591 IMMUNOGENICITY OF DURVALUMAB: ANALYSIS OF POOLED PAN-TUMOR DATA

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Background Durvalumab, an immune checkpoint inhibitor (ICI) targeting PD-L1, has demonstrated clinical activity with or without tremelimumab, a CTLA-4 inhibitor, in Phase 3 studies in multiple tumor types.[1-3] The occurrence of anti-drug antibodies (ADA) could potentially negatively impact ICI safety and efficacy.[4] This analysis assessed the immunogenicity of durvalumab using pooled pan-tumor data.

Methods Durvalumab immunogenicity was assessed using pooled data from 18 clinical studies of 7826 participants with lung cancer (MYSTIC, ATLANTIC, NEPTUNE, Study 6, ARCTIC, PACIFIC), hepatocellular carcinoma (HIMALAYA, Study 22), bladder cancer (DANUBE, Study 10), head and neck cancer (KESTREL, HAWK, CONDOR, EAGLE, Study 11), gastric or gastroesophageal junction adenocarcinoma (Study 21) or advanced solid tumors (Study 1108, Japan Study 2). ADA and neutralizing ADA (nAb) to durvalumab were detected using validated solution-phase bridging electrochemiluminescence immunoassays. Impact of durvalumab ADA on safety was assessed using pan-tumor data from the pool of 18 studies. Impact of ADA on durvalumab pharmacokinetics was assessed using a pooled dataset from Study 1108, PACIFIC, ATLANTIC, CASPIAN, POSEIDON, HIMALAYA, and Study 22. Due to differences in cancer settings of the studies, the impact of durvalumab ADA on efficacy was not assessed.

Results The proportion of durvalumab ADA-positive participants at any visit (ADA prevalence) was 6.2% with durvalumab monotherapy (D), 6.8% with T75+D, and 7.3% with T300+D (STRIDE) (table 1). The proportion of treatment-emergent ADA–positive participants (ADA incidence) was low and similar across data pools: 2.7% with D, 3.4% with T75+D, and 2.8% with T300+D (table 1). Median ADA titers were ≤16 across all ADA categories in all pools (table 1). The proportion of transiently ADA-positive participants out of those with ADA prevalence was 32/191 with D, 22/146 with T75+D, and 3/26 with T300+D. The proportion of participants who tested positive for durvalumab nAb at any visit was 0.5% with D, 0.6% with T75+D, and 1.4% with T300+D (table 1). Incidence of infusion-related reactions was low in ADA-positive participants across treatment regimens (1% with D, and 0% with T75+D and T300+D); there was no marked impact of durvalumab ADA presence on categorical AE data (table 2). Durvalumab ADA presence did not have a clinically meaningful impact on durvalumab exposure metrics.

Conclusions Although incidences of ADA vary greatly among ICI [4], analysis of this large, multi-study, pooled pan-tumor dataset demonstrates that durvalumab has a low-risk immunogenicity profile as monotherapy or in combination with tremelimumab. Immunogenicity of durvalumab appeared to have no marked impact on safety or exposure.

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Trial Registration MYSTIC: NCT02453282
ATLANTIC: NCT02087423
NEPTUNE: NCT02542293
Study 6: NCT02000947
ARCTIC: NCT02352948
PACIFIC: NCT02125461
HIMALAYA: NCT03298451
Study 22: NCT02519348
DANUBE: NCT02516241
Study 10: NCT02261220
KESTREL: NCT02551159
HAWK: NCT02207530
CONDOR: NCT02319044
EAGLE: NCT02369874
Study 11: NCT02262741
Study 21: NCT02340975
Study 1108: NCT01693562
Japan Study 2: NCT01938612
CASPIAN: NCT03043872
POSEIDON: NCT03164616

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Ethics Approval The trial protocol was approved by local institutional review boards.

Abstract 591 Table 1 Summary of ADA responses to durvalumab

Table 1. Summary of ADA responses to durvalumab

Parameter	D pan-tumor pool* (N=4045)	T75+D pan-tumor pool† (N=3319)	T300+D HCC pool‡ (N=462)
ADA-evaluable participants, n (%)	3069 (75.9)	2152 (64.8)	354 (76.6)
ADA positive at any visit (ADA prevalence), n (% of ADA evaluable)	191 (6.2)	146 (6.8)	26 (7.3)
Median of maximum titer (range)	4.0 (1–1024)	2.0 (1–128)	2.0 (1–16)
Treatment-emergent ADA positive (ADA incidence), n (% of ADA evaluable)	84 (2.7)	74 (3.4)	10 (2.8)
Median of maximum titer (range)	4.0 (1–1024)	4.0 (1–128)	6.0 (1–16)
Transiently ADA positive, n (% of ADA evaluable)	32 (1.0)	22 (1.0)	3 (0.8)
Median of maximum titer (range)	4.0 (1–128)	4.0 (1–32)	1.0 (1–16)
nAb positive at any visit, n (% of ADA evaluable)	16 (0.5)	12 (0.6)	5 (1.4)
Median of maximum titer (range)	16.0 (1–1024)	8.0 (2–128)	4.0 (1–16)

