Disclosures

Don L Gibbons – No conflicts of interest to declare

EUROPEAN LUNG CANCER CONFERENCE 2016

Efficacy, safety and tolerability of MEDI4736 (durvalumab), a human IgG1 anti-programmed cell death-ligand-1 (PD-L1) antibody, combined with gefitinib: a Phase I expansion in TKI-naïve patients with *EGFR* mutant NSCLC

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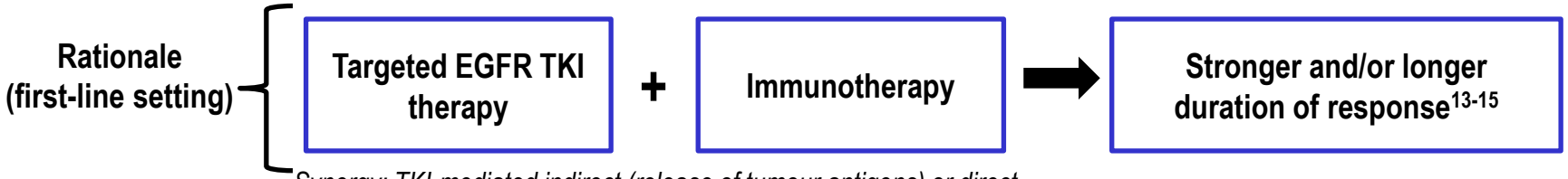
Background

- EGFR TKIs (e.g. gefitinib) are standard first-line therapy for patients with *EGFR* mutation-positive NSCLC[1,2]
  - Gefitinib monotherapy is associated with greater ORR (62–74%) and prolonged PFS (median 6–11 months) compared with chemotherapy (30–48%, median 5–6 months; respectively) in these patients[3-5]
- However, most tumours develop resistance to EGFR TKIs, resulting in disease progression[6]
  - → Need for therapies with more durable responses (e.g. immune-mediated therapies)[7]
- Durvalumab is an immunotherapy that targets PD-L1[8,9]
  - PD-L1 is upregulated on tumour cells from a broad range of cancers (including NSCLC);[10,11] with *EGFR* mutation-positive status in NSCLC associated with upregulated PD-L1 expression[12]



- **We report updated dose-expansion phase data from an ongoing Phase I study (NCT02088112) evaluating durvalumab plus gefitinib in NSCLC**

EGFR, epidermal growth factor receptor; MHC, major histocompatibility complex; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD-L1 programmed death-1 ligand; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

1. Mok et al. 2013; 2. Reck et al. 2014; 3. Maemondo et al. 2010; 4. Mitsudomi et al. 2010; 5. Mok et al. 2009; 6. Jackman et al. 2010; 7. Ott P et al. 2013; 8. Creelan. 2014; 9. Zielinski CC. 2014; 10. Zou et al. 2008; 11. Keir et al. 2008; 12. Azuma et al. 2014; 13. Kumai et al. 2013; 14. Mascia et al. 2003; 15. Pollack et al. 2011

Study design and patients

Patients

- Aged ≥18 years
- Histologically / cytologically confirmed locally advanced / metastatic NSCLC
- Standard treatment: intolerable / ineligible or failed to respond to / relapsed with
- ≥1 lesion assessable by CT / MRI
- ECOG PS of 0 or 1

