LUNG CANCER UPDATES

AACR HIGHLIGHTS

29 MARZO - 3 ABRIL 2019

Iniciativa científica de:

GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

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ATLANTA

Tumor Mutacional Burden as a biomarker of survival in metastatic Non-Small cell Lung cancer: Blood and tissue TMB. Analysis from MYSTIC, a phase 3 study of first-line Durvalumab +/- Tremelimumab vs Chemotherapy

Dr. Juan Felipe Córdoba

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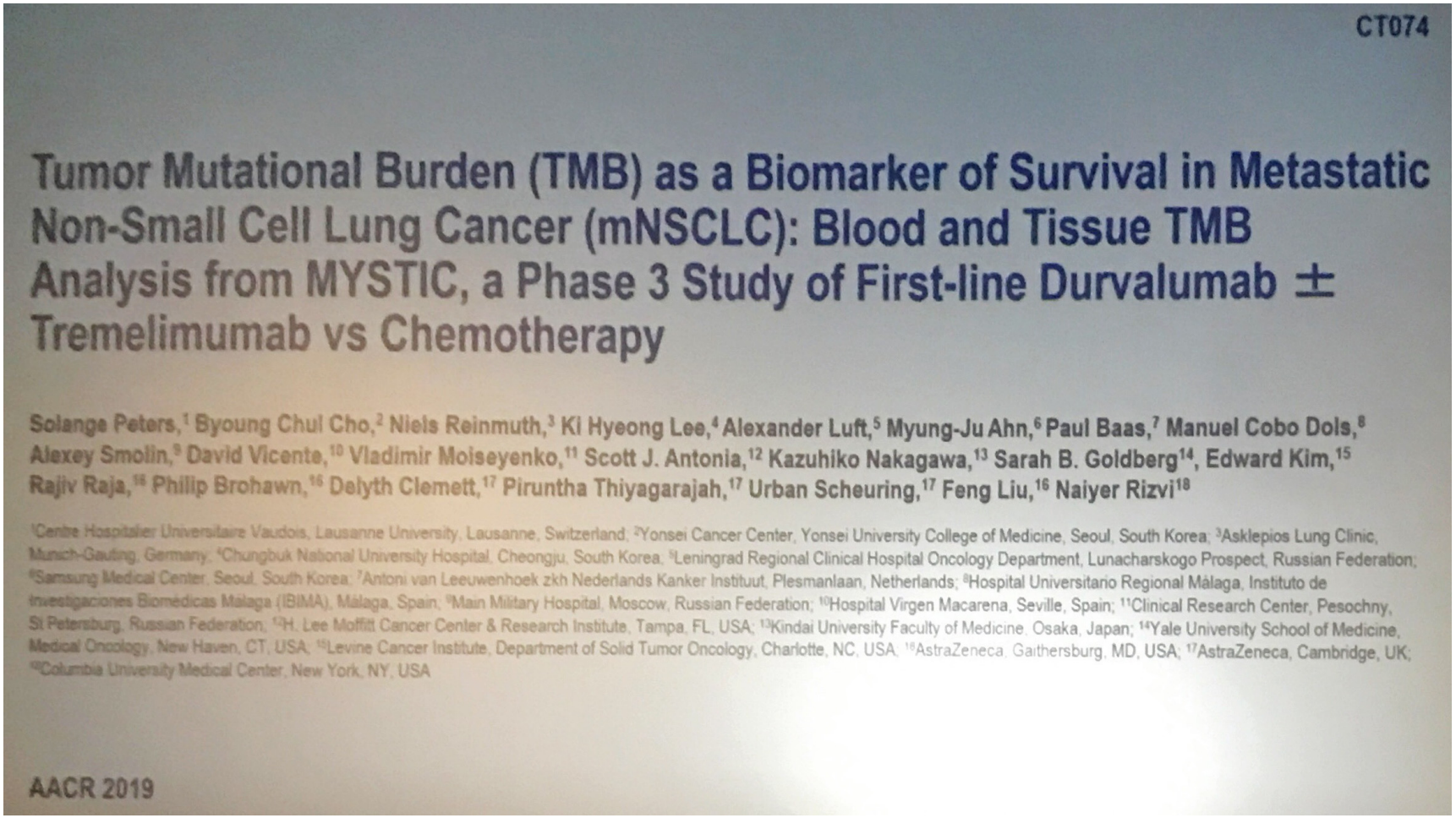

CT074

Tumor Mutational Burden (TMB) as a Biomarker of Survival in Metastatic Non-Small Cell Lung Cancer (mNSCLC): Blood and Tissue TMB Analysis from MYSTIC, a Phase 3 Study of First-line Durvalumab ± Tremelimumab vs Chemotherapy

