Clinical Activity and Safety of MEDI4736, an Anti-PD-L1 Antibody, in Patients with Head and Neck Cancer

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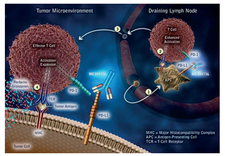
Background

- Tumours can actively evade destruction by the immune system by exploiting inhibitory checkpoint pathways that suppress antitumour T-cell responses. Antibody therapy to block immune checkpoints activated by the programmed cell death ligand-1 (PD-L1) is a promising anti-cancer treatment[1]
- PD-L1 is widely expressed on antigen presenting cells (APC) and other immune cells. PD-L1 is up-regulated on tumour cells from a broad range of human cancers including squamous cell carcinoma of the head and neck (SCCHN) and has been associated with inhibition of antitumour T-cell responses[1–4]
  - Human papilloma virus (HPV)-positive SCCHN[2], expresses viral antigens that are known to be immunogenic,[4] thus they too could be responsive to immune checkpoint blockade therapy
  - Although HPV-negative SCCHN is mainly driven by tobacco use[5], tobacco-related cancers (e.g. SCCHN and non-small cell lung cancer [NSCLC]) are associated with a high mutational burden and neoantigen production[7], which may also generate T-cell immunity
- PD-L1 binds two important regulatory receptors on T-cells: programmed cell death-1 (PD-1) and CD80/B7.1[8,9]
  - Binding to PD-1 delivers an inhibitory signal, reducing cytokine production and T-cell proliferation[8,9]
  - Binding to CD80/B7.1 blocks activation of T-cells through CD28 binding[8,9]
- Anti-PD-L1 antibodies that block binding of PD-L1 to these receptors have shown durable, single-agent antitumour activity across multiple tumour types, with an encouraging safety profile[10]
- There may be advantages to selectively inhibiting PD-L1 (and not PD-L2)[8]
  - PD-L2 plays a role in controlling inflammation in normal lung tissue (with expression in lung macrophages and APC)[11], and in exacerbation of immune-related toxicity in susceptible animal models[12,13]; although its role in modulating tumour immunity has not been identified[10]
- MEDI4736, which targets PD-L1, represents a robust strategy to boost antitumour immune responses by targeting two distinct regulatory pathways that regulate T-cell function, while limiting potential for immune-related toxicity

Figure 1. MEDI4736 Mechanism of Action



- MEDI4736 inhibits PD-L1 interaction with PD-1 (IC_{50} 0.1 nM)[14] and CD80/B7.1 (IC_{50} 0.04 nM)[14], allowing T-cells to recognise and kill tumour cells (Figure 1)[14]
- Other key attributes are:
  - Does not bind to PD-L2[14]
  - No immunogenicity impacting pharmacokinetics/pharmacodynamics (PK-PD) at Phase 3 dose (10 mg/kg) to date[15]
    - 2/196 patients treated at 10 mg/kg showed anti-drug antibodies (ADA) that did not impact PK-PD
    - 1/18 patients treated with doses other than 10 mg/kg showed ADA impacting PK-PD
  - Sustained exposure through dosing interval (>1 year)
  - Uniquely engineered human IgG1κ monoclonal antibody
    - Triple mutation in Fc domain removes antibody-dependent cell-mediated cytotoxicity activity[16]

Objective

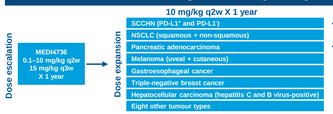
- Here we describe results from the SCCHN cohort of the Phase 1, first-in-human study of MEDI4736 in patients with advanced solid tumours (NCT01693562); data cut-off 21 August, 2014

Methods

Study Design and Dosing Regimen

- Global, multicentre, open-label study with a standard 3+3 dose-escalation phase followed by an expansion phase (Figure 2)
- Since study initiation in October 2012, the once every 2 weeks (q2w) and once every 3 weeks (q3w) dose escalation phases have been completed; recruitment into the q2w dose expansion phase at the 10 mg/kg q2w dose is ongoing
- As of 21 August, 2014 data cut-off, 61 patients in the SCCHN cohort have received MEDI4736 10 mg/kg q2w in the dose expansion phase

Figure 2. Study Design



- After 1 year of treatment, patients enter follow-up
- Upon evidence of progressive disease, patients were offered re-treatment

Patient Population

- Key inclusion and exclusion criteria for SCCHN patients are highlighted in Table 1

Table 1. Key Inclusion and Exclusion Criteria

Key inclusion criteria	Key exclusion criteria
Confirmed recurrent/metastatic SCCHN incurable with local therapy	Active autoimmune disease
ECOG PS 0–1	Prior severe or persistent irAE
Adequate organ function	Prior anti-PD-1 or anti-PD-L1 therapy
Prior anti-CTLA-4 therapy permitted	
PD-L1-positive and PD-L1-negative patients	

ECOG PS, Eastern Cooperative Oncology Group performance status; irAE, immune-related adverse event.

