Tumor Response From Durvalumab (MEDI4736) + Tremelimumab Treatment in Patients with Advanced Non-small Cell Lung Cancer is Observed Regardless of PD-L1 Status

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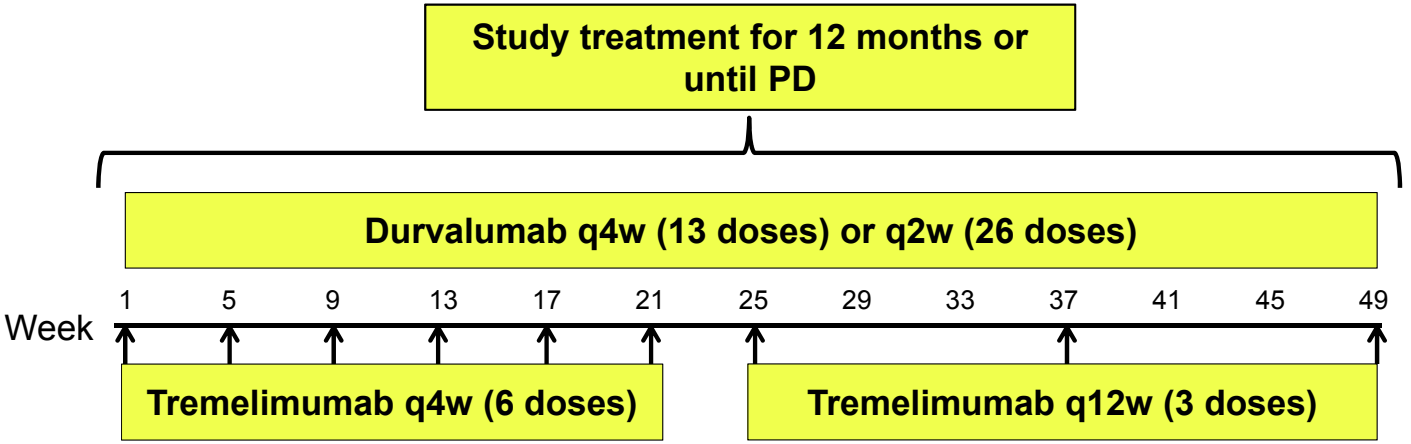
Disclosures

- Study supported by MedImmune/AstraZeneca
- Naiyer Rizvi
  - Consultant/advisory role with BMS, Merck, AstraZeneca, Roche

Study design

- Phase 1b, non-randomized, multicenter, open-label dose-escalation and dose-expansion study evaluating safety and antitumor activity of durvalumab plus tremelimumab combination in patients with advanced NSCLC
- PD-L1 expression evaluated with a Ventana SP263 immunohistochemistry assay



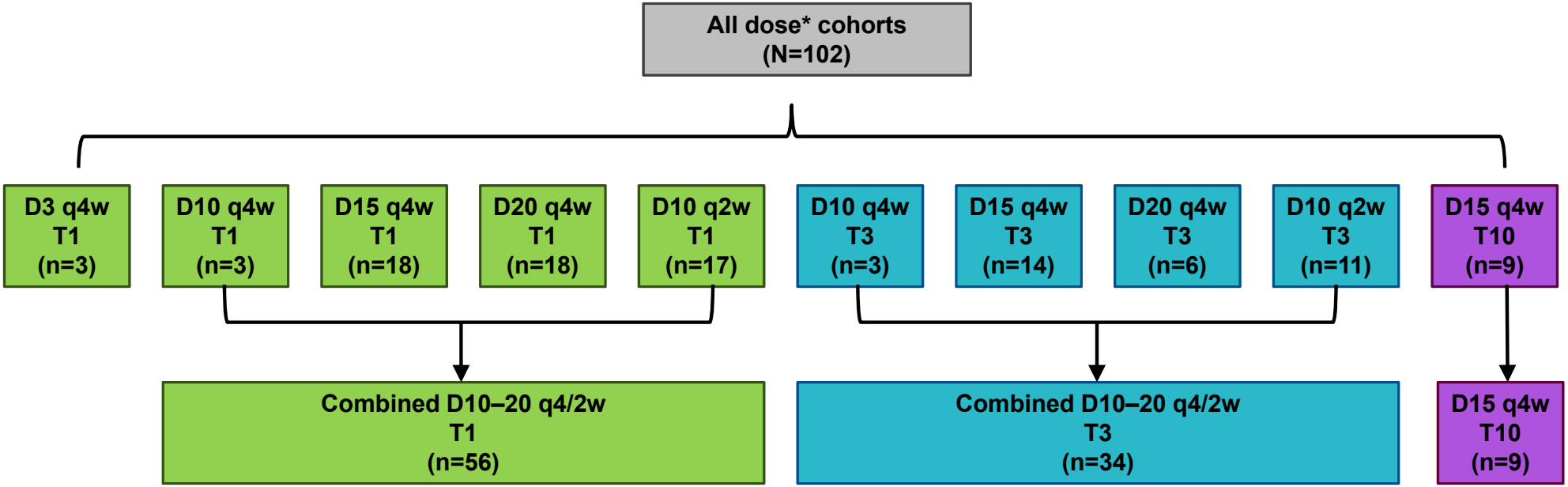
- Modified zone-based design permitted exploration of multiple dose combinations:

