Durvalumab plus tremelimumab in patients with grade 3 neuroendocrine neoplasms of gastroenteropancreatic origin: updated results from the multicenter phase II DUNE trial (GETNE 1601)

POSTER 1107P

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BACKGROUND

The rationale to use immune checkpoint blockade in neuroendocrine neoplasms (NENs) has been scarce, due to the low tumor mutational burden, PD-L1 expression, and lymphocyte infiltration of these tumors. To date, PD-1 inhibitors in monotherapy have demonstrated a limited activity. [1,2] Combination of anti-PD-1 and anti-CTLA-4 recently suggested promising activity in high-grade NENs with an ORR: 44% vs 0% in low/intermediate grades. [3]

In line with these, treatment with durvalumab (D) plus tremelimumab (T) showed limited activity in patients (pts) with well differentiated neuroendocrine tumors (NETs) but surpased the primary endpoint in grade 3 (G3) neuroendocrine neoplasms (NENs) suggesting a promising overall survival (OS) rate in a heavily pretreated population. [4]

Here we update the results of the G3 NENs cohort with central pathological review.

OBJECTIVES

The aim of this trial is to assess the efficacy of durvalumab and tremelimumab in neuroendocrine neoplasms of different origins.

- The primary objective for C1-3 is the efficacy of DT by means of clinical benefit rate (CBR).
- Primary objective for C4 was the 9 months (m) OS, expected to be over 23%.
- Secondary objectives included efficacy by means of objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety, and a traslational molecular substudy to explore prognostic role of tumor and blood biomarkers within the trial population.

METHODS

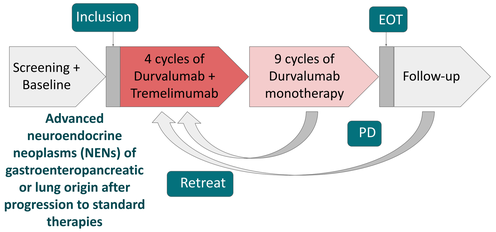

Figure 1. Study Scheme.

C1: Typical/atypical lung carcinoids. Prior therapy with somatostatin analogues and/or targeted therapies or chemotherapy.
C2: G1/2 gastrointestinal. Prior treatment with somatostatin analogues and targeted therapy such as everolimus or radionucleotides.
C3:G1/2 pancreatic. Prior treatment with chemotherapy, somatostatin analogues and targeted therapies. 2-4 systemic treatment lines.
C4: G3 gastroenteropancreatic origin. After first line of chemotherapy with a platinum-based regimen.

DUNE was a prospective open-label trial that recruited pts with advanced NENs after progression to standard therapies in four cohorts (C1-4): typical/atypical lung carcinoids (C1), G1/2 gastrointestinal (C2), G1/2 pancreatic (C3), and G3 NENs of gastroenteropancreatic origin after progression to first-line platinum-based chemotherapy (C4) (**Fig.1**). Pts received 1500 mg durvalumab (up to 13 cycles) plus 75 mg tremelimumab (up to 4 cycles) once every 4 weeks.

RESULTS

Baseline characteristics, n (%)		C4 : LONG SURVIVOR N = 10	C4 : LONG SURVIVOR N = 23	C4: G3 GEP (ALL) N = 33	*p-val.*	OVERALL TRIAL N = 123
Age, median (range)		57 (42-75)	55 (34-78)	55 (34-78)	0.88	62 (34-86)
Gender	Male	8 (80)	14 (60.9)	22 (66.7)	0.43	72 (58.5)
	Female	2 (20)	9 (39.1)	11 (33.3		51 (41.5)
ECOG	0	6 (60)	7 (30.4)	13 (39.4)	0.14	53 (43.1)
	1	4 (40)	16 (69.6)	20 (60.6)		70 (56.9)
Histological grade (Central diagnosis)	NET, Well dif.	3 (30)	12 (52.2)	15 (45.5)	*0.28*	93 (75.6)
	NEC, Poor dif.	7 (70)	11 (47.8)	18 (54.5)		30 (24.4)
KI-67	0-20	0 (0)	0 (0)	0 (0)	*1.00*	93 (75.6)
	20-50	4 (40)	9 (39.1)	13 (39.4)		18 (14.6)
	>50	6 (60)	14 (60.9)	20 (60.6)		20 (16.3)
	uk	-	-	-		2 (1.6)
GEP mitotic index	<2	0 (0)	1 (4.3)	1 (3)	*1.00*	26 (27)
	2-20	3 (30)	2 (8.7)	5 (15.2)		28 (29.2)
	>20	4 (40)	4 (17.4)	8 (24.2)		9 (9.4)
	uk	3 (30)	16 (69.6)	19 (57.6)		60 (62.5)
Clinical stage	II-III	2 (20)	1 (4.3)	3 (9.1)	*0.07*	13 (10.6)
	IV	8 (80)	22 (95.7)	30 (90.9)		109 (88.6)
	uk	-	-	-		1 (0.8)
Extranodal locations	0-2	4 (40)	3 (13)	7 (21.2)	*0.28*	52 (42.3)
	3 or more	1 (10)	5 (21.7)	6 (18.2)		44 (35.8)
	uk	5 (50)	15 (65.2)	20 (60.6)		27 (22)
PD-L1	Neg. (0-1)	4 (80)	10 (62.5)	14 (66.7)	*0.64*	65 (75.6)
	Pos.(>1)	1 (20)	6 (37.5)	7 (33.3)		21 (24.4)

Table 1. Baseline characteristics for C4 stratified by survival status at 12 m (alive, long survivors; and exitus, no long survivors), pvalue for the statified analysis and the reference baseline characteristics from the full dataset of DUNE trial.