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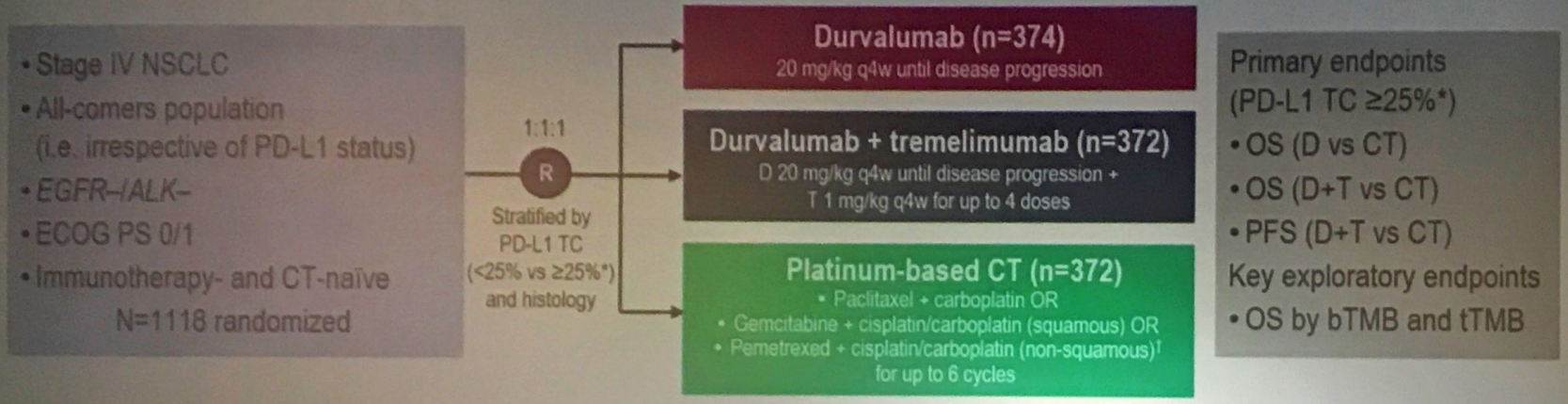
Background

- Durvalumab (anti-PD-L1) is approved for unresectable, Stage III NSCLC and has shown clinical activity in heavily pretreated patients with mNSCLC in Phase 2 and 3 trials[1,2]

MYSTIC study design: Phase 3, open-label, multicenter study[3]



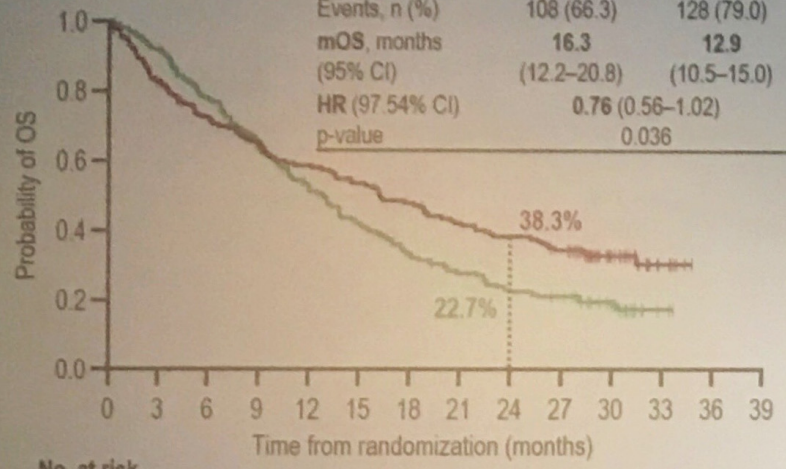
*Ventana PD-L1 (SP263) assay using newly acquired or archival (<3 months) tumor biopsy; †Followed by pemetrexed maintenance therapy if eligible; bTMB, blood tumor mutational burden; CT, chemotherapy; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; mNSCLC, metastatic non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PS, performance status; T, tremelimumab; TC ≥25%, ≥25% of tumor cells with membrane staining for PD-L1; tTMB, tissue tumor mutational burden

1. Garassino MC, et al. Lancet Oncol 2018;19:521–536; 2. Kowalski D, et al. Presented at ESMO 2018, #1378O; 3. Rizvi N, et al. Presented at ESMO I-O 2018, #LBA6

Overall Survival in Patients With PD-L1 TC ≥25% (Primary Endpoint)

Durvalumab vs chemotherapy

	D (n=163)	CT (n=162)
Events, n (%)	108 (66.3)	128 (79.0)
mOS, months (95% CI)	16.3 (12.2–20.8)	12.9 (10.5–15.0)
HR (97.54% CI)	0.76 (0.56–1.02)	
p-value	0.036	