- Durvalumab 3 mg/kg q4w + tremelimumab 1 mg/kg
- Durvalumab 10 mg/kg q4w + tremelimumab 1 mg/kg
- Durvalumab 15 mg/kg q4w + tremelimumab 1 mg/kg
- Durvalumab 20 mg/kg q4w + tremelimumab 1 mg/kg
- Durvalumab 10 mg/kg q4w + tremelimumab 3 mg/kg
- Durvalumab 15 mg/kg q4w + tremelimumab 3 mg/kg
- Durvalumab 20 mg/kg q4w + tremelimumab 3 mg/kg
- Durvalumab 15 mg/kg q4w + tremelimumab 10 mg/kg
- Durvalumab 10 mg/kg q2w + tremelimumab 1 mg/kg
- Durvalumab 10 mg/kg q2w + tremelimumab 3 mg/kg

PD, progressive disease; PD-L1, programmed cell death ligand-1; q#w, every # weeks.

Study treatment – dose cohorts

- As of June 1, 2015, 102 patients have been treated in the dose-escalation phase across 5 centers in the US
- Median follow-up 18.8 weeks (range 2–68)



*Units for durvalumab and tremelimumab doses are mg/kg. D, durvalumab; q#w, every # weeks; T, tremelimumab.

Demographic and baseline characteristics

Characteristic	D10–20 q4/2w T1* (n=56)	D10–20 q4/2w T3 (n=34)	D15 q4w T10 (n=9)	All cohorts (N=102)
Mean age, y (range)	65.7 (43–78)	64.2 (22–86)	63.7 (54–77)	65.3 (22–86)
Male sex, n (%)	28 (50)	22 (65)	4 (44)	55 (54)
Non-squamous histology, n (%)	49 (88)	32 (94)	9 (100)	92 (90)
Smoking status, n (%)				
Never smoked	7 (13)	8 (24)	1 (13)	17 (17)
Former/current smoker	49 (88)	26 (76)	7 (88)	84 (83)
Mutation status, n (%)				
EGFR	8 (14)	3 (9)	2 (22)	13 (13)
ALK	0	1 (3)	0	1 (1)
KRAS	5 (9)	8 (24)	3 (33)	17 (17)
No mutation	37 (66)	19 (56)	3 (33)	59 (58)
Other	1 (2)	1 (3)	1 (11)	3 (3)
Unknown	5 (9)	2 (6)	0	9 (9)
Lines of prior therapy, n (%)				
0	2 (4)	4 (12)	0	6 (6)
1	23 (41)	14 (41)	2 (22)	40 (39)
2	18 (32)	8 (24)	4 (44)	30 (29)
≥3	13 (23)	8 (24)	3 (33)	26 (25)
Median duration of follow-up, weeks (range)	14.0 (2–68)	21.6 (5–67)	33.1 (13–52)	18.8 (2–68)

- Patient characteristics appear similar across all combined cohorts

Data cutoff: June 1, 2015.

