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POSEIDON: Too many fish in the sea?

WCLC Updates in Advanced Non-small Cell Lung Cancer

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Disclosures

- Consulting/Advisory : Pfizer, Merck, Astrazeneca , Blueprint Medicines, Lilly and G1 therapeutics

Introduction

- Immunotherapy has revolutionized the treatment of metastatic NSCLC in combination with chemotherapy and as monotherapy.

  - Carboplatin pemetrexed pembrolizumab
  - Carboplatin abraxane pembrolizumab
  - Carboplatin paclitaxel bevacizumab and atezolizumab
  - Pembrolizumab
  - Carboplatin pemetrexed +/- Bevacizumab
  - etc

- There is early data that adding CTLA-4 inhibitors to PD-L1 inhibitors with or without chemotherapy may provide additional clinical and long term OS benefit in a specific patient cohort.

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POSEIDON : a randomized, open label, global phase III study evaluating durvalumab with and without tremelimumab in combination with chemotherapy regimens as first-line treatment for squamous or non-squamous mNSCLC

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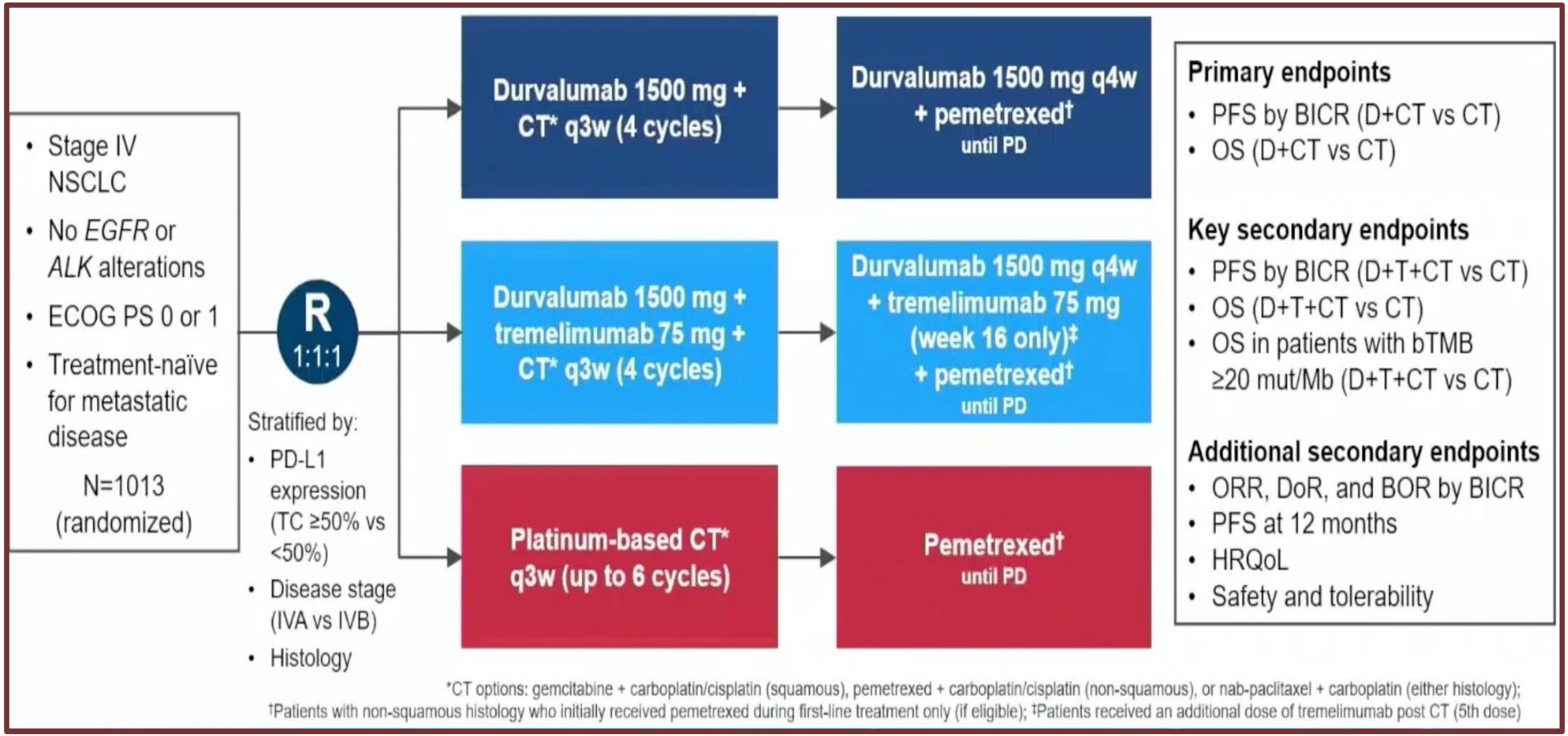