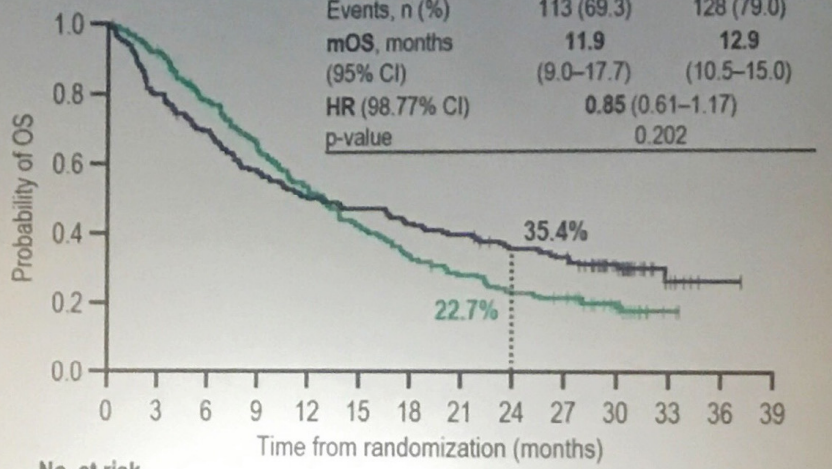


No. at risk

D	163	134	116	104	93	85	76	66	60	53	25	6	0	0
CT	162	147	123	101	83	67	53	43	35	32	20	2	0	0

Durvalumab + tremelimumab vs chemotherapy

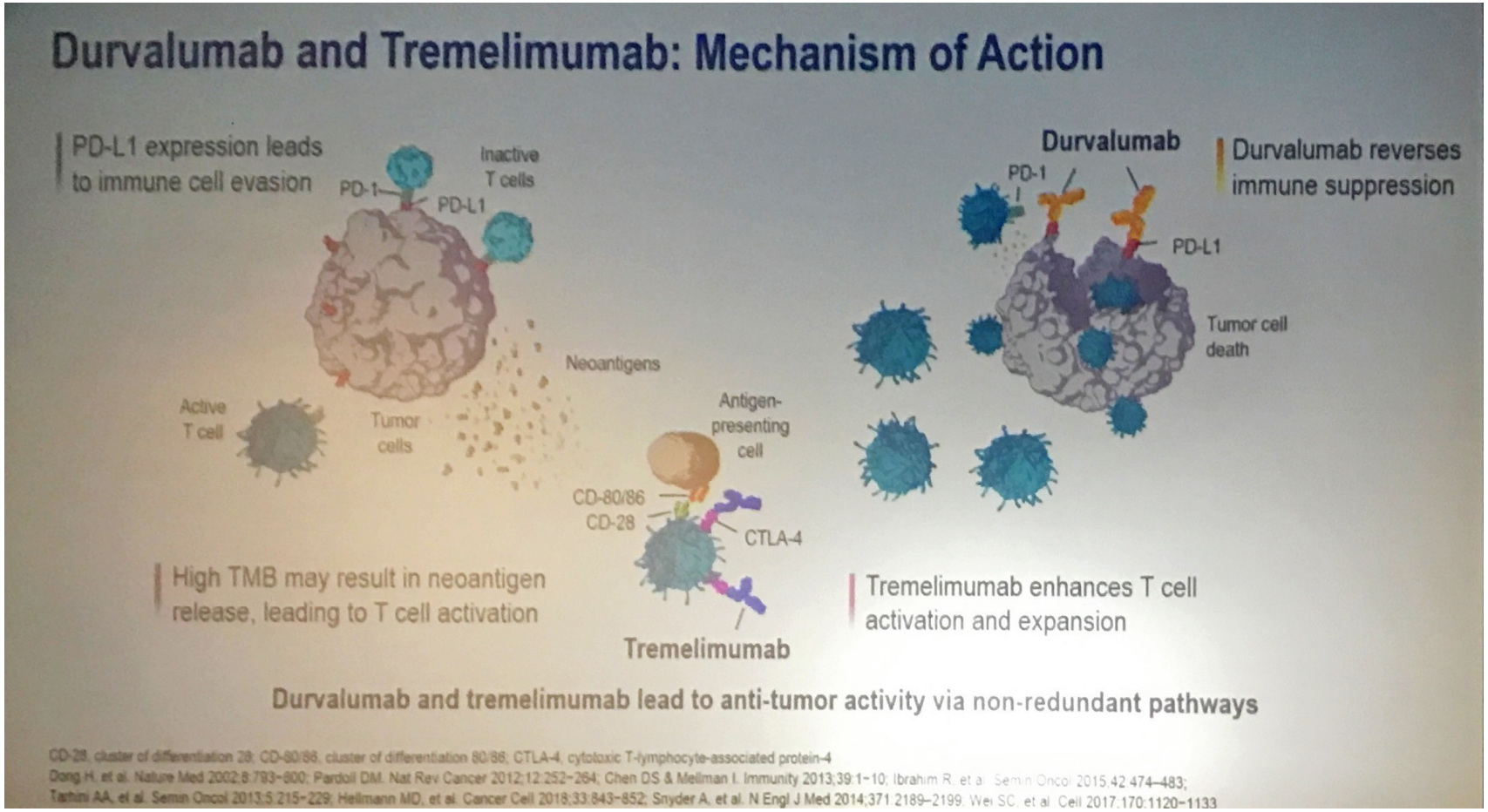
	D+T (n=163)	CT (n=162)
Events, n (%)	113 (69.3)	128 (79.0)
mOS, months (95% CI)	11.9 (9.0–17.7)	12.9 (10.5–15.0)
HR (98.77% CI)	0.85 (0.61–1.17)	
p-value	0.202	