*Excludes D3 q4w T1 cohort (n=3). ALK, anaplastic lymphoma kinase; D, durvalumab; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; q#w, every # weeks; T, tremelimumab.

Safety summary

Event, n (%)	D10–20 q4/2w + T1* (n=56)	D10–20 q4/2w + T3 (n=34)	D15 q4w + T10 (n=9)	All cohorts (N=102)
Related AE	41 (73)	32 (94)	8 (89)	82 (80)
Related Grade 3/4 AE	17 (30)	19 (56)	7 (78)	43 (42)
Related death†	2 (4)	1 (3)	0	3 (3)
Related SAE	12 (21)	18 (53)	7 (78)	37 (36)
Related AE leading to discontinuation	9 (16)	15 (44)	5 (56)	29 (28)

Selected treatment-related AEs of interest		Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3	Any grade	≥Grade 3
Clinical conditions	Diarrhea	13 (23)	4 (7)	16 (47)	6 (18)	4 (44)	1 (11)	33 (32)	11 (11)
	Colitis	2 (4)	1 (2)	8 (24)	6 (18)	2 (22)	2 (22)	12 (12)	9 (9)
	Enteritis	1 (2)	1 (2)	0	0	0	0	1 (1)	1 (1)
	Pruritus	11 (20)	0	7 (21)	0	3 (33)	0	21 (21)	0
	Rash	6 (11)	0	7 (21)	0	2 (22)	0	15 (15)	0
	Hypothyroidism	5 (9)	1 (2)	4 (12)	0	1 (11)	0	10 (10)	1 (1)
	Pneumonitis	0	0	3 (9)	2 (6)	2 (22)	2 (22)	5 (5)	4 (4)
Investigations	Amylase increased	9 (16)	1 (2)	5 (15)	2 (6)	2 (22)	0	17 (17)	3 (3)
	Lipase increased	7 (13)	5 (9)	4 (12)	2 (6)	1 (11)	1 (11)	12 (12)	8 (8)
	ALT increased	6 (11)	2 (4)	4 (12)	1 (3)	0	0	10 (10)	3 (3)
	AST increased	4 (7)	3 (5)	3 (9)	1 (3)	0	0	7 (7)	4 (4)

Data cut-off: June 1, 2015. *Excludes D3 q4w T1 cohort (n=3).
†These patients also had Grade 3/4 AEs. Deaths: D10/T1 = polymyositis, D20/T1 = pericardial effusion, D20/T3 = neuromuscular disorder
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; D, durvalumab; q#w, every # weeks; SAE, serious adverse event; T, tremelimumab.

ORR (confirmed + unconfirmed response) by PD-L1 status

PD-L1 status	D10–20 q4/2w T1		All cohorts*	
	n/N	95% CI	n/N	95% CI
All patients	11/39 (28%)	15–45	21/84 (25%)	16–36
PD-L1⁺ ≥25%	3/9 (33%)	8–70	7/20 (35%)	15–59
PD-L1⁻ <25%	6/23 (26%)	10–48	11/49 (22%)	12–37
All 2L patients	7/16 (44%)	20–70	15/32 (47%)	29–65
PD-L1⁺ ≥25%	2/3 (67%)	9 – 99	6/8 (75%)	35–97
PD-L1⁻ <25%	4/11 (36%)	11–69	7/18 (39%)	17–64

