Preliminary results of TATTON, a multi-arm Phase Ib trial of AZD9291 combined with MEDI4736, AZD6094 or selumetinib in EGFR-mutant lung cancer

[1]Geoffrey R. Oxnard, [2]Suresh S. Ramalingam, [3]Myung-Ju Ahn, [4]Sang-We Kim, [5]Helena Yu, [6]Hideo Saka, [7]Leora Horn, [8]Koichi Goto, [9]Yuichiro Ohe, [10]Mireille Cantarini, [10]Paul Frewer, [11]Michael Lahn, [12]James Chih-Hsin Yang

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Emory University School of Medicine, Atlanta, GA, USA; [3]Samsung Medical Center, Seoul, Republic of Korea; [4]Asan Medical Center, Seoul, Republic of Korea; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]National Hospital Organization Nagoya Medical Center, Nagoya, Japan; [7]Vanderbilt Ingram Cancer Center, Nashville, TN, USA; [8]National Cancer Center Hospital East, Kashiwa, Japan; [9]National Cancer Center Hospital, Tokyo, Japan; [10]AstraZeneca, Macclesfield, UK; [11]AstraZeneca, Gaithersburg, MD, USA; [12]National Taiwan University Hospital, Taipei, Taiwan

Poster #225

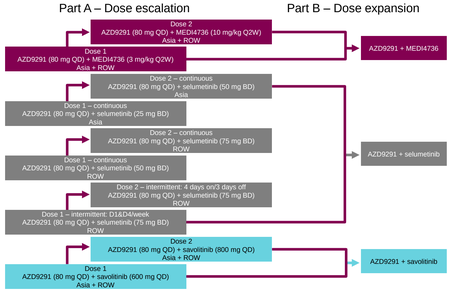
Introduction

- Most patients treated with an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) develop resistance and in approximately 60% of cases this is due to an EGFR exon 20 T790M mutation.[1–6]
- Other resistance mechanisms include immune escape via programmed cell death-1/ligand-1 (PD-1/PD-L1) pathway, MET amplification, and activation of the RAS/RAF/MEK/ERK pathway.[7,8]
- AZD9291 is an oral, potent, irreversible EGFR-TKI selective for sensitizing EGFRm and T790M resistance mutations.[9]
- In the Phase I study of AZD9291, EGFR-mediated toxicity was reduced compared to available EGFR-TKIs.[10] It was therefore hypothesized that the safety profile would permit combinations with other targeted therapies in a tolerable fashion.

Methods

- TATTON (NCT02143466) is a multi-arm Phase Ib trial studying AZD9291 in combination with MEDI4736 (anti-PD-L1 monoclonal antibody), selumetinib (MEK1/2 inhibitor; AZD6244, ARRY-142886), or savolitinib (MET inhibitor; HMPL-504, volitinib, AZD6094).
- Primary objectives: safety and tolerability of AZD9291 in combination with MEDI4736, selumetinib, or savolitinib.
- Key secondary objectives: preliminary assessment of anti-tumor activity by evaluation of tumor response (objective response rate, duration of response, and change in tumor size).
- Key inclusion criteria: EGFR-mutant non-small cell lung cancer (NSCLC) (dose escalation: locally confirmed T790M mutation status); progression on any prior EGFR-TKI; measurable disease; adequate performance status (0–1), and organ function.
- AZD9291 was dosed at 80 mg orally, once daily (QD) and the combination agent escalated (MEDI4736 intravenously, once every 2 weeks [Q2W]; savolitinib orally, QD; selumetinib orally, twice daily [BD]) from a dose below the Phase II monotherapy dose (Figure 1).
- Using a rolling six design, patients were allocated to a combination arm, in a semi-random manner depending on eligibility and slot availability, leading to definition of three global doses/schedules.