ADA prevalence includes pre-treatment ADA present at baseline. Transient ADA positivity was defined as ≥1 post-baseline ADA-positive measurement and if ≥2, less than 16 weeks between the first and last and not ADA positive at the last assessment.
*Participants with various tumor types from studies (HIMALAYA, Study 22, MYSTIC, ATLANTIC, Study 1108, ARCTIC, PACIFIC, HAWK, CONDOR, EAGLE, Japan Study 2, DANUBE, KESTREL) who have received at least one dose of durvalumab monotherapy at 10 mg/kg Q2W (or equivalent) or 20 mg/kg Q4W (or equivalent) for any line of therapy.
†Participants with various tumor types from studies (HIMALAYA, Study 22, MYSTIC, NEPTUNE, Study 6, ARCTIC, CONDOR, EAGLE, Study 10, Japan Study 2, Study 11, Study 21, DANUBE, KESTREL) who have received at least one dose of durvalumab at 20 mg/kg Q4W (or equivalent) in combination with tremelimumab 1 mg/kg Q4W (or equivalent) for any line of therapy.
‡Participants with HCC from HIMALAYA and Study 22 who have received at least one dose of durvalumab at 1500 mg Q4W (or equivalent) in combination with tremelimumab 300 mg x 1 dose (or equivalent).
ADA, anti-drug antibody; D, durvalumab; HCC, hepatocellular carcinoma; nAb, neutralizing antibody; T75+D, tremelimumab 1 mg/kg Q4W + durvalumab; T300+D (Single Tremelimumab Regular Interval Durvalumab; STRIDE), tremelimumab 300 mg x 1 dose + durvalumab; QXW, every X weeks.

Abstract 591 Table 2 Summary of safety data by ADA status

Table 2. Summary of safety data by ADA status

	D pan-tumor pool* (N=4045)		T75+D pan-tumor pool† (N=3319)		T300+D HCC pool‡ (N=462)	
ADA category, n (%)	ADA+	ADA-	ADA+	ADA-	ADA+	ADA-
ADA-evaluable participants	191	2878	146	2006	26	328
Any AE	184 (96.3)	2762 (96.0)	138 (94.5)	1944 (96.9)	25 (96.2)	322 (98.2)
Any durvalumab-related AE	122 (63.9)	1806 (62.8)	102 (69.9)	1506 (75.1)	19 (73.1)	259 (79.0)
Grade 3/4 AE	97 (50.8)	1166 (40.5)	76 (52.1)	1067 (53.2)	12 (46.2)	166 (50.6)
Grade 3/4 durvalumab-related AE	29 (15.2)	339 (11.8)	34 (23.3)	473 (23.6)	6 (23.1)	85 (25.9)
Serious AE	81 (42.4)	909 (31.6)	59 (40.4)	855 (42.6)	9 (34.6)	123 (37.5)
Serious durvalumab-related AE	20 (10.5)	178 (6.2)	23 (15.8)	362 (18.0)	1 (3.8)	50 (15.2)
Any AESI / AEPI	129 (67.5)	1846 (64.1)	106 (72.6)	1528 (76.2)	21 (80.8)	283 (86.3)
Any durvalumab-related AESI / AEPI	93 (48.7)	1219 (42.4)	82 (56.2)	1245 (62.1)	17 (65.4)	235 (71.6)
AE leading to durvalumab discontinuation	20 (10.5)	222 (7.7)	23 (15.8)	286 (14.3)	2 (7.7)	31 (9.5)
Durvalumab-related AE leading to durvalumab discontinuation	14 (7.3)	109 (3.8)	14 (9.6)	181 (9.0)	1 (3.8)	21 (6.4)
AE leading to death	7 (3.7)	106 (3.7)	4 (2.7)	90 (4.5)	2 (7.7)	10 (3.0)
Durvalumab-related AE leading to death	0	10 (0.3)	0	10 (0.5)	0	3 (0.9)
Infusion-related reaction	2 (1.0)	4 (0.1)	0	2 (<0.1)	0	1 (0.3)

*Participants with various tumor types from studies (HIMALAYA, Study 22, MYSTIC, ATLANTIC, Study 1108, ARCTIC, PACIFIC, HAWK, CONDOR, EAGLE, Japan Study 2, DANUBE, KESTREL) who have received at least one dose of durvalumab monotherapy at 10 mg/kg Q2W (or equivalent) or 20 mg/kg Q4W (or equivalent) for any line of therapy.
†Participants with various tumor types from studies (HIMALAYA, Study 22, MYSTIC, NEPTUNE, Study 6, ARCTIC, CONDOR, EAGLE, Study 10, Japan Study 2, Study 11, Study 21, DANUBE, KESTREL) who have received at least one dose of durvalumab at 20 mg/kg Q4W (or equivalent) in combination with tremelimumab 1 mg/kg Q4W (or equivalent) for any line of therapy.
‡Participants with HCC from HIMALAYA and Study 22 who have received at least one dose of durvalumab at 1500 mg Q4W (or equivalent) in combination with tremelimumab 300 mg x 1 dose (or equivalent).
ADA, anti-drug antibody; AE, adverse events; AEPI, adverse events of potential interest; AESI, adverse event of special interest; D, durvalumab; HCC, hepatocellular carcinoma; T75+D, tremelimumab 1 mg/kg Q4W + durvalumab; T300+D (Single Tremelimumab Regular Interval Durvalumab; STRIDE), tremelimumab 300 mg x 1 dose + durvalumab; QXW, every X weeks.

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