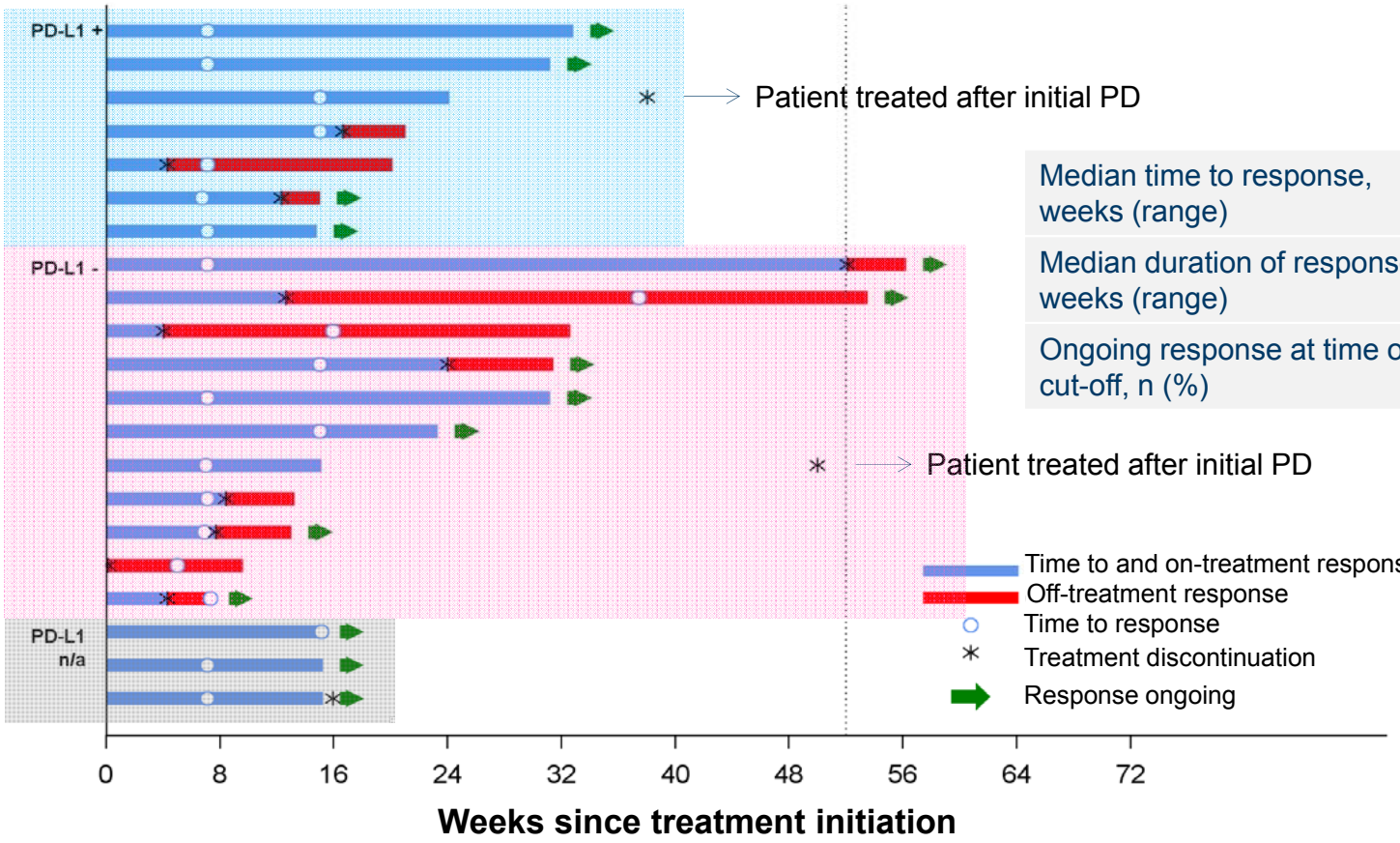
Data cut-off: June 1, 2015. Investigator-reported ORR based on RECIST 1.1.
*Eleven of the 84 patients had EGFR or ALK mutations; none of these patients had a response.
Response evaluable population includes those with measurable disease at baseline + ≥1 follow-up scan including discontinuations due to disease progression or death without any follow-up scan; all patients were dosed ≥16 weeks prior to data cut-off.
2L, receiving D+T in second line. CI, confidence interval; D, durvalumab; q#w, every # weeks; PD-L1, programmed cell death ligand-1; q#w, every # weeks; T, tremelimumab.