Figure 1. TATTON study design

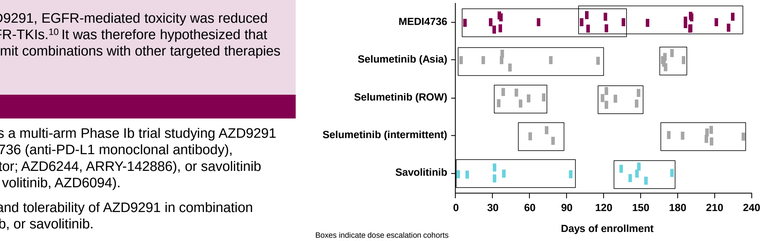


BD, twice daily; D, day; Q2W, once every 2 weeks; QD, once daily; ROW, rest of the world

Results

- As of April 30, 2015, 71 patients have been enrolled to receive AZD9291 in combination with MEDI4736 (23 patients), selumetinib (36 patients), or savolitinib (12 patients) (Figure 2).
  - Enrollment occurred over a 34-week period with no significant interruptions.
- Selumetinib and savolitinib were escalated to their Phase II monotherapy doses and MEDI4736 to its Phase III monotherapy dose.

Figure 2. Study enrollment over time using rolling arm allocation



Boxes indicate dose escalation cohorts
ROW, rest of the world

Table 1. Patient demographics

Characteristic	AZD9291/MEDI4736 N=23	AZD9291/selumetinib N=36	AZD9291/savolitinib N=12
Sex: male/female, n (%)	9/14 (39/61)	18/18 (50/50)	2/10 (17/83)
Median age, years	59	66	64
Region: Japan/Asia/US, n (%)	5/8/10 (22/35/43)	6/7/23 (17/19/64)	0/8/4 (0/67/33)
Smoking status*: never/current/former, n (%)	15/1/4 (65/4/17)	17/2/12 (47/6/33)	8/0/3 (67/0/25)
Prior treatment, n (%)			
≥2 prior TKIs	8 (35)	12 (33)	7 (58)
Prior T790M directed treatment[#]	1 (4)	4[##] (11)	2 (17)
≥2 prior chemotherapy	7 (30)	12[##] (33)	6 (50)
Prior radiotherapy	17 (74)	14[##] (39)	6 (50)

Population: all patient dosed
*Smoking status unknown: selumetinib n=5, savolitinib n=1, MEDI4736 n=3
[#]All patients received AZD9291 except one patient in the selumetinib combination who received CO-1686
[##]Eight patients unknown
TKI, tyrosine kinase inhibitor.

As of April 7, 2015, of more than 1100 patients across all studies dosed with AZD9291, interstitial lung disease (ILD) grouped term events were reported in approximately 2.6% of patients (31 events): seven Grade 1, seven Grade 2, 16 Grade ≥3, one currently ungraded. Of these, a total of three patients are reported to have died due to ILD (Grade 5)

Conclusions

- Preliminary data suggest the toxicity and efficacy profile of AZD9291 allows combinations with MEDI4736, selumetinib, and savolitinib at biologically active doses.
- Expansion cohorts in approximately 120 patients are planned for AZD9291 (80 mg QD) in combination with MEDI4736 (10 mg/kg Q2W), selumetinib (75 mg BD [4 days on/3 days off]), and savolitinib (600 mg QD).

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Acknowledgments
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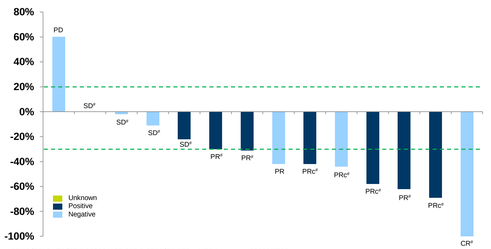
Table 2. All-causality adverse events – AZD9291/MEDI4736*