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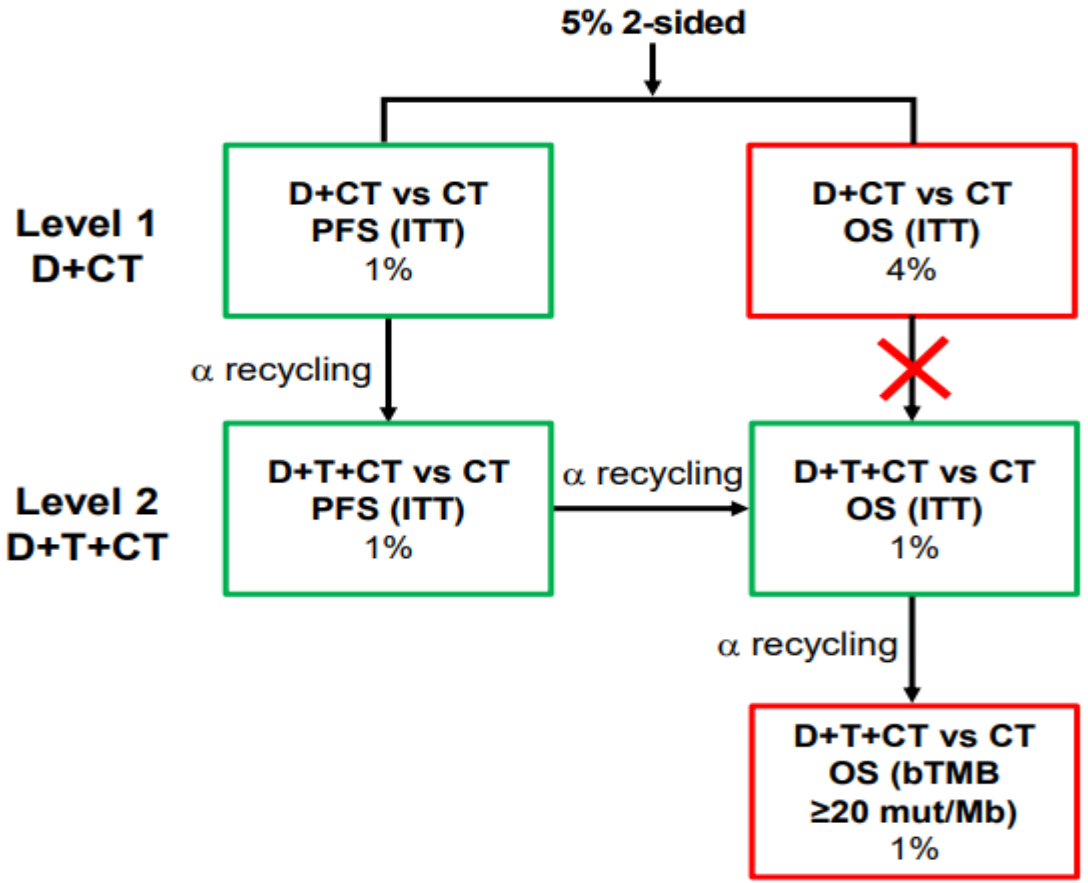
Statistical Analysis

- Final PFS analysis planned at 75% maturity
  - At data cut-off (Jul 24, 2019) there were 511 events across the D+CT and CT arms (76% maturity)
- Final OS analysis planned at 80% maturity
  - At data cut-off (Mar 12, 2021) there were 549 events across the D+CT and CT arms (81% maturity)
- Positivity for either of the primary endpoints (Level 1) triggered analysis of the key secondary endpoints (Level 2)
  - Positivity for either endpoint at Level 2 enabled alpha recycling to the other endpoint
- PFS and OS were analysed using a stratified log-rank test, adjusting for PD-L1 expression, disease stage, and histology
  - HRs and 95% CIs were estimated from a stratified Cox proportional hazards model

Actual MTP at Final Analysis



CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; MTP, multiple testing procedure

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Baseline Characteristics

	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 region, %	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*, %	37.9 / 61.8	36.7 / 63.3	36.2 / 63.5
AJCC disease stage IVA / IVB*, %	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%* / 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

*Stratification factors
AJCC, American Joint Committee on Cancer; CNS, central nervous system

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Primary Endpoints

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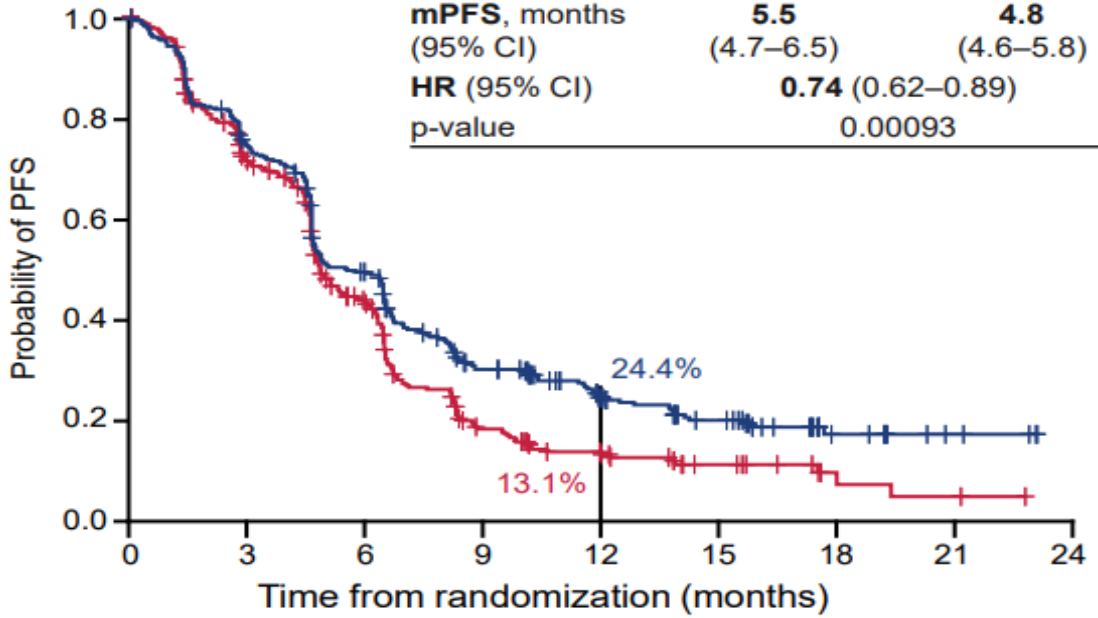
Durvalumab + CT vs CT: PFS and OS