Endpoints and Assessments

- Primary endpoints include:
  - Safety and tolerability
    - Adverse events (AEs) and serious AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v4.03)
- Secondary endpoints include:
  - Antitumour activity; assessed by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
    - Tumour size; assessed by CT or MRI at baseline and at 6, 12 and 16 weeks, and every 8 weeks thereafter
- Exploratory objectives include:
  - Analysis of tissue and blood samples collected before, during and after treatment is being performed to explore the relationships between immune capacity, specificity, activation state and clinical outcome to help elucidate the determinants of response to immunotherapy
    - Tumour tissue samples were taken at baseline for assessment of PD-L1 status (via an immunohistochemical assay developed in collaboration with VENTANA [PD-L1 staining performed on VENTANA BenchMark ULTRA using VENTANA PD-L1 (SP263) clone])
    - Blood samples were also collected for exploratory analysis of HPV (via local laboratory analysis)

Results

Table 2. Baseline Demographics and Disease Characteristics

Characteristic	MEDI4736 10 mg/kg q2w SCCHN (n=61)
Mean age, years (range)	58 (24–96)
Sex, n (%)	
Male	52 (85)
Female	9 (15)
HPV status	
HPV-positive	24 (39)
HPV-negative	25 (41)
Unknown	12 (20)
Tobacco use, n (%)	
Never smoker	22 (36)
Former/current smoker	39 (64)
ECOG PS, n (%)	
0	23 (38)
1	37 (62)
Unknown	1 (2)
Prior systemic therapy, n (%)	
1	13 (21)
2	18 (30)
3	13 (21)
≥4	16 (26)
Unknown	1 (2)
Median (range)	2 (1–10)

Treatment Exposure

- Sixty-one patients received a median of five doses (range 1–21) of MEDI4736 administered as 10 mg/kg q2w

Data for all advanced solid tumours and the NSCLC cohort are presented in ESMO presentations #1058PD and #1325P, respectively

Safety and Tolerability

- The safety profile in SCCHN was consistent with the overall study population
  - Drug-related Grade ≥3 AEs were reported in 7% of patients
  - No drug-related AEs leading to discontinuation
  - No drug-related colitis of any grade, and no Grade ≥3 pneumonitis were reported
  - No drug-related AEs leading to death

Table 3. Safety Summary

	MEDI4736 10 mg/kg q2w Total (n=408)	MEDI4736 10 mg/kg q2w SCCHN (n=61)
All events, n (%)		
Any AE	372 (91)	54 (89)
Grade ≥3 AE	170 (42)	23 (38)
Serious AE	143 (35)	20 (33)
Drug-related events[a] only, n (%)		
Any AE	189 (46)	32 (53)
Grade ≥3 AE	30 (7)	4 (7)
Serious AE	10 (3)	1 (2)
AEs leading to discontinuation	5 (1)	0
AEs leading to death	0	0

[a]Causality assigned by the investigator.

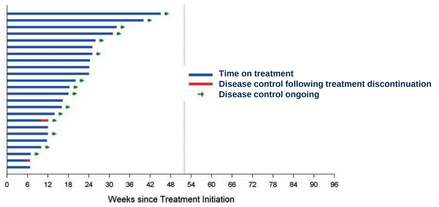
Table 4. Select Drug-related AEs of Interest

System organ class	Event	MEDI4736 10 mg/kg q2w (n=61) All grades n (%)	MEDI4736 10 mg/kg q2w (n=61) Grade ≥3 n (%)*
Constitutional – general	Fatigue	5 (8)	1 (2)
	Pyrexia	4 (7)	0
Gastrointestinal	Vomiting	1 (2)	0
	Diarrhoea	5 (8)	0
	Abdominal pain	0	0
	Colitis	0	0
Endocrine	Hypothyroidism	2 (3)	0
	Hyperthyroidism	0	0
	Hyperglycaemia	0	0
Skin	Rash/pruritus	3/3 (5/5)	0/0
Respiratory	Dyspnoea	1 (2)	0
	Pneumonitis	2 (3)	0
Laboratory investigations	AST/ALT elevation	2/0 (3/0)	0/0
Nervous system	Peripheral neuropathy	0	0

Causality assigned by the investigator; *Other Grade ≥3 AEs were: n=1 gamma-glutamyltransferase elevation, n=1 oncologic complication, n=1 not yet coded. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Efficacy