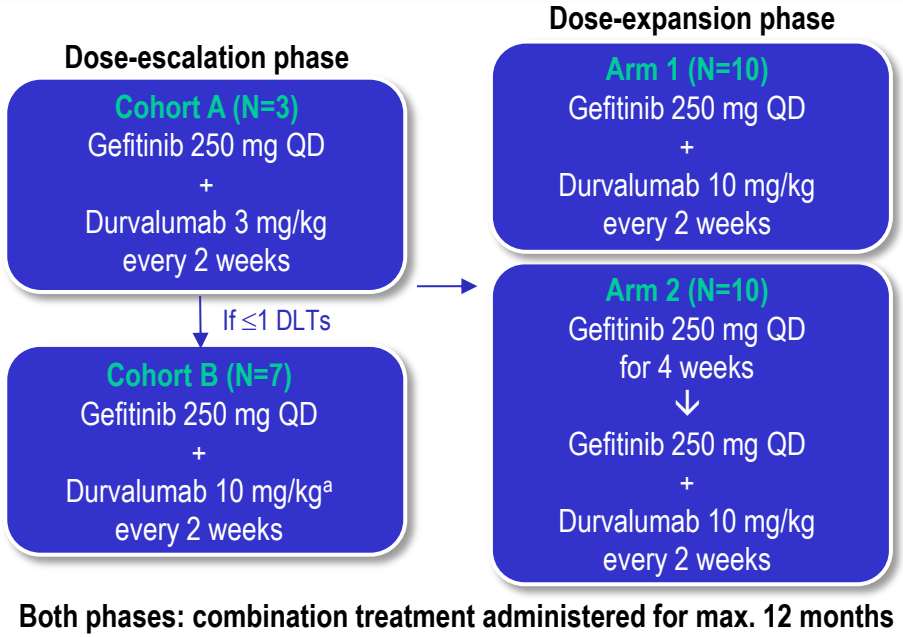
- **Dose-escalation phase:** ≤4 previous lines of therapy
- **Dose-expansion phase:** TKI-naïve, *EGFR* mutation-positive

Objectives

Primary
- Safety / tolerability of durvalumab plus gefitinib

Secondary
- Tumour response (RECIST v1.1): ORR and DoR
- PK / PD; immunogenicity

Exploratory
- Biomarkers



Both phases: combination treatment administered for max. 12 months

CT, computed tomography; DLT, dose-limiting toxicity; DoR; duration of response; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; PD, pharmacodynamics; PK, pharmacokinetic; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors
[a]Dose with adequate safety and tolerability profile

Dose-escalation phase: key results

Safety data from the dose-escalation phase support the combination of 10 mg/kg durvalumab with 250 mg gefitinib for the dose-expansion phase

Patients experiencing an event	Cohort A N=3 (%)	Cohort B N=7 (%)	Total N=10 (%)
Any treatment-related AE	3 (100)	6 (86)	9 (90)
All-cause CTC Grade 3–4 AE	3 (100)	4 (57)	7 (70)
Treatment-related CTC Grade 3–4 AE	2 (67)	2 (29)	4 (40)
All-cause serious AE	3 (100)	3 (43)	6 (60)
Treatment-related AE leading to discontinuation	2 (67)	2 (29)	4 (40)

- Maximum tolerated dose not reached; no DLTs observed
- Of 9 evaluable patients: 2 patients in Cohort A and 1 patient in Cohort B experienced stable disease at ≥8 weeks; 1 patient in Cohort A experienced stable disease at ≥24 weeks
- Durvalumab and gefitinib PK profiles similar to their monotherapy exposures; no antagonism observed
- Complete inhibition of soluble PD-L1 observed, and anti-drug antibodies not detected post-treatment

AE, adverse event; CTC, Common Terminology Criteria
Cohort A: gefitinib 250 mg QD plus durvalumab 3 mg/kg every 2 weeks
Cohort B: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks

Data as of 15 Sept 2015 (except PK / PD / anti-drug antibody data as of August 2014)