PFS

	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	

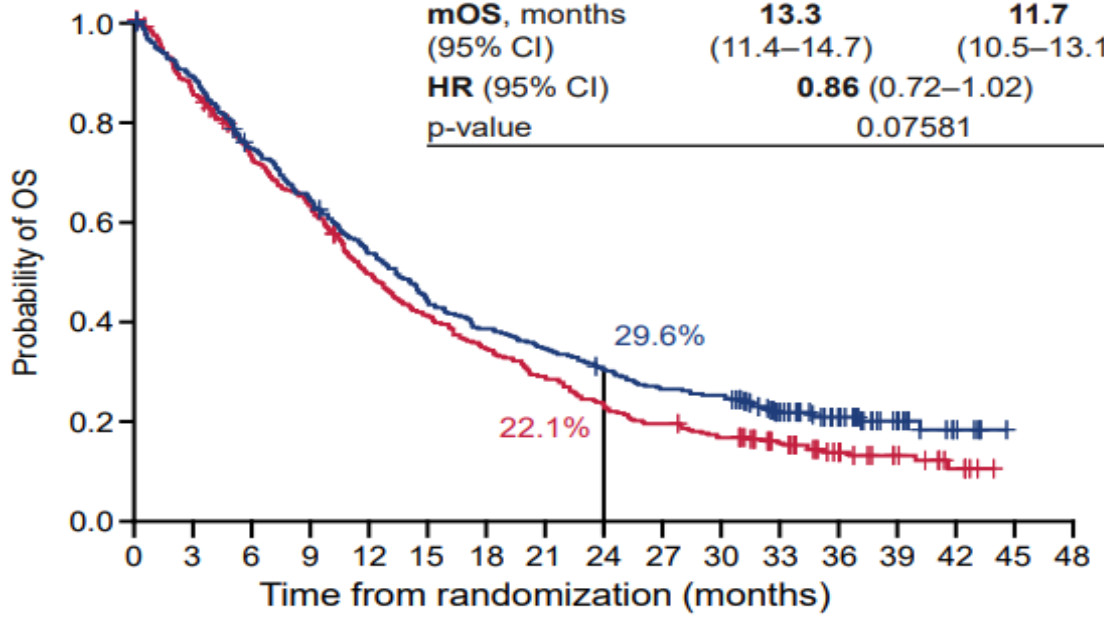


No. at risk									
D+CT	338	246	158	88	53	35	11	4	0
CT	337	219	121	43	23	12	3	2	0

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

OS

	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)

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DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

DCO, data cut-off; FA, final analysis; mOS, median OS; mPFS, median PFS

Secondary Endpoints

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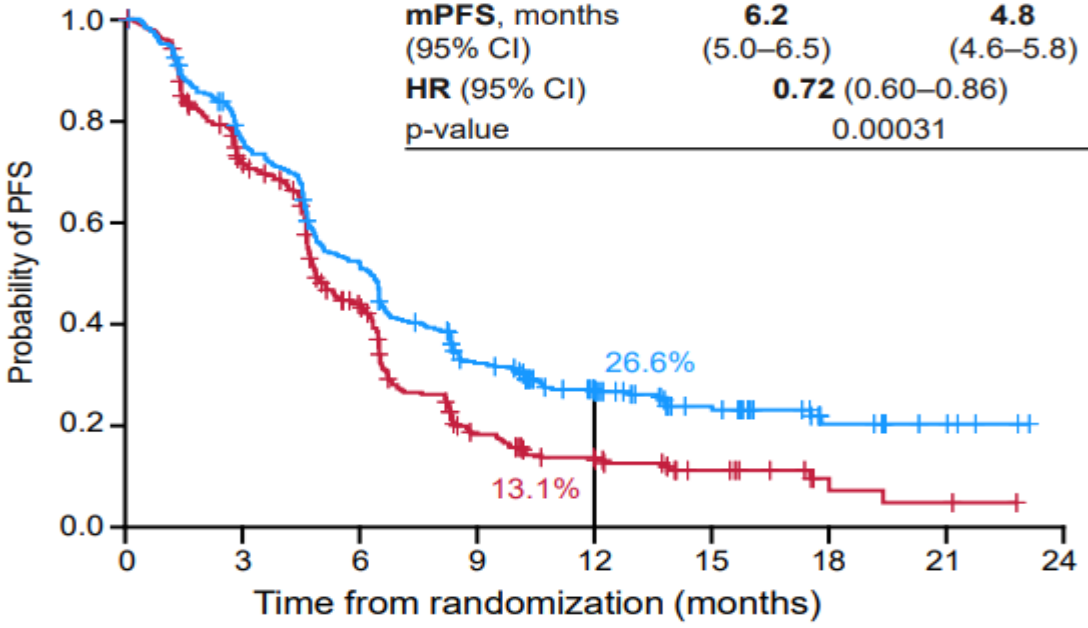
Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

