimumab + CTX vs CTX**
CTX regimen	**Gemcitabine / platinum (n=330[a]) or carboplatin / nab-paclitaxel (n=42[a])**	Paclitaxel / carboplatin
PFS HR (95% CI)	**0.77 (0.581–1.014)+**	0.57 (0.42–0.78)
PFS median, months	**4.6** vs 4.6	5.6 vs 4.3
PFS at 12 months, %	**12.3** vs 3.6	33 vs 9
Confirmed ORR, %	**27.4** vs 25.6	48.7 vs 31.3
Median DoR, months	**5.6** vs 4.8	10.4 vs 3.9
OS HR (95% CI)	**0.88 (0.678–1.155)**	0.62 (0.45–0.86)
OS median, months	**10.4** vs 10.5	14.5 vs 9.1
OS at 12 months, %	**44.3** vs 39.7	64 vs 40

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

[a]Across all three arms; [b]HR from unstratified analysis; PFS by BICR

BICR, blinded independent central review; KN407, KEYNOTE-407

1. AstraZeneca. Data on file, Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.

2. Paz-Ares L, et al. *Lancet Oncol* 2021;22:198–211; 3. Paz-Ares L, et al. *N Engl J Med* 2018;379:2040–2051;
4. Robinson AG, et al. *J Thorac Oncol* 2021;16(Suppl):S748–S749; Abstract 97O

POSEIDON: Conclusions

- In the phase III POSEIDON study, **first-line durvalumab + tremelimumab + chemotherapy significantly improved both PFS and OS vs chemotherapy alone**
  - PFS HR: 0.72 (95% CI: 0.60-0.86; *P* = .00031)
  - OS HR: 0.77 (95% CI: 0.65-0.92; *P* = .00304)
  - Survival benefits **more prominent in patients with nonsquamous histology**

Durvalumab + tremelimumab + chemotherapy can be potential treatment option for metastatic NSCLC

Johnson et al. Presented at: WCLC Virtual Congress; September 8-14, 2021.

Watch out :Oral Presentation at WCLC 2022

POSEIDON trial exploratory analysis of **OS outcomes in patients with STK11, KEAP1 and KRAS mutations** will be read out at IASLC World Conference on Lung Cancer, 8th August 2022

- **OA15.04 - Association Between KRAS/STK11/KEAP1 Mutations and Outcomes in POSEIDON: Durvalumab ± Tremelimumab + Chemotherapy in mNSCLC**

14:42 - 14:52 | Presenter: Solange Peters | Author(s): Byoung Chul Cho, Alexander Luft, Jorge Alatorre-Alexander, Sarayut Lucien Geater, Sang-We Kim, Grygorii Ursol, Maen Hussein, Farah Louise Lim, Cheng-Ta Yang, Luiz Henrique Araujo, Haruhiro Saito, Niels Reinmuth, Ross Stewart, Zhongwu Lai, Ruth Doake, Lee Krug, Edward B. Garon, Tony S. Mok, Melissa L Johnson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Thank You