No. at risk

D+T	163	130	111	92	80	75	68	63	54	50	30	6	1	0
CT	162	147	123	101	83	67	53	43	35	32	20	2	0	0

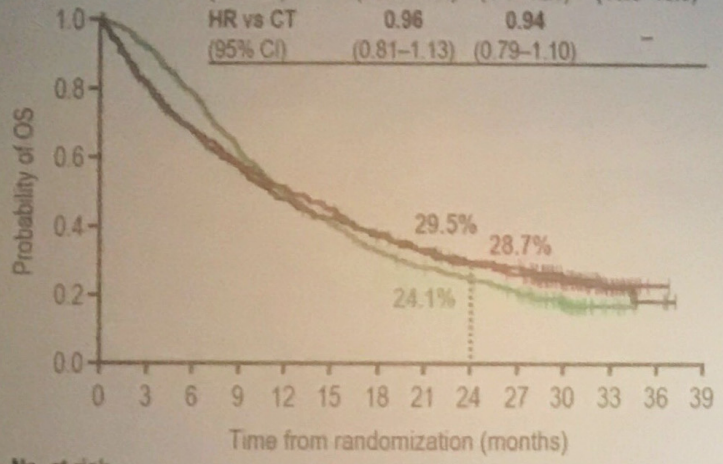
Data cut-off October 4, 2018; mOS, median overall survival
Rizvi N. et al. Presented at ESMO I-O 2018, #LBA6


Durvalumab and Tremelimumab: Mechanism of Action
PD-L1 expression leads to immune cell evasion
Inactive T cells
PD-1
PD-L1
Neoantigens
Active T cell
Tumor cells
Antigen-presenting cell
CD-80/86
CD-28
CTLA-4
Tremelimumab
High TMB may result in neoantigen release, leading to T cell activation
Durvalumab
PD-1
PD-L1
Durvalumab reverses immune suppression
Tumor cell death
Tremelimumab enhances T cell activation and expansion
Durvalumab and tremelimumab lead to anti-tumor activity via non-redundant pathways
CD-28, cluster of differentiation 28; CD-80/86, cluster of differentiation 80/86; CTLA-4, cytotoxic T-lymphocyte-associated protein-4
Dong H, et al. Nature Med 2002;8:793–800; Pardoll DM. Nat Rev Cancer 2012;12:252–264; Chen DS & Mellman I. Immunity 2013;39:1–10; Ibrahim R, et al. Semin Oncol 2015;42:474–483;
Tarhini AA, et al. Semin Oncol 2013;5:215–229; Hellmann MD, et al. Cancer Cell 2018;33:843–852; Snyder A, et al. N Engl J Med 2014;371:2189–2199; Wei SC, et al. Cell 2017;170:1120–1133

Overall Survival in ITT and Tissue TMB Evaluable Populations

ITT population

	D (n=374)	D+T (n=372)	CT (n=372)
mOS, months	12.3	11.2	11.8
(95% CI)	(10.1–14.9)	(9.5–12.9)	(10.5–13.3)
HR vs CT	0.96	0.94	–
(95% CI)	(0.81–1.13)	(0.79–1.10)	