	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	

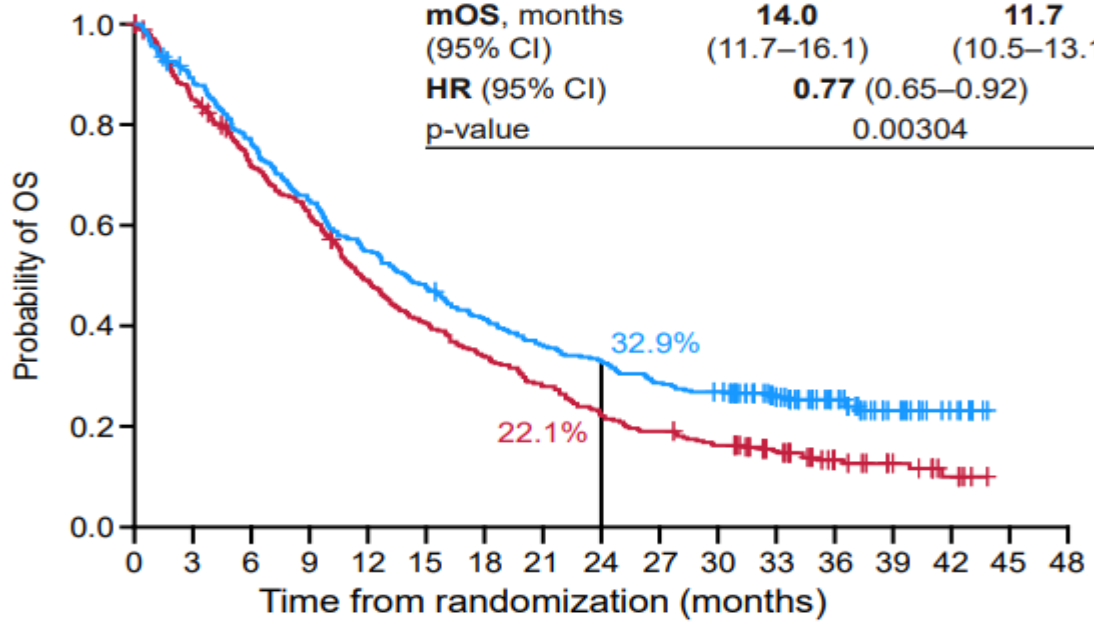


No. at risk									
D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

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

OS

	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)

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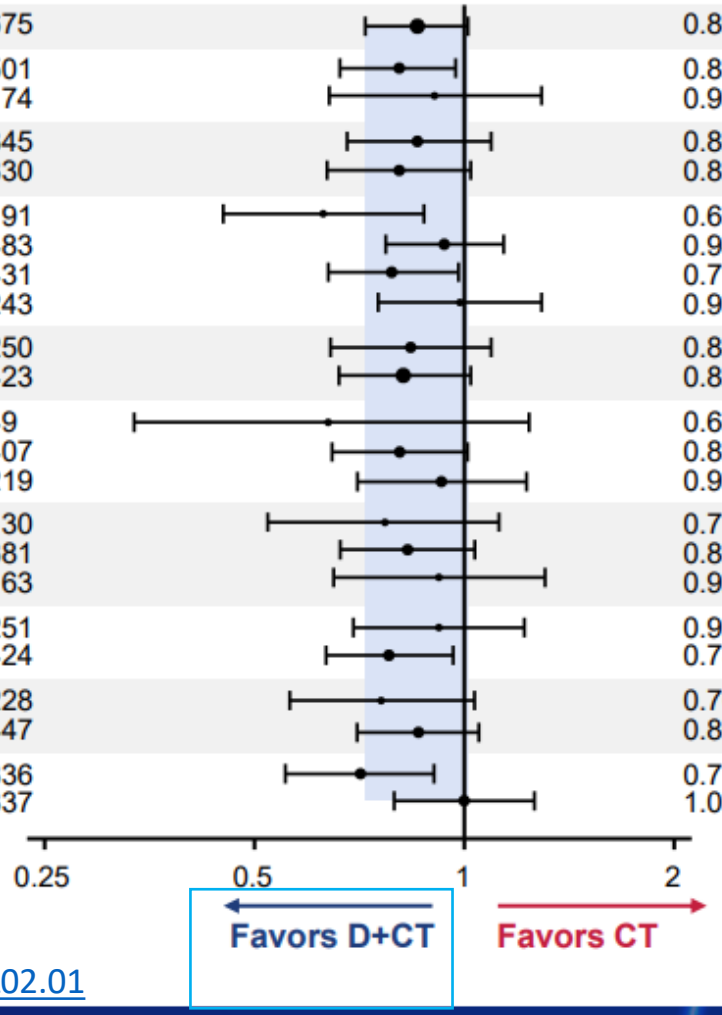
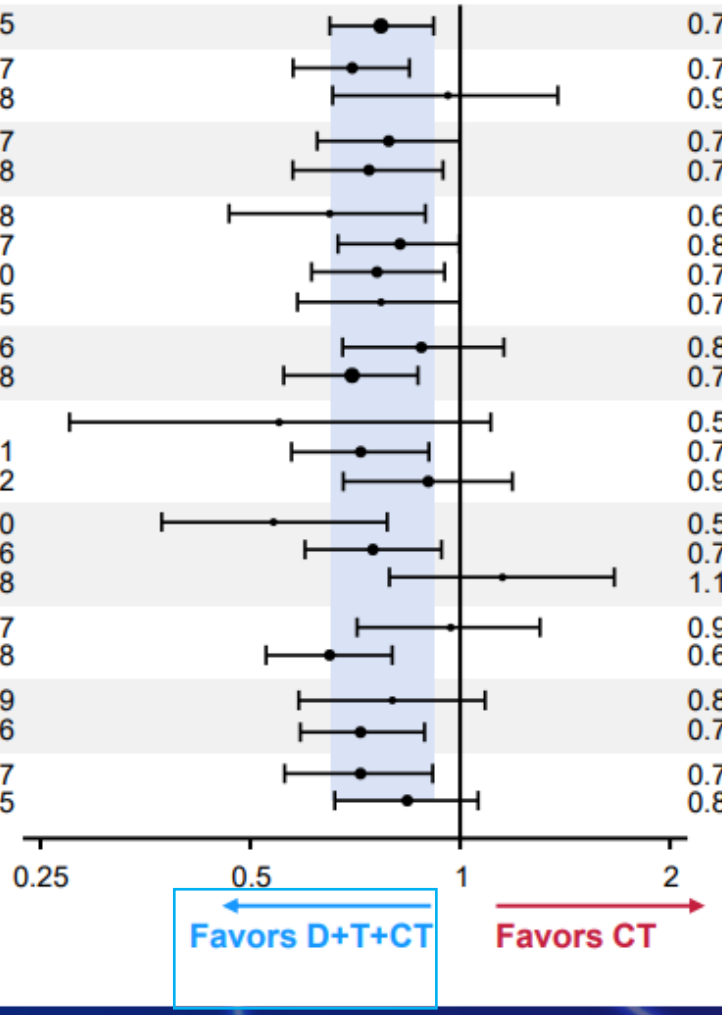
DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