From 2017 to 2019, 123 pts were enrolled. The C4 included 33 G3 NEN pts with a median age of 55-y, 67% male, ECOG 0 in 39% (**Table 1**). By central pathological review, 18 (54.5%) were poorly differentiated neuroendocrine carcinomas (NECs) and 15 (45.5%) were G3 NETs (**Table 1**). Ki67 between 20-50% was reported in 13 cases (39.4%) and 20 (60.6%) had Ki67 >50% (**Table 1**). Overall response rate by irRECIST was 9.1% (**Fig.2**). After a median follow up of 5.9 m, the median PFS for C4 was 2.4 m (95% CI: 1.9-2.8)(**Fig.3**). At the data cutoff point, 30 (91%) pts died, 2 were alive and 1 lost to follow up. The 9-m OS rate was 36.1%, with a median OS of 5.9 m (95%CI: 2-9.7)(**Fig.4**). Ten (30%) pts had prolonged survival (> 12 m after initiation of D+T therapy). Of them, 7 had NECs and 3 NETs (p=0.28), and 6 had Ki67 >50% (**Table 1**). PD-L1 combined positive score (tumor cells, lymphocytes and macrophages) determination was feasible in 21 pts (63.6%), being positive in 7 (33%)(**Table 1**) with no impact in PFS or OS (p=0.43 / 0.87) (**Figs. 5&6**)(**Table 2**).

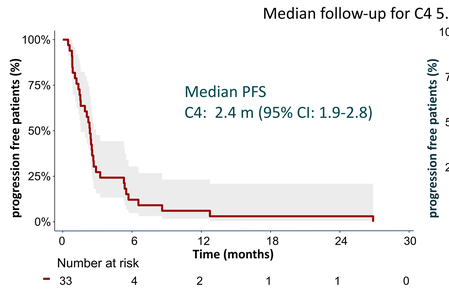

Figure 3. PFS for C4.

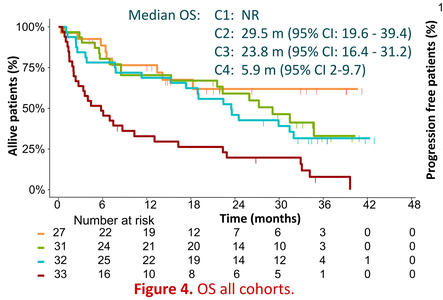

Figure 4. OS all cohorts.

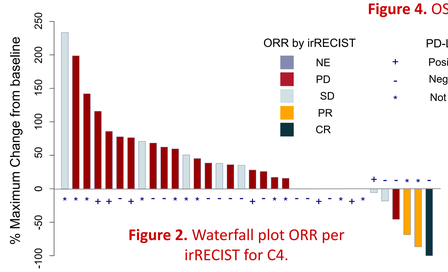

Figure 2. Waterfall plot ORR per irRECIST for C4.

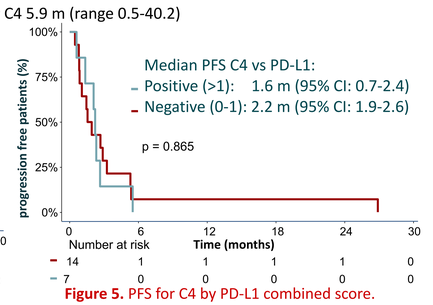

Figure 5. PFS for C4 by PD-L1 combined score.

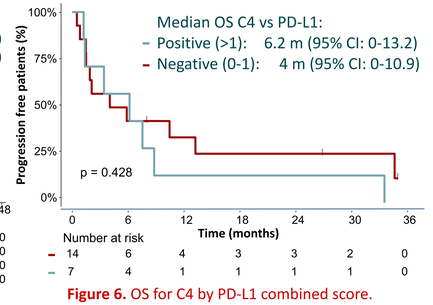

Figure 6. OS for C4 by PD-L1 combined score.

Characteristic		PFS n	PFS Median (95% CI)	PFS *p-val.*	OS n	OS Median (95% CI)	OS *p-val.*
PD-L1 combined index	Positive (>1)	7	2.2 (1.9-2.6)	0.87	7	6.2 (0-13.2)	*0.43*
	Negative (0-1)	14	1.5 (0.7-2.4)		11	4 (0-10.9)	
Ki-67	20-50	13	2.5 (1-3.9)	0.88	12	4.5 (1.6-7.3)	0.95
	>50	20	2.3 (2-2.6)		18	6.2 (0-13.7)	

Table 2. Stratified analysis of survival.

CONCLUSIONS

- D+T reached the primary endpoint of OS rate at 9 months in G3 NENs.
- ORR and PFS did not improve significantly from benchmarck studies.
- One third of G3 NENs pts experienced a prolonged OS of over one year regardless of tumor differentiation, Ki67 level or PD-L1 expression, confirmed by central pathological review.
- Immunotherapy deserves further evaluation in G3 NENs.

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