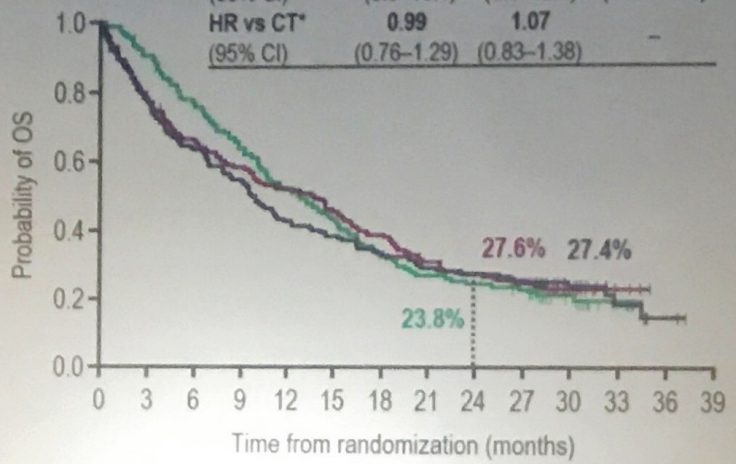


No. at risk

D	374	303	249	212	185	161	136	115	103	92	41	14	1	0
D+T	372	303	253	212	175	154	136	119	104	98	55	16	3	0
CT	372	336	287	227	180	148	118	100	85	71	37	6	0	0

tTMB evaluable population

	D (n=145)	D+T (n=164)	CT (n=151)
mOS, months	13.9	10.0	12.9
(95% CI)	(9.3–16.1)	(8.0–12.4)	(10.5–15.1)
HR vs CT*	0.99	1.07	–
(95% CI)	(0.76–1.29)	(0.83–1.38)	



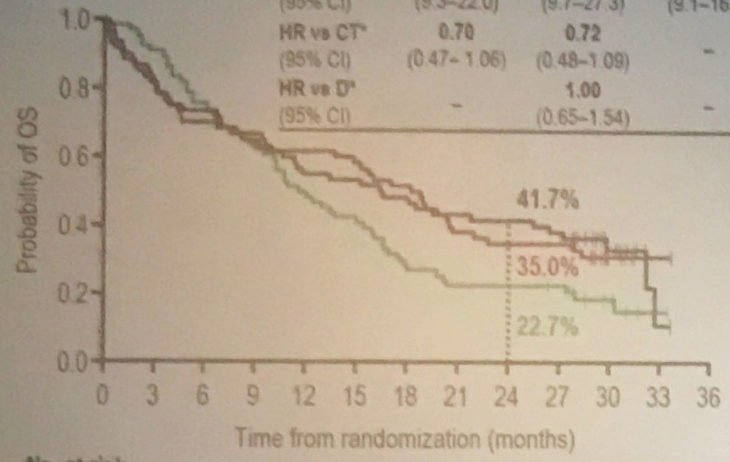
	145	115	97	85	76	66	56	45	40	35	15	4	0	0
	164	129	106	90	70	63	55	48	45	42	23	7	2	0
	151	135	116	98	78	64	49	39	35	33	17	3	0	0

*Unadjusted; data cut-off October 4, 2018

Overall Survival in Patients With Tissue TMB ≥10 and <10 mut/Mb

tTMB ≥10 mut/Mb

	D (n=60)	D+T (n=60)	CT (n=67)
mOS, months (95% CI)	18.6 (9.3–22.0)	16.6 (9.7–27.3)	11.9 (9.1–16.0)
HR vs CT* (95% CI)	0.70 (0.47–1.06)	0.72 (0.48–1.09)	–
HR vs D* (95% CI)	–	1.00 (0.65–1.54)	–