Overall Survival: 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





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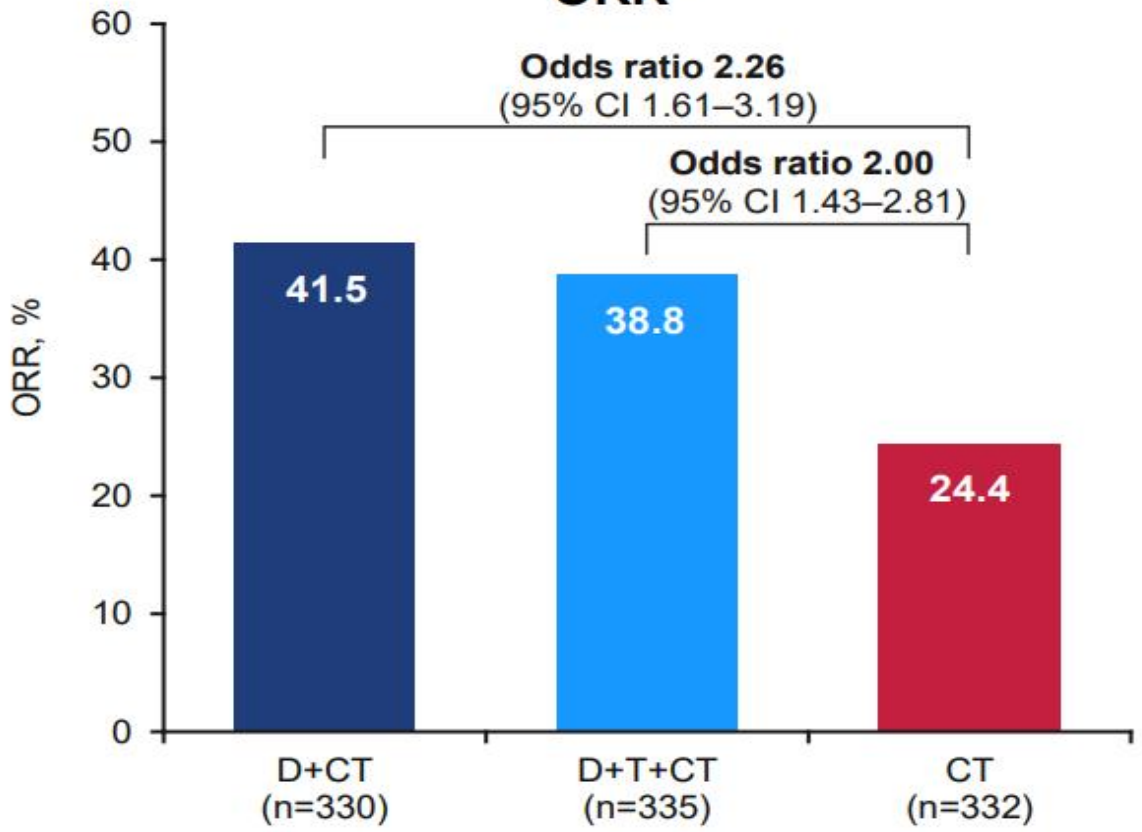
ITT analysis stratified, subgroup analysis unstratified
Size of circle is proportional to the number of events across both treatment groups
DCO OS FA: Mar 12, 2021

Confirmed Objective Response Rate and Duration of Response

ORR*



Duration of Response

	D+CT	D+T+CT	CT
Responders*, 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**

