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Osimertinib combined with durvalumab in EGFR-mutant non-small cell lung cancer: results from the TATTON Phase Ib trial

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Disclosures

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James C-H Yang – Advisory board member: AstraZeneca, Boehringer Ingelheim, Novartis, Eli Lilly, Merck, Bayer, Roche/Genentech, Astellas, MSD, Pfizer, Clovis Oncology, Celgene

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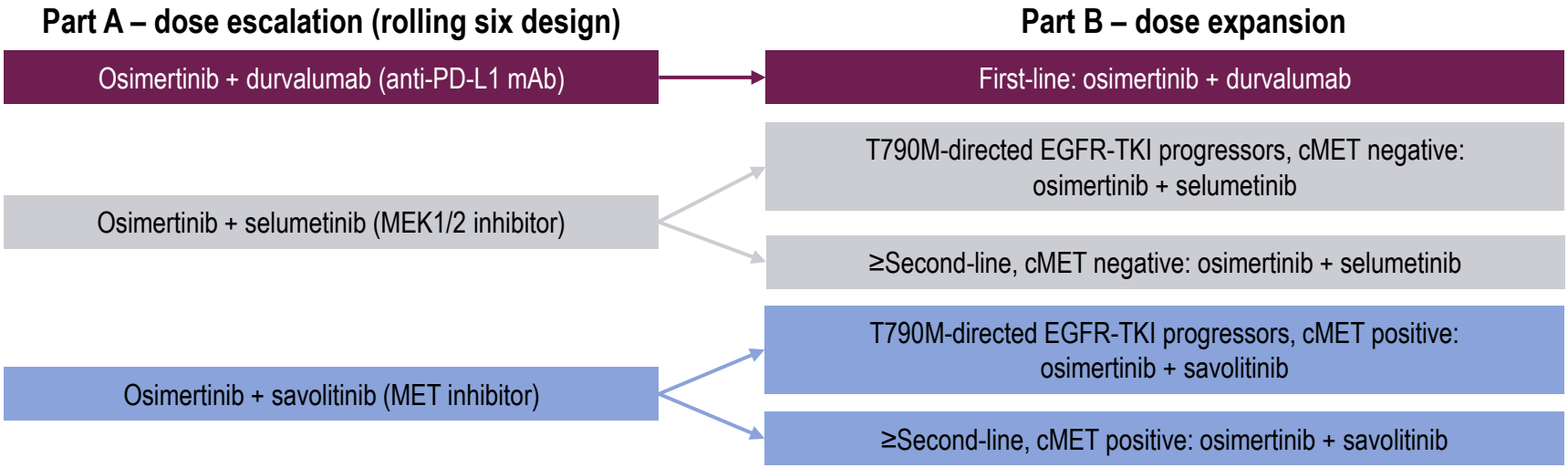
Mireille Cantarini, Andrew Walding, Xiangning Huang – AstraZeneca employees and shareholders

Liu Yang – AstraZeneca employee

Introduction

- Osimertinib (AZD9291) is a potent, irreversible EGFR-TKI selective for sensitising EGFRm and T790M resistance mutations[1,2]
- Resistance to EGFR-TKIs can occur through a number of mechanisms. Combinations of molecularly targeted agents may offer clinical benefit by addressing or delaying resistance
- The TATTON multi-arm, open-label, Phase Ib study (NCT02143466) evaluates osimertinib-based combinations in patients with EGFRm advanced NSCLC[3]



1. Cross et al. Cancer Discov 2014;4:1046–1061; 2. Jänne et al. Ann Oncol 2015;26(Suppl 1):i60, LBA3; 3. Ahn et al. J Clin Oncol 2015;33(Suppl): Abstract 2509
EGFR, epidermal growth factor receptor; EGFRm, EGFR mutation-positive; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death-ligand 1;TKI, tyrosine kinase inhibitor
Durvalumab (MEDI4736); savolitinib (HMPL-504, volitinib, AZD6094); selumetinib (AZD6244, ARRY-142886)