Number of events, n / AE occurring in ≥3 instances at any dose	3 mg/kg (Asia) N=6		3 mg/kg (ROW) N=7		10 mg/kg (Asia) N=4		10 mg/kg (ROW) N=6	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Diarrhea	4	0	1	0	2	0	0	0
Vomiting	6	0	0	0	1	0	0	0
Anemia	3	0	1	0	0	0	2	0
Constipation	3	0	1	0	1	0	1	0
Cough	1	0	1	0	1	0	3	0
Nausea	3	0	0	0	0	0	3	0
WBC count decreased	4	1	0	0	1	1	0	0
Urinary tract infection	3	0	0	0	0	0	0	0

*Phase III MEDI4736 dose: 10 mg/kg Q2W
As of April 10, 2015, three cases of pneumonitis were reported across all cohorts treated with the combination of AZD9291 and MEDI4736
AE, adverse event; Gr, grade; Q2W, every 2 weeks; ROW, rest of the world; WBC, white blood cell

Figure 3. Best percentage change from baseline in target lesion size in patients* receiving AZD9291/MEDI4736 by T790M status

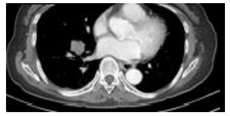


*Population: all patients dosed who had a baseline and 6-week RECIST assessment
[#]Patients ongoing treatment at data cut-off
CR, complete response; PD, progressive disease; PR, partial response; PRc, confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

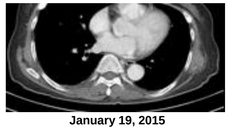
AZD9291/MEDI4736

- Most common adverse events (AEs) were diarrhea, vomiting, anemia, constipation, cough and nausea (Table 2).
- One dose-limiting toxicity (DLT) was reported as neutropenia (Grade [Gr] 3 at 10 mg/kg).
- Complete response was reported in one patient.
- Partial responses were reported in 8/14 patients (four confirmed) (Figure 3).

Figure 4. Tumor response to treatment with AZD9291/ MEDI4736



November 26, 2014



January 19, 2015

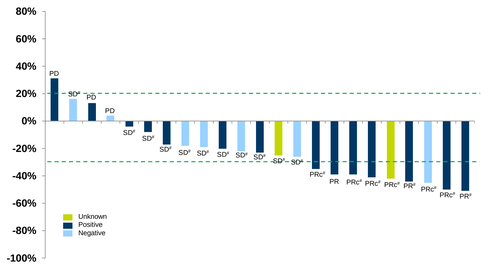
- 73-year-old Asian female with T790M positive NSCLC containing EGFR exon 21 mutation; study treatment: AZD9291/MEDI4736 10 mg/kg, Q2W, now in cycle 6.
- All AEs reported were generally mild.

Table 3. All-causality adverse events – AZD9291/selumetinib*

Number of events, n / AE occurring in ≥3 instances at any dose	Continuous dosing								Intermittent dosing (ROW)			
	25 mg (Asia) N=7		50 mg (Asia) N=6		50 mg (ROW) N=6		75 mg (ROW) N=6		75 mg (D1&4) N=3		75 mg (4 on/3 off) N=8	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Diarrhea	5	0	7	0	5	0	12	0	1	0	1	0
Nausea	2	0	1	0	3	0	7	0	1	0	2	0
Fatigue	0	0	1	0	4	0	3	0	3	0	2	0
Decreased appetite	3	0	2	0	1	0	4	0	0	0	2	0
Vomiting	1	0	1	0	1	0	8	0	0	0	1	0
Rash	4	0	3	0	0	0	2	0	1	0	0	0
Stomatitis	3	0	3	0	3	0	1	0	0	0	0	0
AST increased	2	1	3	0	3	0	1	0	0	0	0	0
Dry skin	3	0	2	0	2	0	2	0	0	0	0	0
ALT increased	2	1	2	0	3	0	0	0	0	0	1	0
Paronychia	1	0	4	0	0	0	1	0	0	0	0	0
Edema peripheral	0	0	1	0	3	0	1	0	0	0	0	0
Blood ALP increased	0	0	0	0	3	0	0	0	0	0	1	0
Dehydration	0	0	0	0	0	0	4	1	0	0	0	0