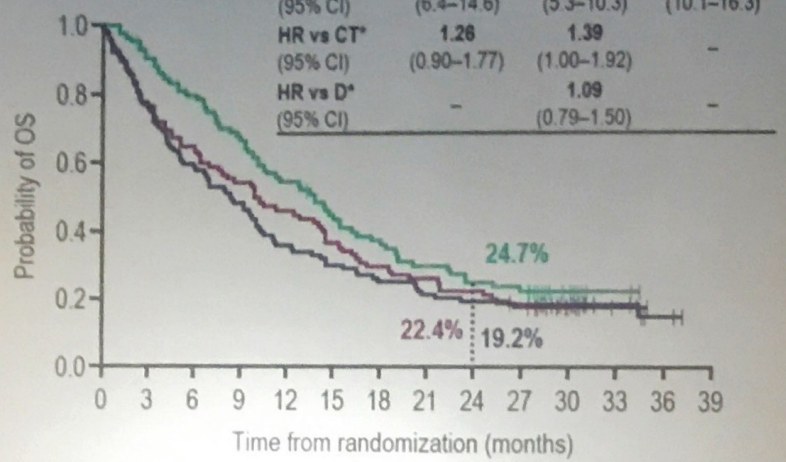


No. at risk

D	60	50	42	39	37	35	31	23	21	21	9	2	0
D+T	60	49	44	40	33	32	29	26	25	23	10	1	0
CT	67	60	50	42	33	28	19	15	15	14	7	1	0

tTMB <10 mut/Mb

	D (n=85)	D+T (n=104)	CT (n=84)
mOS, months (95% CI)	10.1 (6.4–14.6)	8.4 (5.3–10.3)	13.8 (10.1–16.3)
HR vs CT* (95% CI)	1.26 (0.90–1.77)	1.39 (1.00–1.92)	–
HR vs D* (95% CI)	–	1.09 (0.79–1.50)	–



85	65	55	46	39	31	25	22	19	14	6	2	0	0
104	80	62	50	37	31	26	22	20	19	13	6	2	0
84	75	66	56	43	36	30	24	20	19	10	2	0	0

*Unadjusted; data cut-off October 4, 2018

Blood Tumor Mutational Burden in MYSTIC

- bTMB was evaluated with the GuardantOMNI sequencing platform (Guardant Health) comprised of a 500-gene panel (1.0 Mb DNA footprint [coding regions only])
- The GuardantOMNI bTMB algorithm incorporates somatic single nucleotide variants and insertions/deletions and accounts for low tumor shedding or low ctDNA input
- The large bTMB dataset included baseline samples from 809 patients (72.4% of ITT) in the MYSTIC trial

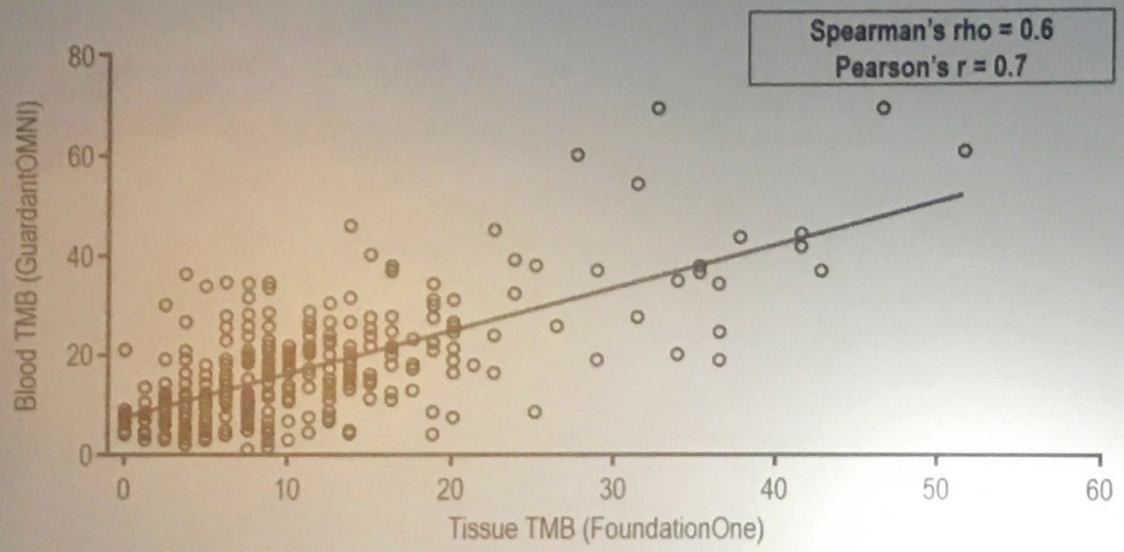
bTMB evaluable dataset

	Durvalumab (n=374)	Durvalumab + tremelimumab (n=372)	Chemotherapy (n=372)
Patients with bTMB data, n (%)	286 (76.5)	268 (72.0)	255 (68.5)