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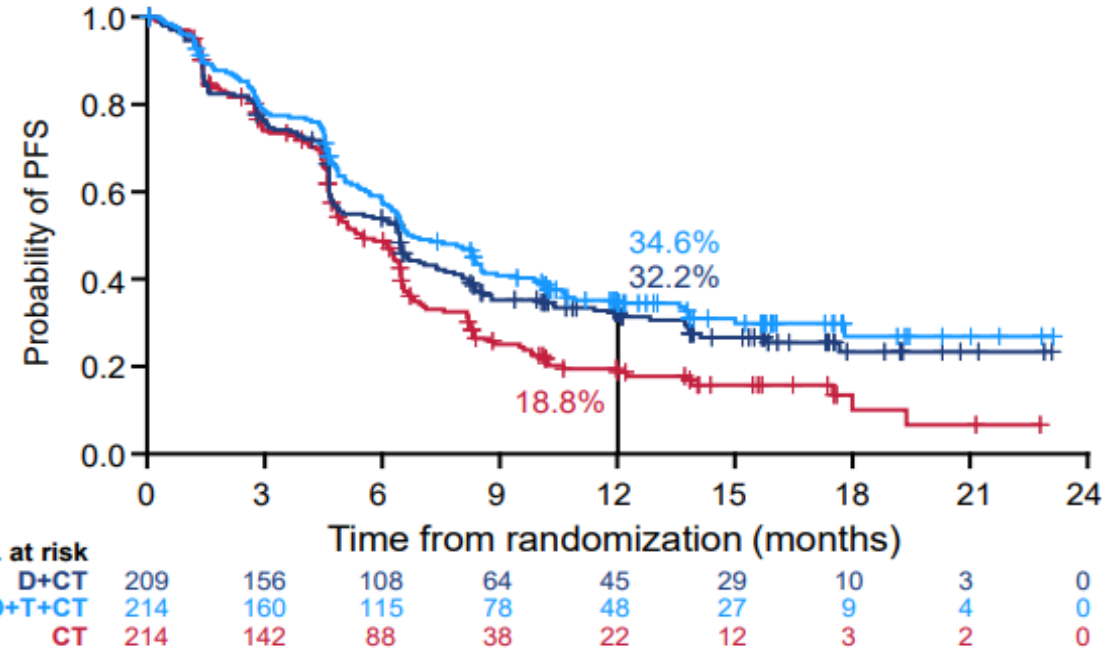
*Confirmed objective response by BICR assessed in patients with measurable disease at baseline; confirmation was not required per protocol (post-hoc analysis)
DCO PFS FA: Jul 24, 2019
NE, not estimable

Outcomes in Patients with Non-Squamous Histology

95.5% of patients with non-squamous histology receiving CT had pemetrexed + platinum

PFS and ORR

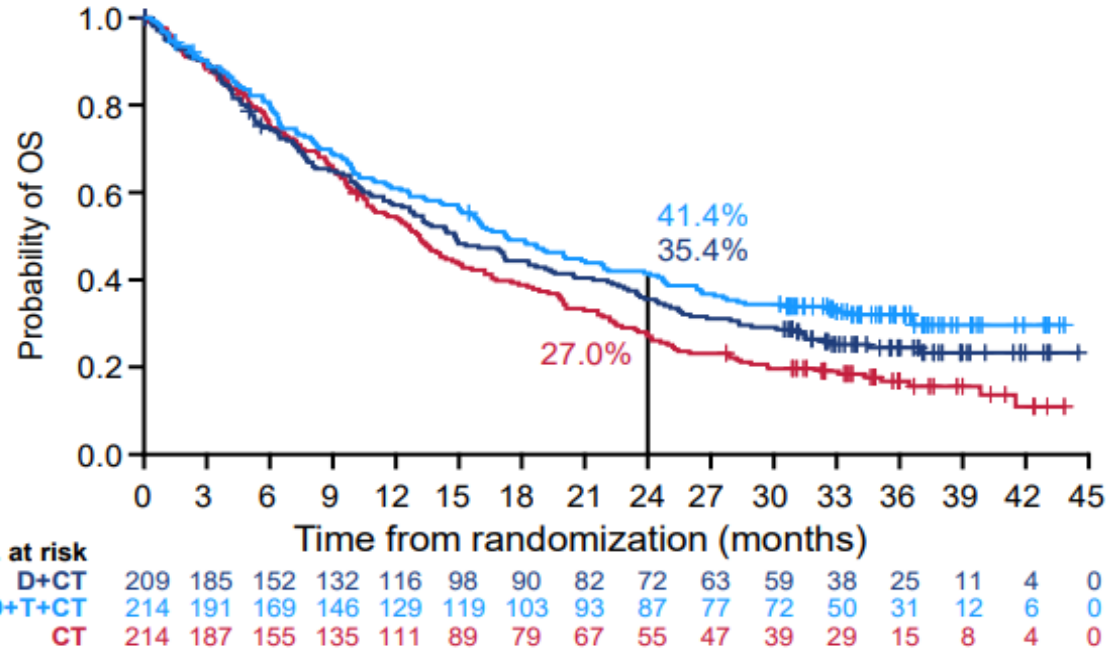
	D+CT	D+T+CT	CT
Events, n/N (%)	144/209 (68.9)	136/214 (63.6)	154/214 (72.0)
mPFS, months (95% CI)	**6.4** (4.7–7.4)	**6.8** (6.1–8.5)	**5.5** (4.8–6.4)
HR* (95% CI)	**0.77** (0.61–0.96)	**0.66** (0.52–0.84)	–
Confirmed ORR†, % (n/N)	**44.3** (90/203)	**45.5** (96/211)	**23.7** (50/211)
mDoR†, months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

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*HR <1 favors D (± T) + CT versus CT
†Analysis of ORR and DoR by histology was post hoc
DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021
mDoR, median duration of response

Outcomes in Patients with Squamous Histology

88.3% of patients with squamous histology receiving CT had gemcitabine + platinum