TATTON: osimertinib + durvalumab arm

Primary objective: safety and tolerability

Treatment location: Asia and USA

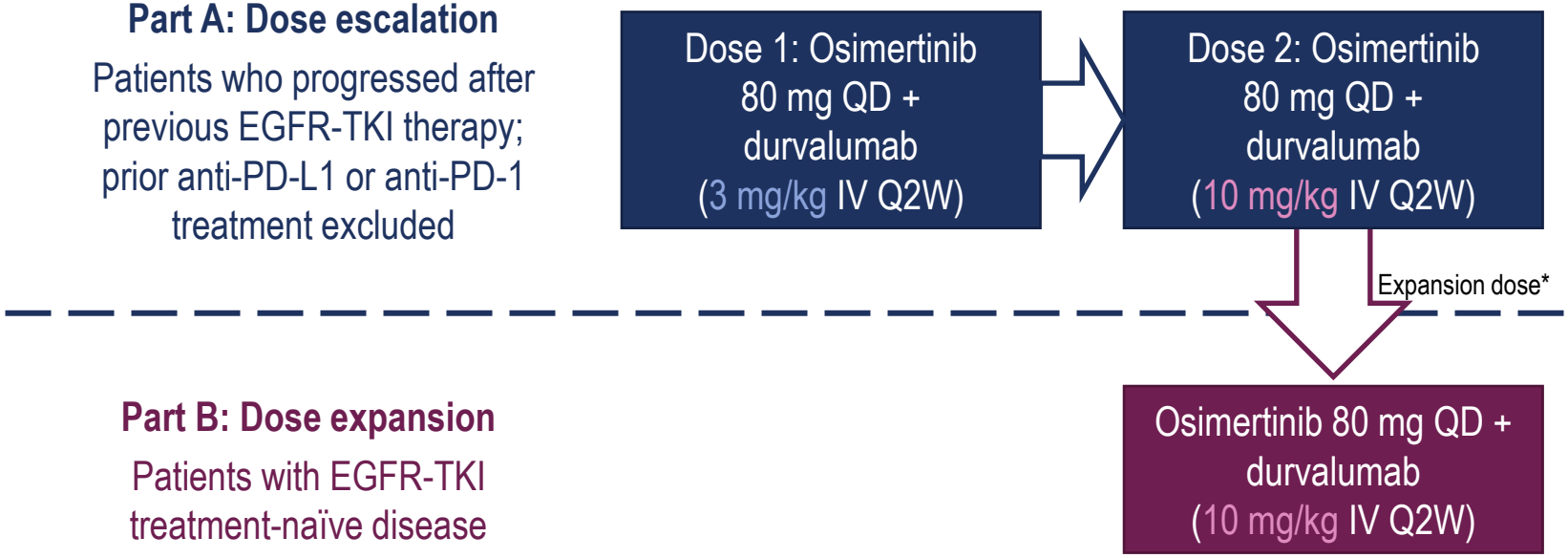
Key inclusion criteria: EGFRm NSCLC, adequate performance status and organ function

Key exclusion criteria: History of ILD, live vaccine or immunosuppressants within 1 month

Data cut-off: 13 November 2015

Part A: Dose escalation

Patients who progressed after previous EGFR-TKI therapy; prior anti-PD-L1 or anti-PD-1 treatment excluded



Part B: Dose expansion

Patients with EGFR-TKI treatment-naïve disease

*Part B combination dose chosen based on preliminary signal of clinical efficacy and an acceptable safety and tolerability profile

ILD, interstitial lung disease; IV, intravenous; QD, once daily; Q2W, once every 2 weeks

Baseline characteristics

Characteristic, n	Part A		Part B
	Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W (N=10)	Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=13)	Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=11)
Gender Male / Female	3 / 7	6 / 7	6 / 5
Age, median (range), years	67 (46–78)	58 (44–73)	57 (46–70)
Treatment location and ethnicity Asia / USA Japanese / Asian / Black / White	 6 / 4 3 / 5 / 1 / 1	 7 / 6 2 / 8 / 1 / 2	 10 / 1 5 / 6 / 0 / 0
Smoker Current / Former / Never / Unknown	0 / 3 / 7 / 0	1 / 1 / 9 / 2	1 / 5 / 5 / 0
Therapy line, median (range)	3.5 (2–10)	3 (2–5)	N/A: all treatment naïve
Immediate prior therapy Gefitinib / Erlotinib / Afatinib / Other	4 / 1 / 3 / 2	2 / 5 / 1 / 5	N/A: all treatment naïve
EGFRm Ex19 del/ L858R / Other / Unknown	6 / 4 / 1 / 0	5 / 7 / 0 / 1	8 / 2 / 0 / 1
T790M status Negative / Positive	7 / 3	7 / 6	11 / 0