ORR (confirmed + unconfirmed response) by PD-L1 status

PD-L1 status	D10–20 q4/2w T1 n/N	D10–20 q4/2w T1 95% CI	All cohorts* n/N	All cohorts* 95% CI	D10 q2w monotherapy† n/N	D10 q2w monotherapy† 95% CI
All patients	11/39 (28%)	15–45	21/84 (25%)	16–36	32/200 (16%)	11–22
PD-L1⁺ ≥25%	3/9 (33%)	8–70	7/20 (35%)	15–59	23/84 (27%)	18–38
PD-L1⁻ <25%	6/23 (26%)	10–48	11/49 (22%)	12–37	5/92 (5%)	2–12
0%	6/12 (50%)	21–79	9/27 (33%)	17–54	1/33 (3%)	0–16
All 2L patients	7/16 (44%)	20–70	15/32 (47%)	29–65	10/54 (19%)	9–31
PD-L1⁺ ≥25%	2/3 (67%)	9 – 99	6/8 (75%)	35–97	8/25 (32%)	15–54
PD-L1⁻ <25%	4/11 (36%)	11–69	7/18 (39%)	17–64	0/19 (0%)	0–18
0%	4/5 (80%)	28–100	6/8 (75%)	35–97	0/5 (0%)	0–52

Data cut-off: June 1, 2015. Investigator-reported ORR based on RECIST 1.1.
*Eleven of the 84 patients had EGFR or ALK mutations; none of these patients had a response. †Rizvi et al, ASCO 2015 abstract 8032; patients with 12 week follow-up. Response evaluable population includes those with measurable disease at baseline + ≥1 follow-up scan including discontinuations due to disease progression or death without any follow-up scan; all patients were dosed ≥16 weeks prior to data cut-off.
2L, receiving D+T in second line. CI, confidence interval; D, durvalumab; q#w, every # weeks; PD-L1, programmed cell death ligand-1; q#w, every # weeks; T, tremelimumab.

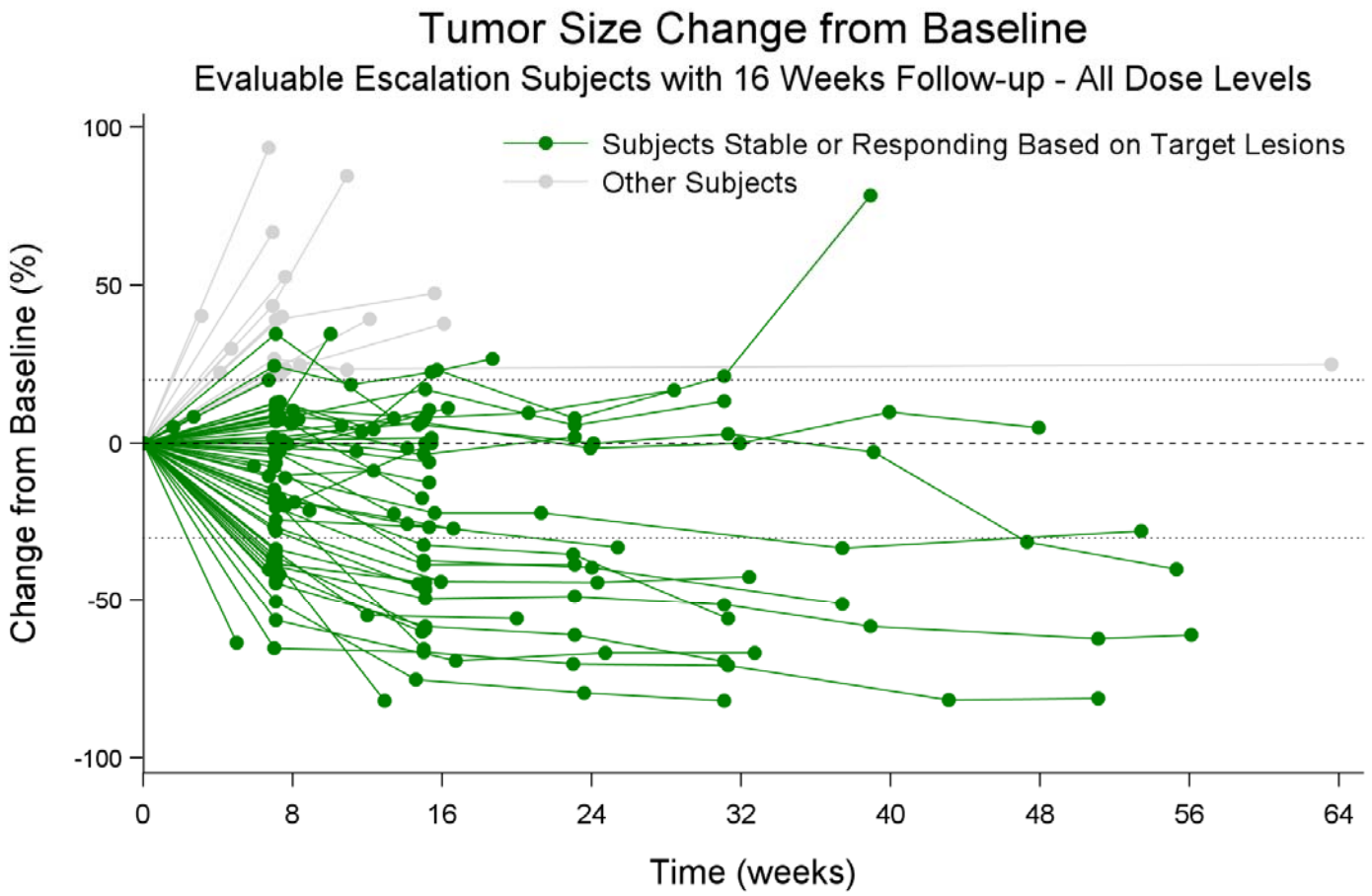
Durable response seen regardless of PD-L1 status