ITT, intent to treat

Correlation of Tissue and Blood Tumor Mutational Burden

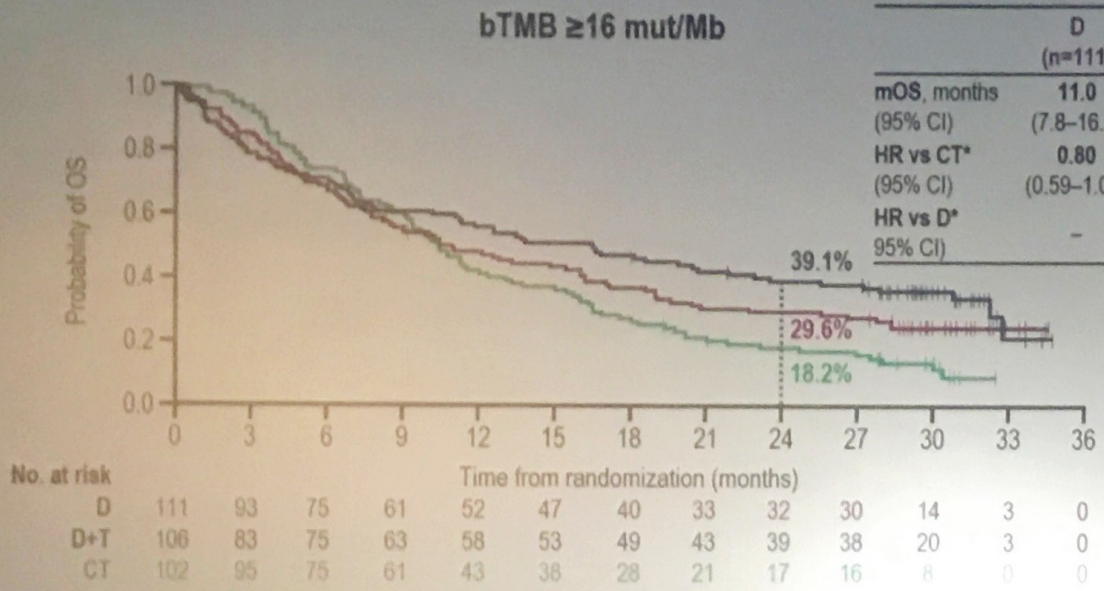
- In 352 (31.5% of ITT) matched patient specimens, tTMB values positively correlated with bTMB values



Reference line in correlation plot is from linear regression

OS Analysis by bTMB ≥16 mut/Mb (ESMO I-O 2018)

- In preliminary analyses, OS was improved with durvalumab + tremelimumab vs CT in patients with bTMB ≥16 mut/Mb[1]



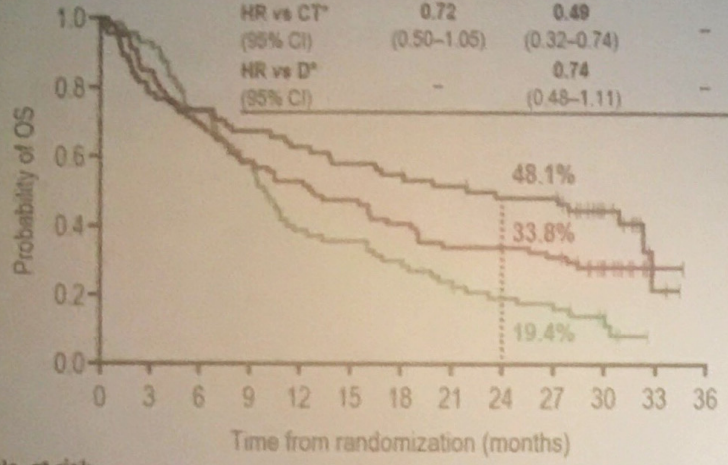
	D (n=111)	D+T (n=106)	CT (n=102)
mOS, months	11.0	16.5	10.5
(95% CI)	(7.8–16.1)	(10.3–22.9)	(8.8–12.4)
HR vs CT*	0.80	0.62	–
(95% CI)	(0.59–1.08)	(0.45–0.86)	
HR vs D*	–	0.82	–
95% CI)		(0.60–1.13)	

*Unadjusted, data cut-off October 4, 2018
1. Rizvi N, et al. Presented at ESMO I-O 2018. #LBA8

Overall Survival in Patients With Blood TMB ≥20 and <20 mut/Mb

bTMB ≥20 mut/Mb

	D (n=77)	D+T (n=64)	CT (n=70)
mOS, months	12.6	21.9	10.0
(95% CI)	(7.8–18.6)	(11.4–32.8)	(8.1–11.7)
HR vs CT*	0.72	0.49	–
(95% CI)	(0.50–1.05)	(0.32–0.74)	
HR vs D*	–	0.74	–
(95% CI)		(0.48–1.11)	