Population: safety analysis set; data cut-off: 13 Nov 2015
Ex19 del, exon 19 deletion; N/A, not applicable

Patient exposure

	Part A				Part B	
	Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W (N=10)		Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=13)		Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=11)	
	Osimertinib	Durvalumab	Osimertinib	Durvalumab	Osimertinib	Durvalumab
Median duration of exposure, weeks	43.9	13.9	20.1	16.1	14.1	12.3
Duration of exposure range, weeks	3.1–57.6	0.1–47.4	1.3–41.6	0.1–37.3	5.1–21.4	4.4–22.4

- Part A dose 1: 3/10 patients ongoing (2 monotherapy, 1 combination)
- Part A dose 2: 5/13 patients ongoing (1 monotherapy, 4 combination)
- Part B: 4/11 patients ongoing (2 monotherapy, 2 combination)

Population: safety analysis set; data cut-off: 13 Nov 2015

Summary of adverse events

Patients with an AE	Part A						Part B‡		
	Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W (N=10)			Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=13)			Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=11)		
	Any AE	Drug-related*		Any AE	Drug-related*		Any AE	Drug-related*	
		Osi	Durva		Osi	Durva		Osi	Durva
Total AE	10	10	8	13	9	7	10	8	10
AE Grade ≥3	6	3	2	4	2	2	6	6	5
AE leading to osimertinib discontinuation†	2	1	N/A	2	2	N/A	5	5	N/A
AE leading to durvalumab discontinuation†	4	N/A	3	4	N/A	4	5	N/A	5
AE leading to death	0	0	0	1	0	0	0	0	0
SAE	6	2	4	3	1	1	4	4	4

Population: safety analysis set; data cut-off: 13 Nov 2015

*Possibly-related, as assessed by the investigator; †Patients could discontinue either one or both agents dependent on causality assessment; ‡Part B combination dose chosen based on preliminary signal of clinical efficacy and an acceptable safety and tolerability profile

AE, adverse event; Durva, durvalumab; N/A, not applicable; Osi, osimertinib; SAE, serious adverse event

All-causality adverse events

Patients with an AE AE by preferred term, occurring in more than three patients at any dose	Part A				Part B	
	Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W (N=10)		Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=13)		Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=11)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Rash (grouped terms)	5	1	6	0	7	0
ILD (grouped terms)	2	1	4	1	7*	3
Diarrhoea	3	0	3	0	5	0
Pyrexia	2	0	2	0	4	0
Stomatitis	1	0	1	0	4	0
Nausea	3	0	5	0	3	0
Anaemia	4	0	4	1	1	0
Vomiting	7	1	2	0	0	0
Decreased appetite	3	1	4	0	1	0

*One patient reported ILD following 13 Nov 2015 data cut-off
Population: safety analysis set; data cut-off: 13 Nov 2015

Frequency of interstitial lung disease

- Total time to ILD onset in TATTON (n=13): Mean 80 days (11.4 weeks), Median 69 days (9.9 weeks)