Dose-expansion phase: patient demographics

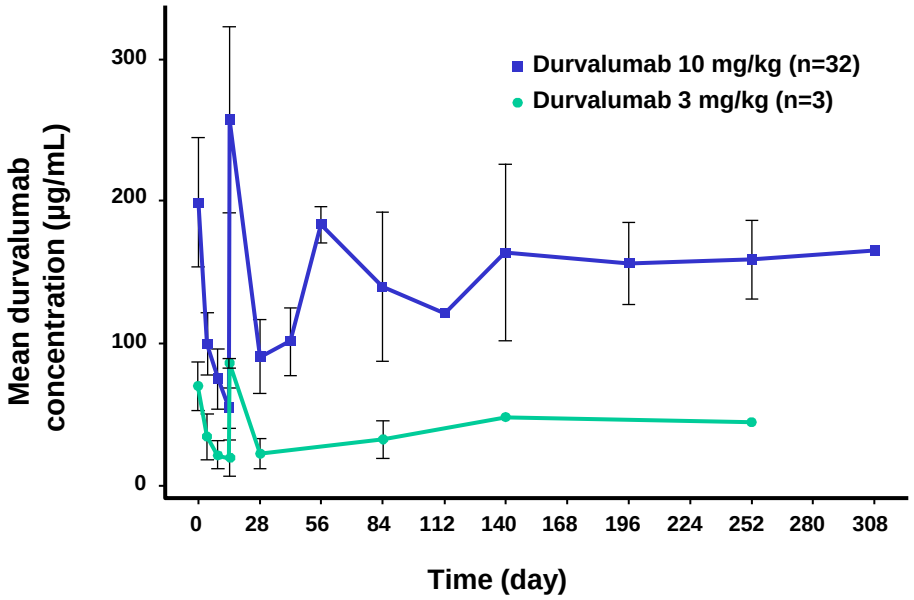
	Arm 1 N=10	Arm 2 N=10
Median age, years (range)	54.5 (27–68)	66.0 (57–76)
Female, n (%)	5 (50)	5 (50)
Non-squamous histology, n (%)	10 (100)	10 (100)
Never-smoker, n (%)	4 (40)	6 (60)
ECOG PS, n (%)		
0	2 (20)	2 (20)
1	8 (80)	8 (80)
***EGFR* mutations, n (%)**		
Exon 19 deletion	6 (60)	5 (50)
Exon 21 L858R	4 (40)	4 (40)
L858R or L861Q	0	1 (10)
Prior systemic therapy, n (%)		
1	0	1 (10)[a]
None	10 (100)	9 (90)

[a]First-line gemcitabine + cisplatin (4 cycles), palliative care
Arm 1: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Arm 2: gefitinib 250 mg QD monotherapy for 4 weeks followed by gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks

Data as of 15 Sept 2015

Dose-escalation / -expansion phase combined data: PK, PD and immunogenicity

- Durvalumab and gefitinib PK profiles were similar to their monotherapy exposures



- Durvalumab exhibited approximately linear PK over the dose range of 3–10 mg/kg
- Gefitinib plasma trough concentration remained within the range predicted from patients treated with gefitinib only in previous clinical studies

- Complete inhibition of soluble PD-L1 (pharmacodynamic marker) was observed for all patients
- No anti-drug antibodies were detected post-treatment

Dose-escalation:
Cohort A: gefitinib 250 mg QD plus durvalumab 3 mg/kg every 2 weeks
Cohort B: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Dose-expansion:
Arm 1: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Arm 2: gefitinib 250 mg QD monotherapy for 4 weeks followed by gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks.

Data as of 19 June 2015 (gefitinib) / 31 July 2015 (durvalumab, sPD-L1, anti-drug antibodies)

Dose-expansion phase: overall tolerability (safety analysis set)

Patients experiencing an event[a]	Arm 1 N=10 (%)	Arm 2 N=10 (%)	Total N=20 (%)
Treatment-related AE	10 (100)	10 (100)	20 (100)
All-cause CTC Grade 3–4 AE	5 (50)	7 (70)	12 (60)
ALT increased	3 (30)	5 (50)	8 (40)
Aplastic anaemia	0	1 (10)	1 (5)
AST increased	0	3 (30)	3 (15)
Bone pain	1 (10)	0	1 (5)
Diarrhoea	0	1 (10)	1 (5)
Dry skin	1 (10)	0	1 (5)
Hyperglycaemia	1 (10)	0	1 (5)
Hyponatraemia	1 (10)	0	1 (5)
Pneumonitis	0	1 (10)	1 (5)
Urinary tract infection	1 (10)	0	1 (5)
Treatment-related CTC Grade 3–4 AE	4 (40)	7 (70)	11 (55)
All-cause serious AE	2 (20)	2 (20)	4 (20)
Treatment-related AE → discontinuation	0	4 (40)	4 (20)