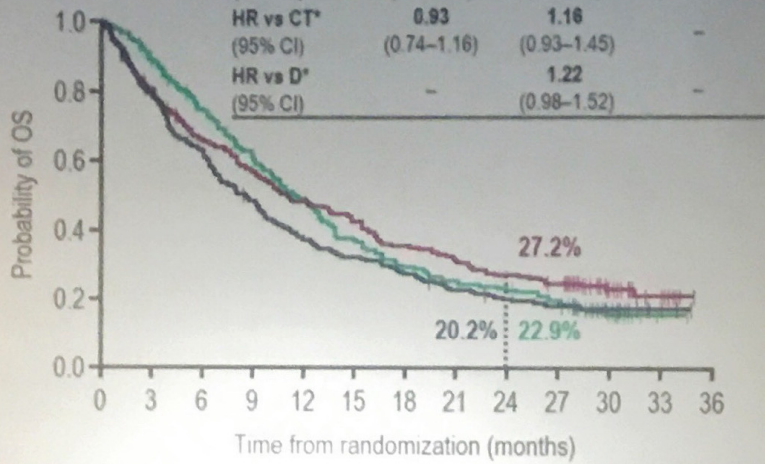
No. at risk

D	77	64	53	44	39	35	30	25	25	23	10	1	0
D+T	64	50	47	43	40	37	35	32	29	29	14	2	0
CT	70	65	51	41	27	25	21	16	12	11	6	0	0

*Unadjusted; data cut-off October 4, 2018

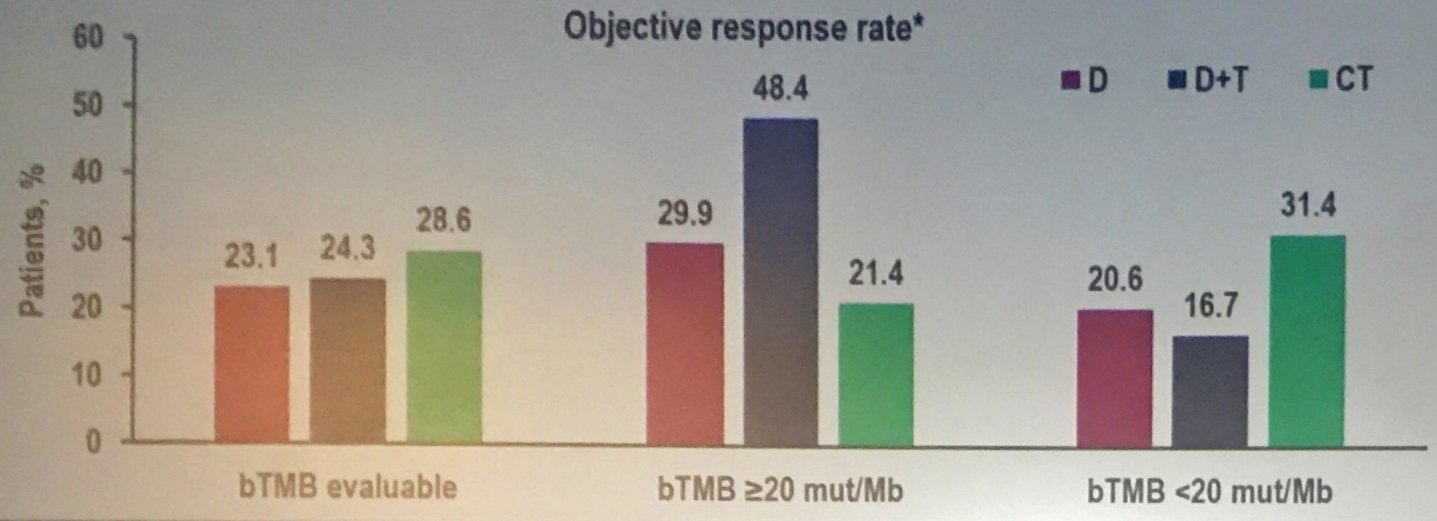
bTMB <20 mut/Mb

	D (n=209)	D+T (n=204)	CT (n=185)
mOS, months	11.0	8.5	11.6
(95% CI)	(8.9–14.9)	(6.7–9.8)	(9.6–13.1)
HR vs CT*	0.93	1.16	–
(95% CI)	(0.74–1.16)	(0.93–1.45)	
HR vs D*	–	1.22	–
(95% CI)		(0.98–1.52)	



209	167	134	114	98	86	72	63	55	49	21	8	0
204	161	129	98	78	65	55	45	39	35	18	4	0
185	162	135	112	92	78	63	45	41	34	17	1	0

Tumor Response in Patients With Blood TMB ≥20 and <20 mut/Mb



	bTMB ≥20 mut/Mb			bTMB <20 mut/Mb		
	D (n=77)	D+T (n=64)	CT (n=70)	D (n=209)	D+T (n=204)	CT (n=185)
Patients with response, n	23	31	15	43	34	58
Remaining in response at 6 mo, %	86.5	85.6	14.4	64.0	66.6	33.3
Remaining in response at 12 mo, %	80.3	81.7	7.2	59.1	48.2	14.3

*Blinded independent central review per RECIST v1.1; responses include unconfirmed responses; data cut-off June 1, 2017