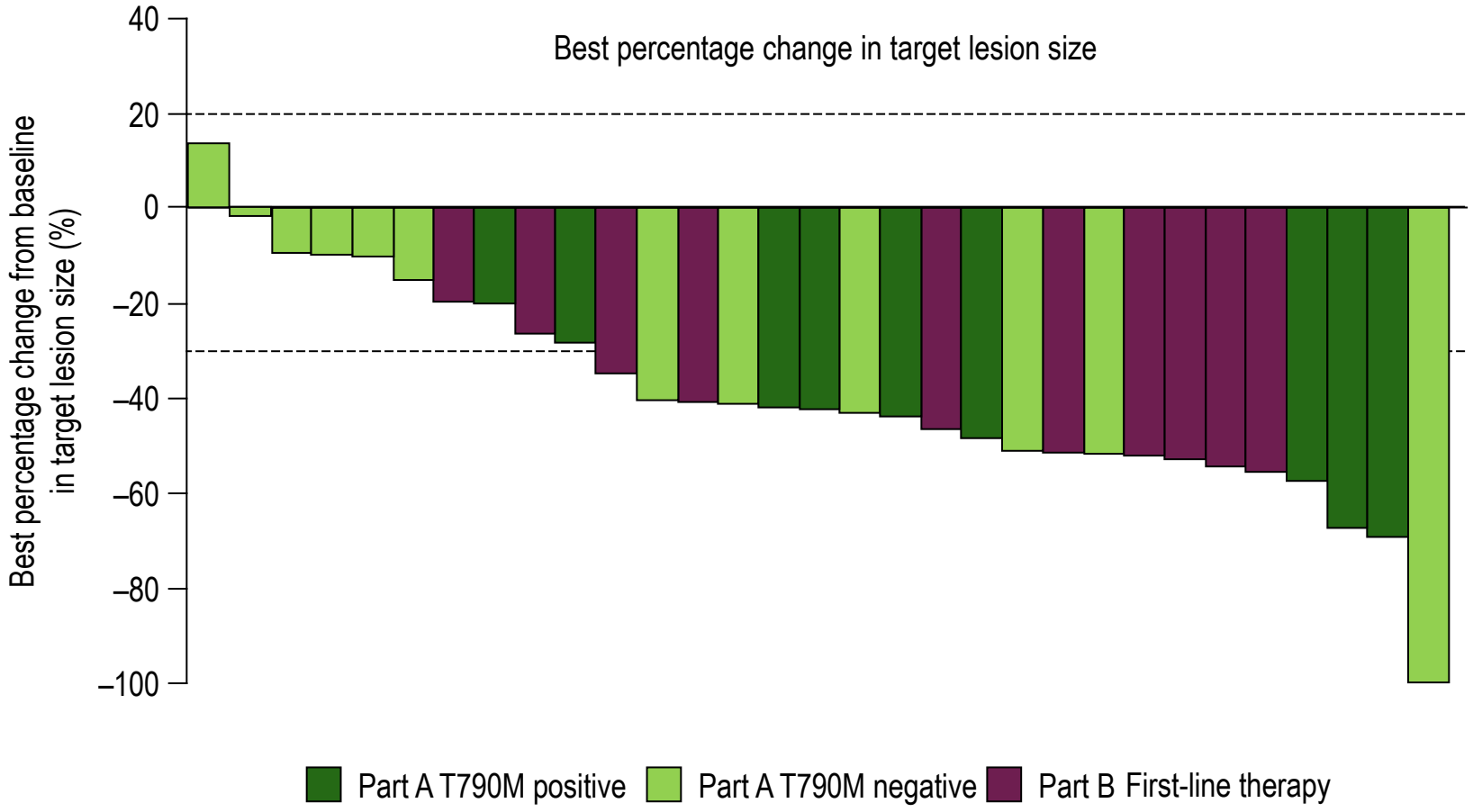
Part A	6/23 (26%)
Dose 1: Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W	2/10 (20%)
Dose 2: Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W	4/13 (31%)
Part B: Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W	7*/11 (64%)
Part A and Part B	13/34 (38%; 95% CI 18, 52)†

†5 events were Grade 3/4 and there were no fatalities; most cases were managed using steroids

Entire osimertinib clinical programme (Phase I and II)	
Osimertinib monotherapy	35/1207 (3%)
Durvalumab monotherapy	23/1149 (2%)