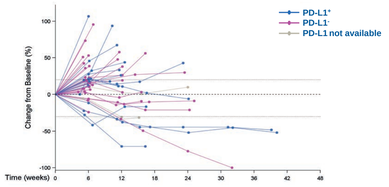
Figure 3. Duration of Disease Control* (Patients with Baseline and ≥1 Follow-up Scan, 10 mg/kg q2w)



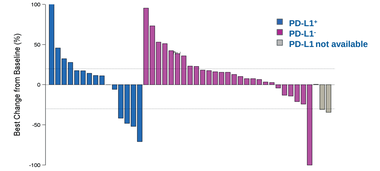
*Disease control = RECIST response (confirmed/unconfirmed complete response [CR] or partial response [PR]) + stable disease (SD).

Figure 4. Antitumour Activity of MEDI4736

A. Tumour shrinkage by PD-L1 status (n=45)



B. Best change in tumour size from baseline by PD-L1 status (n=45)

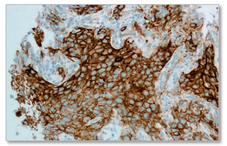


Patients with baseline and ≥1 on-treatment scan. Disease assessment at 6 weeks, 12 weeks, 16 weeks, and then every 8 weeks. PD-L1 status defined by VENTANA assay.

C. Response in a patient with SCCHN

Ninety-six year-old female, progressed on previous cetuximab, HPV-, PD-L1+, and no treatment-related toxicities reported to date. Treatment ongoing at 16 weeks; confirmed PR ongoing.

Figure 5. PD-L1+ Tumour Sample from a Patient with Response to MEDI4736



- Sixty-four year-old male with SCCHN (HPV-negative, PD-L1-positive)
- Status post two lines of systemic therapy: fluorouracil, docetaxel, cisplatin and cisplatin docetaxel
- On treatment for 20 doses with an ongoing confirmed PR at 39 weeks (48% reduction in tumour burden)

PD-L1 staining performed on VENTANA BenchMark ULTRA using VENTANA PD-L1 (SP263) clone.

Table 5. Disease Control Rate (DCR) and Objective Response Rate (ORR), Duration of Response (DoR), and Ongoing Responders by PD-L1 and HPV Status

	MEDI4736 10 mg/kg q2w	MEDI4736 10 mg/kg q2w PD-L1+	MEDI4736 10 mg/kg q2w PD-L1-	MEDI4736 10 mg/kg q2w HPV+	MEDI4736 10 mg/kg q2w HPV-
DCR 12 weeks, % (n/N)	28 (15/53)	35 (6/17)	21 (7/33)	22 (5/23)	33 (7/21)
RECIST response (ORR), % (n/N)	11 (6/53)	24 (4/17)	3 (1/33)	4 (1/23)	19 (4/21)
DoR, weeks (range)	0.1+ to 28+	4+ to 28+	20+	0.1+	4+ to 28+
Ongoing responders, % (n/N)	100 (6/6)	100 (4/4)	100 (1/1)	100 (1/1)	100 (4/4)

Response evaluable = patients with ≥12 weeks' follow-up + measurable disease at baseline + ≥1 follow-up scan (includes discontinuations due to disease progression or death prior to first follow-up scan); DCR 12 weeks = RECIST response (confirmed/unconfirmed CR or PR) + SD ≥12 weeks. n=50 patients were assessed for PD-L1 status (defined by VENTANA assay).

Summary

- MEDI4736 has a manageable safety profile in patients with SCCHN
  - Approximately 53% of patients experienced drug-related AEs, 7% were Grade ≥3 AEs
  - Frequency, spectrum, nature and severity of events appears similar to other tumour types
  - No drug-related colitis of any grade, no Grade ≥3 pulmonary toxicities and no drug-related deaths or discontinuations of treatment were reported
- Encouraging antitumour activity was observed in patients with SCCHN, with responses as early as the first disease assessment (7 weeks)
  - DCR at 12 weeks of 28% and ORR of 11%, were achieved among 53 evaluable patients (including PD-L1-positive and PD-L1-negative patients)
  - All six objective responses are ongoing (duration ranging from 0.1+ to 28.1+ weeks)
  - Responses were more common in HPV-negative tumours, but further study is needed to determine if HPV status is associated with efficacy of PD-L1 blockade
  - Initial observations indicate that PD-L1 expression may correlate with response (ORRs: PD-L1-positive 24%; PD-L1-negative 3%); analyses are ongoing
- Current experience supports the accelerated development of MEDI4736 in SCCHN; pivotal trials with monotherapy (NCT02207530) and in combination with tremelimumab are planned

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Disclaimer

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