*Phase II selumetinib dose: 75 mg BD, 4 days on/3 days off
One additional case of Gr 3 diarrhea (75 mg continuous dosing) was reported as a DLT
As of April 10, 2015 one case of pneumonitis was reported in the AZD9291/selumetinib 75 mg continuous dosing cohort
AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BD, twice daily; D, day; Gr, grade; ROW, rest of the world

Figure 5. Best percentage change from baseline in target lesion size in patients* receiving AZD9291/selumetinib by T790M status

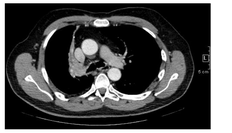


*Population: all patients dosed who had a baseline and 6-week RECIST assessment
[#]Patients ongoing treatment at data cut-off
PD, progressive disease; PR, partial response; PRc, confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

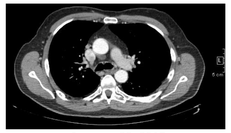
AZD9291/selumetinib

- Most common AEs were diarrhea, nausea, and fatigue (Table 3).
- Five DLTs during continuous dosing were reported as liver function test elevation (Gr 3 at 25 mg), diarrhea (Gr 2 n=1 and Gr 3 n=1, at 75 mg), pneumonitis (Gr 3 at 75 mg), and nausea (Gr 2 at 75 mg).
- Partial responses were reported in 9/23 patients (six confirmed) (Figure 5).

Figure 6. Tumor response to treatment with AZD9291/selumetinib



November 9, 2014



January 22, 2015

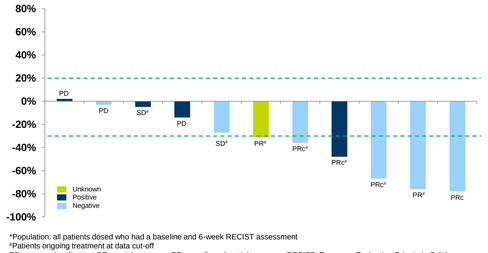
- 69-year-old male with T790M negative NSCLC containing EGFR exon 19 deletion responds to AZD9291/selumetinib 50 mg BD continuous dosing.
- Significant improvement in cough and dyspnea were reported.
- Toxicities reported included diarrhea, fatigue, and mucositis; treatment discontinued after cycle 4 due to intolerance.

Table 4. All-causality adverse events – AZD9291/savolitinib*

Number of events, n / AE occurring in ≥3 instances at any dose	600 mg N=6		800 mg N=6	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Vomiting	7	0	3	0
Nausea	3	0	6	1
Rash	4	0	3	0
Pyrexia	3	0	3	0
WBC count decreased	4	0	1	1
Decreased appetite	1	0	3	0

*Phase II savolitinib dose: 600 mg QD
AE, adverse event; Gr, grade; QD, once daily; WBC, white blood cell

Figure 7. Best percentage change from baseline in target lesion size in patients* receiving AZD9291/savolitinib by T790M status

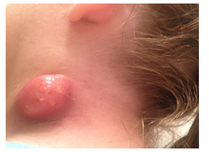


*Population: all patients dosed who had a baseline and 6-week RECIST assessment
[#]Patients ongoing treatment at data cut-off
PD, progressive disease; PR, partial response; PRc, confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

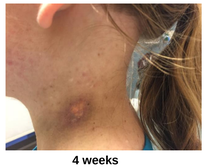
AZD9291/savolitinib

- Most common AEs were vomiting, nausea and rash (Table 4).
- Three DLTs were reported as fatigue (Gr 3 at 600 mg), neutropenia (Gr 4 at 800 mg), and nausea (Gr 3 at 800 mg).
- Partial responses were reported in 6/11 patients (four confirmed) (Figure 7).

Figure 8. Tumor response to treatment with AZD9291/ savolitinib



Pre-treatment



4 weeks

- 32-year-old female with a tumor harboring exon 19 deletion and high MET amplification responds to AZD9291/savolitinib 800 mg.

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