Most common[b] treatment-related AEs:

Arm 1

- Diarrhoea (n=8), ALT increased (n=7), rash (n=6)

Arm 2

- Diarrhoea (n=6), ALT increased (n=6), pruritis (n=6)

Treatment-related AEs leading to discontinuation:

Arm 2 only

- Increased ALT and / or AST (n=3), pneumonitis (n=1)

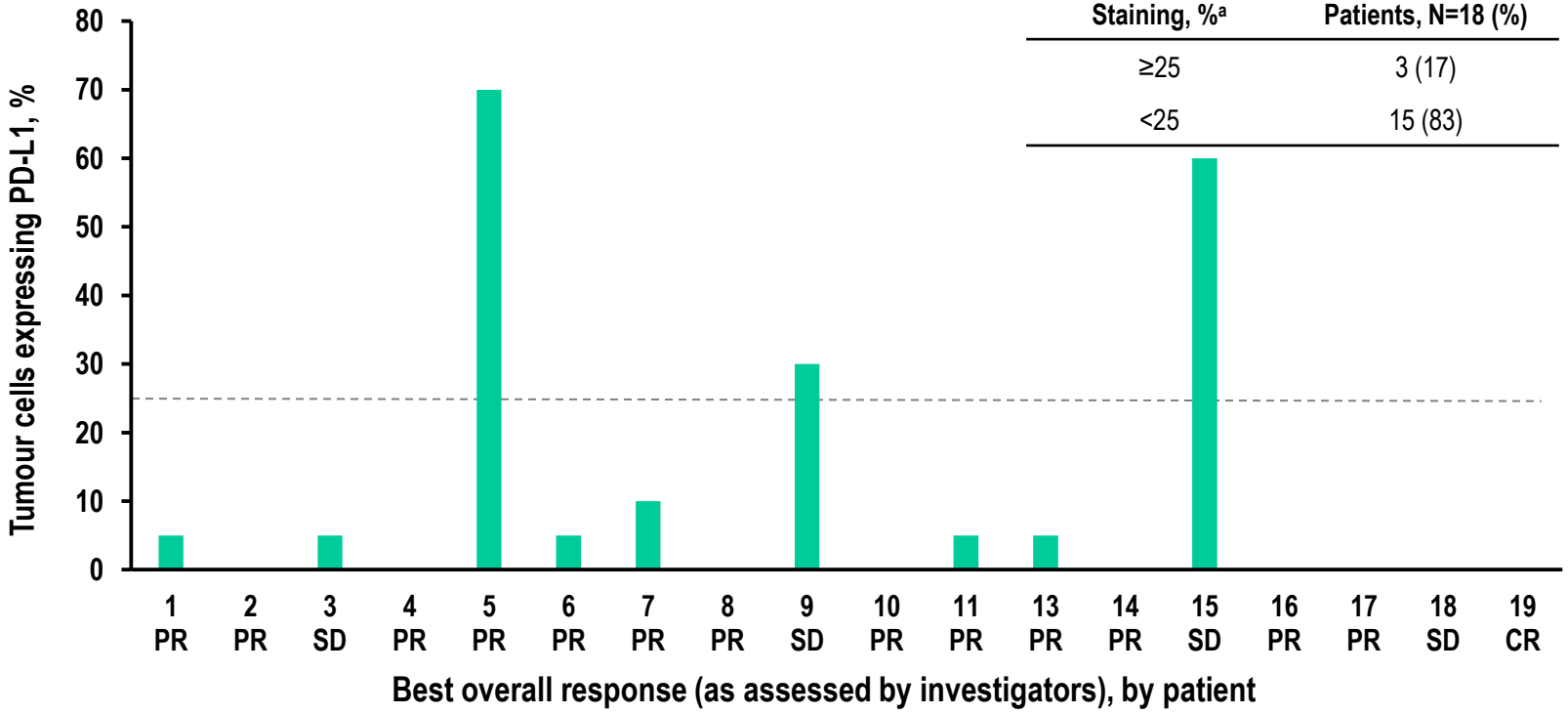
ALT, alanine aminotransferase; AST, aspartate aminotransferase
[a]Patients may have experienced >1 AE; [b]occurring in over half (>5) of patients in each Arm
Arm 1: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Arm 2: gefitinib 250 mg QD monotherapy for 4 weeks followed by gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks

Data as of 15 Sept 2015

Dose-expansion phase: baseline PD-L1 expression

- **Evaluation of tumour PD-L1 staining in fresh biopsies (Ventana SP263 antibody)**

Staining, %[a]	Patients, N=18 (%)
≥25	3 (17)
<25	15 (83)



CR, complete response; N/A, not available; PR, partial response; SD, stable disease
18/20 biopsies evaluable (samples from patients #12 and #20 contained insufficient tumour cells)
[a]25% cut-off was validated clinically based upon findings of the durvalumab study in NSCLC[1]
Arm 1: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Arm 2: gefitinib 250 mg QD monotherapy for 4 weeks followed by gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks

Response data as of 15 Sept 2015

1. Antonia et al. 2016

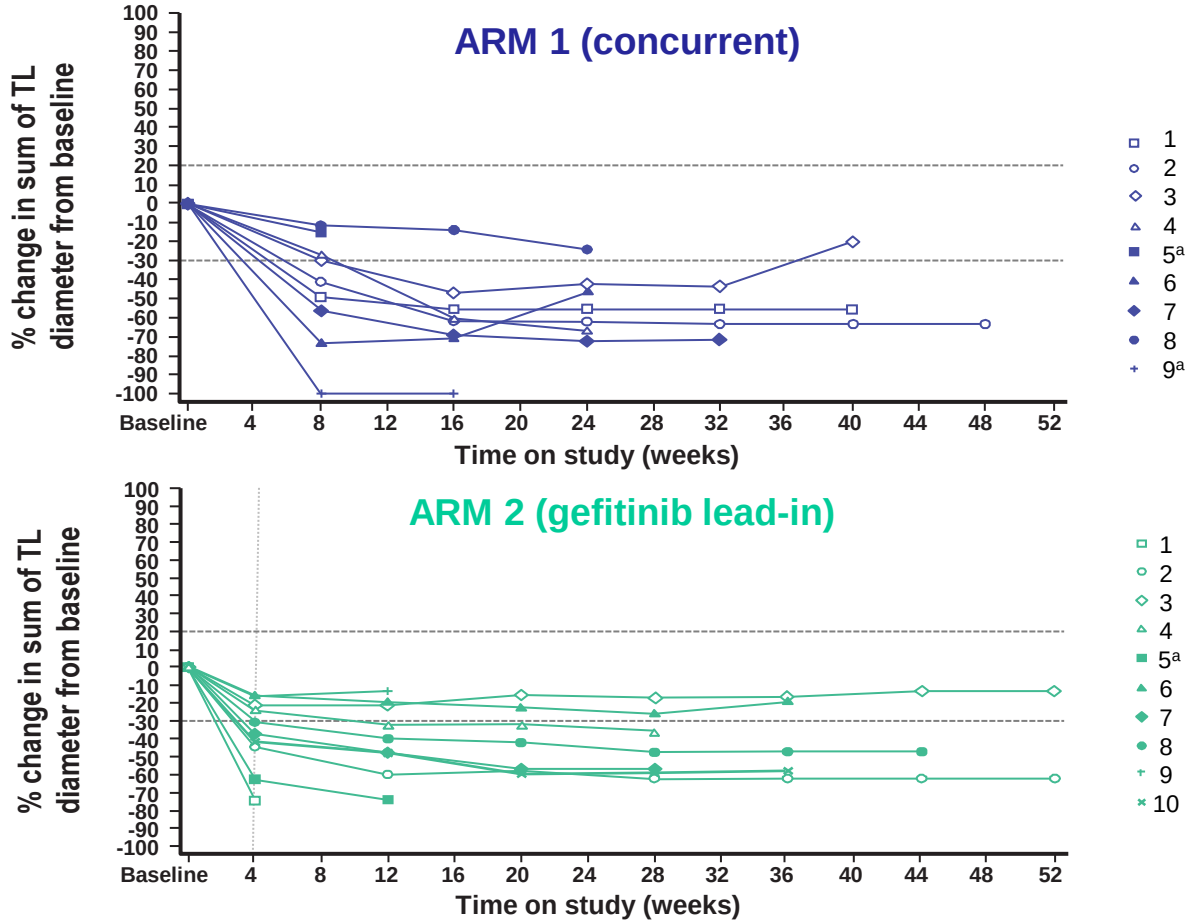
Dose-expansion phase: investigator-determined objective response rates (tumour response analysis set)