Median time to response, weeks (range)	7.1 (5.0–37.4)
Median duration of response, weeks (range)	16.7 (0.1–49.1)
Ongoing response at time of data cut-off, n (%)	14/21 (66)

Data cut-off: June 1, 2015. Response evaluable population includes those with measurable disease at baseline + ≥1 follow-up scan including discontinuations due to disease progression or death without any follow-up scan ; all patients were dosed ≥16 weeks prior to data cut-off. ≥25% tumor cell membrane staining for PD-L1 was prespecified as PD-L1 positive status. PD, progressive disease; PD-L1, programmed cell death ligand-1.

Durability seen in patients with response or with stable disease



Conclusions

- Increasing dose of tremelimumab over 1 mg/kg resulted in increased toxicity without increase in efficacy
  - Majority of AEs in the combined T1 cohort were manageable and reversible using standard treatment guidelines
- 28% overall and 16% in the combined T1 cohort discontinued treatment due to a related AE
- In the combined T1 cohort, response rates were
  - 33% (95% CI 8–70) for tumor cell membrane staining PD-L1 ≥25%
  - 26% (10–48) for PD-L1 <25%; 50% (21–79) for PD-L1 0%
- Based on the safety profile, PK/PD data, and antitumor activity of the T1 cohorts, a Phase 3 dose of D20 q4w/T1 q4w was selected

AE, adverse event; PD-L1, programmed cell death ligand-1; PK/PD, pharmacokinetic/pharmacodynamic; q#w, every # weeks.

Conclusions

- Phase 3 trials of durvalumab + tremelimumab are open and enrolling:
  - ARCTIC: 3rd+ line NSCLC (NCT02352948)
  - KESTREL: 1st line SCCHN (NCT02551159)
  - MYSTIC: 1st line NSCLC (NCT02453282)
  - NEPTUNE: 1st line NSCLC (NCT02542293)
  - EAGLE: 2nd line SCCHN (NCT02369874)
  - DANUBE: 1st line metastatic bladder cancer (NCT02516241)

AE, adverse event; PD-L1, programmed cell death ligand-1; PK/PD, pharmacokinetic/pharmacodynamic; q#w, every # weeks; SCCHN, squamous cell carcinoma of the head and neck.

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  - Yale Cancer Center, New Haven, CT
  - Angeles Clinic and Research Institute, Los Angeles, CA
  - Earle A Chiles Research Institute, Providence Cancer Center, Portland, OR
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