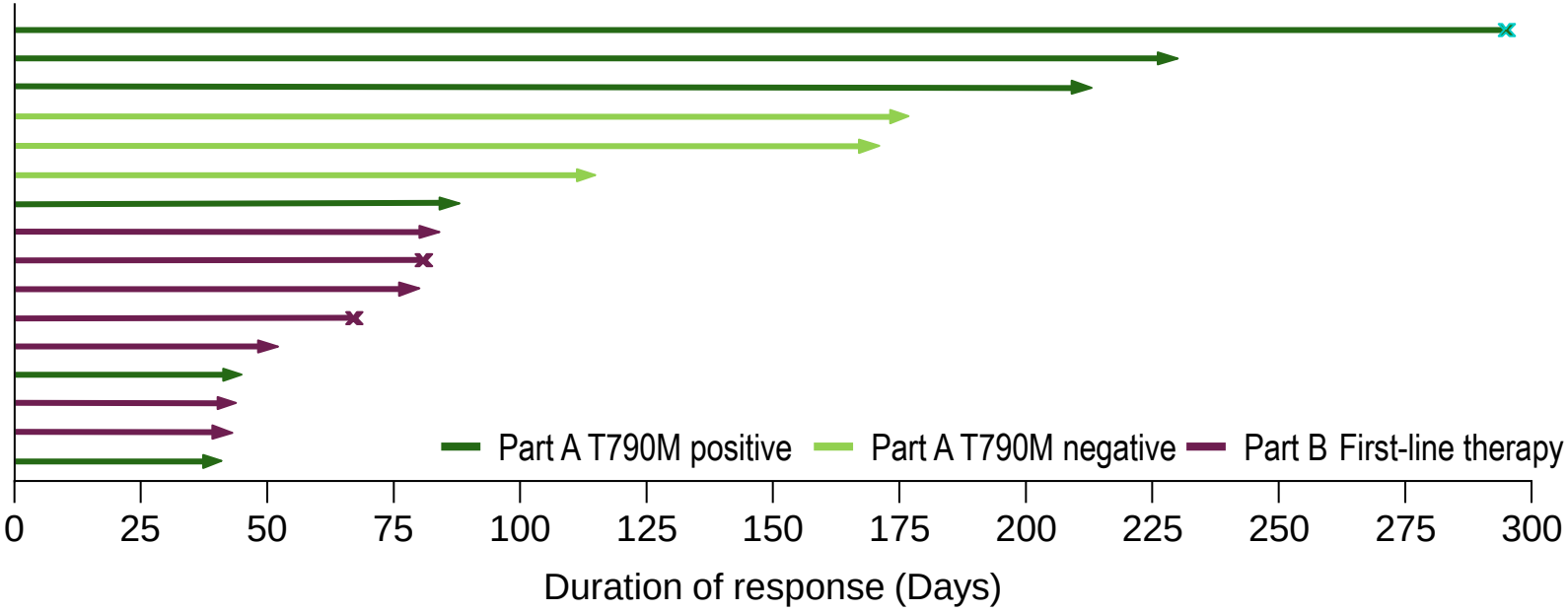
*One patient reported ILD following 13 Nov 2015 data cut-off
TATTON Population: safety analysis set; data cut-off: 13 Nov 2015

Tumour response



Population: evaluable for response set; data cut-off: 13 Nov 2015

Duration of response



	Part A		Part B
	Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W (N=10)	Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=13)	Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W (N=10)
Confirmed responses, n (%)	4 (40%)	5 (38%)	7 (70%)
Patients with T790M positive NSCLC	6/9 (67%)		N/A
Patients with T790M negative NSCLC	3/14 (21%)		N/A

Population: evaluable for response set; data cut-off: 13 Nov 2015
x = end of response. Arrow represents censored observations at the data cut-off

Conclusions

- An increase in ILD was reported with the combination of osimertinib and durvalumab compared to what would be expected with either drug alone. Etiology is being investigated
- ILD (grouped terms) was reported in 38% (13/34) of patients
  - Five events at Grade 3/4 and no fatalities
  - Osimertinib monotherapy: ILD (grouped terms) reported in 2.9% (35/1207) of patients
  - Durvalumab monotherapy: ILD (grouped terms) reported in 2.0% (23/1149) of patients
- In patients with prior EGFR-TKI therapy, investigator-assessed ORR was 67% and 21% in those with T790M positive and T790M negative tumour status, respectively, and 70% in EGFRm treatment-naïve patients
- Based on the observed safety data, the recruitment into the osimertinib + durvalumab treatment arm of TATTON is currently on hold
  - TATTON continues to enrol expansion cohorts of MET and MEK inhibitor combinations
- Biomarker investigation into the safety and efficacy profile of EGFR-TKIs in combination with immunotherapy for the treatment of EGFRm/T790M NSCLC is being explored

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