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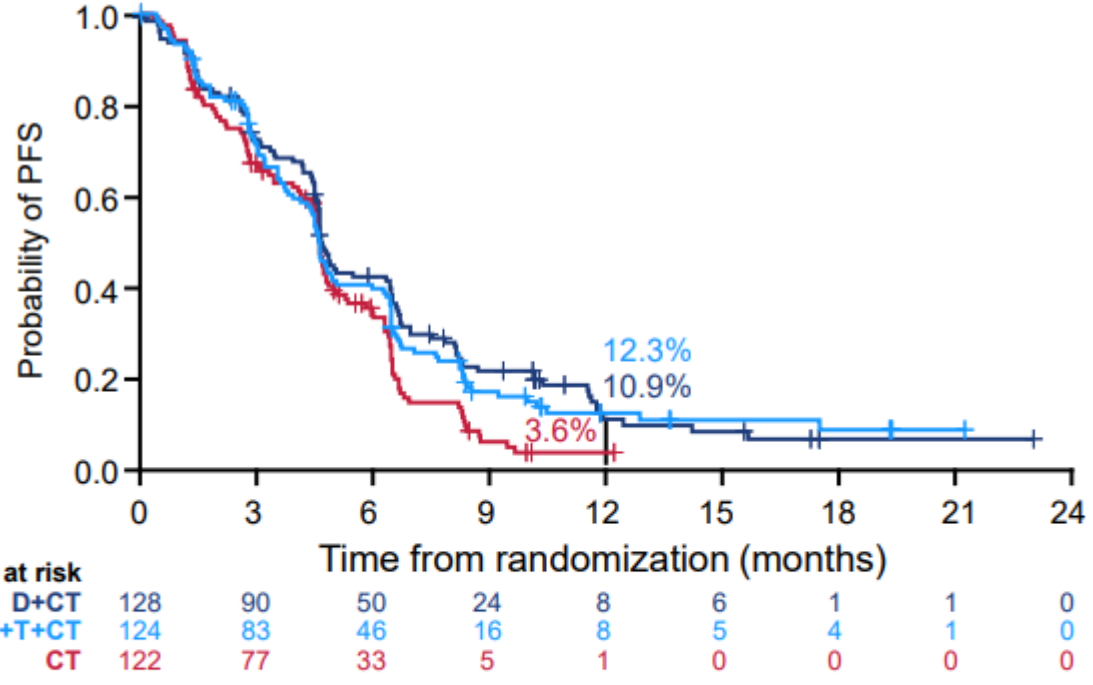
PFS and ORR

	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* (95% CI)	**0.68** (0.52–0.90)	**0.77** (0.58–1.01)	–
Confirmed ORR†, % (n/N)	**37.3** (47/126)	**27.4** (34/124)	**25.6** (31/121)
mDoR†, months (95% CI)	**5.5** (4.9–6.7)	**5.6** (4.3–7.2)	**4.8** (3.7–5.2)

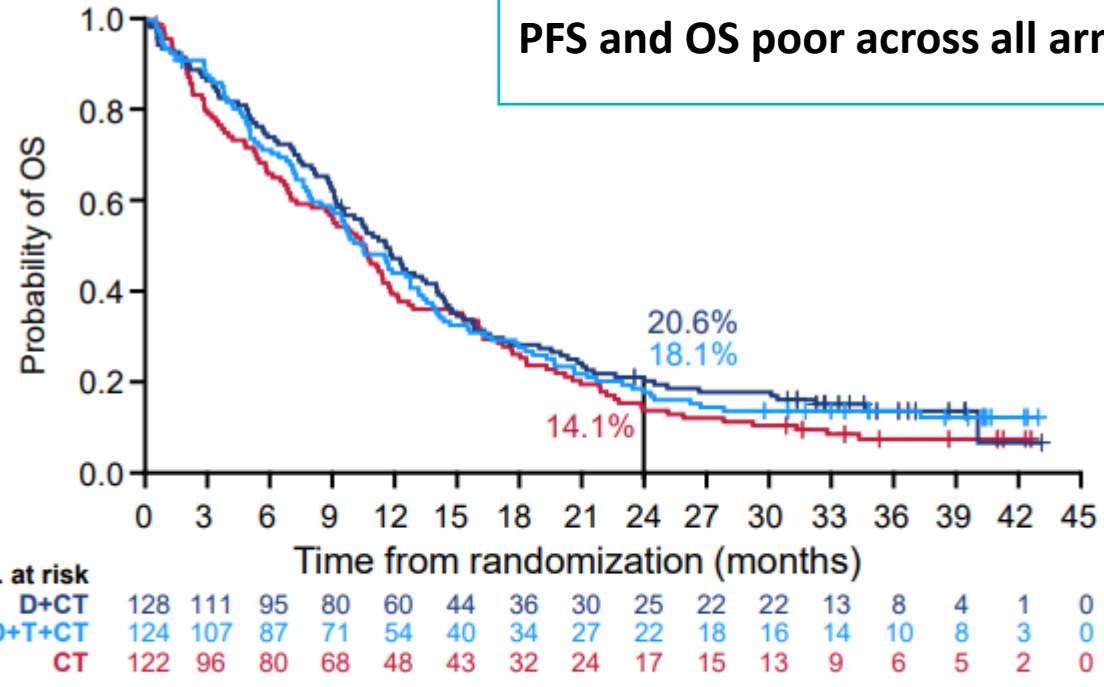


No. at risk

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* (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

PFS and OS poor across all arms

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*HR <1 favors D (± T) + CT versus CT
†Analysis of ORR and DoR by histology was post hoc
DCO PFS FA: Jul 24, 2019; DCO OS FA: Mar 12, 2021

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Patient Disposition and Subsequent Anticancer Therapy

	D+CT (n=338)	D+T+CT (n=338)	CT (n=337)
Received treatment, n	335*	331*	331
Ongoing durvalumab	31	36	–
Ongoing maintenance pemetrexed	21	19	5
Received subsequent systemic anticancer therapy, n (%)	139 (41.1)	123 (36.4)	194 (57.6)
Subsequent immunotherapy	22 (6.5)	22 (6.5)	112 (33.2)