Patients experiencing response	Arm 1 n=9 (%)	Arm 2 n=10 (%)	Total n=19 (%)
Best overall response (CR + PR)	7 (78)	8 (80)	15 (79)
CR	1 (11)	0	1 (5)
PR	6 (67)	8 (80)	14 (74)
Stable disease lasting ≥8 weeks	2 (22)	1 (10)	3 (16)
Stable disease lasting ≥24 weeks	0	1 (10)	1 (5)

n=19 patients with tumour data available for analysis (one withdrawal: patient decision)
Arm 1: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Arm 2: gefitinib 250 mg QD monotherapy for 4 weeks followed by gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks

Data as of 15 Sept 2015

Dose-expansion phase: investigator-determined changes in tumour lesions (tumour response analysis set)



n=19 patients with tumour data available for analysis (one withdrawal: patient decision)
[a]PD-L1 positive
Arm 1: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Arm 2: gefitinib 250 mg QD monotherapy for 4 weeks followed by gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks

Data as of 15 Sept 2015

Conclusions

- Durvalumab 10 mg/kg plus gefitinib 250 mg was generally well tolerated when dosed concurrently (Arm 1)
  - Elevated AST / ALT (asymptomatic) seen in both arms with higher incidence / severity in Arm 2 (gefitinib monotherapy lead-in)
  - Increased ALT / AST managed by dose interruption / steroid use; patients able to continue on treatment in Arm 1 (concurrent durvalumab and gefitinib)
- Reduction in tumour size was observed in all TKI-naïve patients with *EGFR* mutation-positive NSCLC
- PK profiles showed similarity to monotherapy; complete inhibition of sPD-L1 and absence of anti-drug antibody activity was observed
- These results therefore support potential future investigations of combined durvalumab/gefitinib treatment in NSCLC
- Additional exploratory biomarker analyses in pre- / post-treatment tumour biopsies (e.g. pEGFR, PD-L1) and whole blood samples are in progress to further elucidate the mechanism of action of EGFR-TKIs in combination with immunotherapies
  - See Yeh et al poster (poster discussion #60PD)

Arm 1: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Arm 2: gefitinib 250 mg QD monotherapy for 4 weeks followed by gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks

Acknowledgements

- This study was sponsored by MedImmune, the global biologics R&D arm of AstraZeneca
- Medical writing support was provided by Louise Brown, from Complete Medical Communications, and was funded by AstraZeneca