After median 3 yr follow up approx. 10% pts who got IO and CT remain on study

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*Among these patients, 1 patient in the D+CT arm and 1 patient in the D+T+CT arm did not receive immunotherapy and were included in the CT arm for the safety analysis set

DCO OS FA: Mar 12, 2021

Treatment Exposure (Safety Analysis Set)

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	D+CT (n=334)	D+T+CT (n=330)	CT (n=333)
Received CT in combination stage, n	334	329*	333
Pemetrexed + carboplatin/cisplatin, n (%)	198 (59.3)	198 (60.2)	204 (61.3)
Gemcitabine + carboplatin/cisplatin, n (%)	107 (32.0)	107 (32.5)	112 (33.6)
Nab-paclitaxel + carboplatin, n (%)	29 (8.7)	24 (7.3)	17 (5.1)
No. of cycles of CT in combination stage, n (%)			
≥4 cycles	273 (81.7)	259 (78.5)	247 (74.2)
≥5 cycles	8 (2.4)†	4 (1.2)†	91 (27.3)
≥6 cycles	1 (0.3)†	2 (0.6)†	77 (23.1)
Received maintenance pemetrexed‡, n (%)	159 (80.3)	149 (75.3)	131 (64.2)
Median number of durvalumab doses, n (range)	8.0 (1–48)	8.0 (1–49)	
Received 5 tremelimumab doses, n (%)	–	218 (66.1)	

Addition of T did not affect exposure of pts to CT or durvalumab

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*1 patient received D+T but did not receive CT (reported percentages receiving each regimen are based on 329 patients)
†Only 4 cycles of CT permitted in the D+CT and D+T+CT arms per the protocol
‡Reported percentages are based on the number of patients who received pemetrexed doublet in the combination stage
DCO OS FA: Mar 12, 2021

Safety Summary

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	D+CT (n=334)	D+T+CT (n=330)	CT (n=333)
Any-grade all-cause AEs, n (%)	321 (96.1)	321 (97.3)	320 (96.1)
Grade 3/4 AEs*	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†	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‡, n (%)	296 (88.6)	306 (92.7)	298 (89.5)
Grade 3/4 AEs*	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†	47 (14.1)	51 (15.5)	33 (9.9)
AEs leading to death	7 (2.1)	11 (3.3)	8 (2.4)

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*Maximum reported CTCAE grade; †Includes patients who permanently discontinued at least one study drug
‡AEs assessed by the investigator as possibly related to any study treatment
DCO OS FA: Mar 12, 2021
AE, adverse event; CTCAE, common terminology criteria for adverse events

Immune-Mediated Adverse Events (Grouped Terms)

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mostly grade 1 or 2 and manageable	D+CT (n=334)		D+T+CT (n=330)		CT (n=333)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any imAE*, n (%)	64 (19.2)	23 (6.9)	111 (33.6)	33 (10.0)	17 (5.1)	5 (1.5)
Hypothyroid events	20 (6.0)	0	27 (8.2)	0	3 (0.9)	0
Pneumonitis	10 (3.0)	4 (1.2)	12 (3.6)	3 (0.9)	2 (0.6)	2 (0.6)
Rash	5 (1.5)	2 (0.6)	13 (3.9)	3 (0.9)	6 (1.8)	2 (0.6)
Hepatic events	11 (3.3)	8 (2.4)	12 (3.6)	7 (2.1)	0	0
Dermatitis	4 (1.2)	1 (0.3)	14 (4.2)	1 (0.3)	1 (0.3)	0
Colitis	4 (1.2)	1 (0.3)	13 (3.9)	5 (1.5)	0	0
Hyperthyroid events	4 (1.2)	1 (0.3)	9 (2.7)	0	1 (0.3)	0
Adrenal insufficiency	4 (1.2)	1 (0.3)	8 (2.4)	2 (0.6)	0	0
Rare/miscellaneous	1 (0.3)	1 (0.3)	11 (3.3)	3 (0.9)	2 (0.6)	1 (0.3)

imAEs leading to death occurred in 1 patient receiving D+CT (myocarditis) and in 2 patients receiving D+T+CT (pneumonitis in 1 patient; and hepatic, renal, and pancreatic events and myocarditis in 1 patient)

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*imAEs with an incidence >2% in any treatment arm; an imAE was defined as an AE of special interest consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology, and requiring the use of systemic steroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy. DCO OS FA: Mar 12, 2021
imAE, immune-mediated AE

Summary

- PFS was significantly improved with first-line durvalumab +CT vs CT alone in patients with mNSCLC with a positive trend towards OS that was not statistically significant
- First-line durvalumab + tremelimumab+ CT demonstrated statistically significant and clinically meaningful improvements in both PFS and OS compared to CT alone in patients with mNSCLC
- The safety profile was similar across all 3 arms, with no new safety signals identified.
- The addition of tremelimumab to durvalumab +CT did not lead to a clinically meaningful increase in treatment discontinuation
- D+T+CT represents a potential frontline treatment option in mNSCLC

Poseidon- too many fish in the sea?

- Never too many fish but…
  - Do we need another approval in this space that is not clearly better than what we have already?
  - Are more drugs better?
  - Financial toxicity 4 drugs vs other options with less agents
  - Who is the right patient for this combination?
    - ❖ Perhaps the pd-l1 low population may benefit the most based on subset analysis

Thank you to the NY Lung Cancer Foundation for having me, patients that participated in this study and their families and of course all of you for listening tonight!

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