5th Annual Brain Mets congress

AstraZeneca
IMED Biotech Unit

Phase I study of AZD3759, an EGFR inhibitor with blood brain barrier (BBB) penetration, for the treatment of EGFRm+ non-small cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM)

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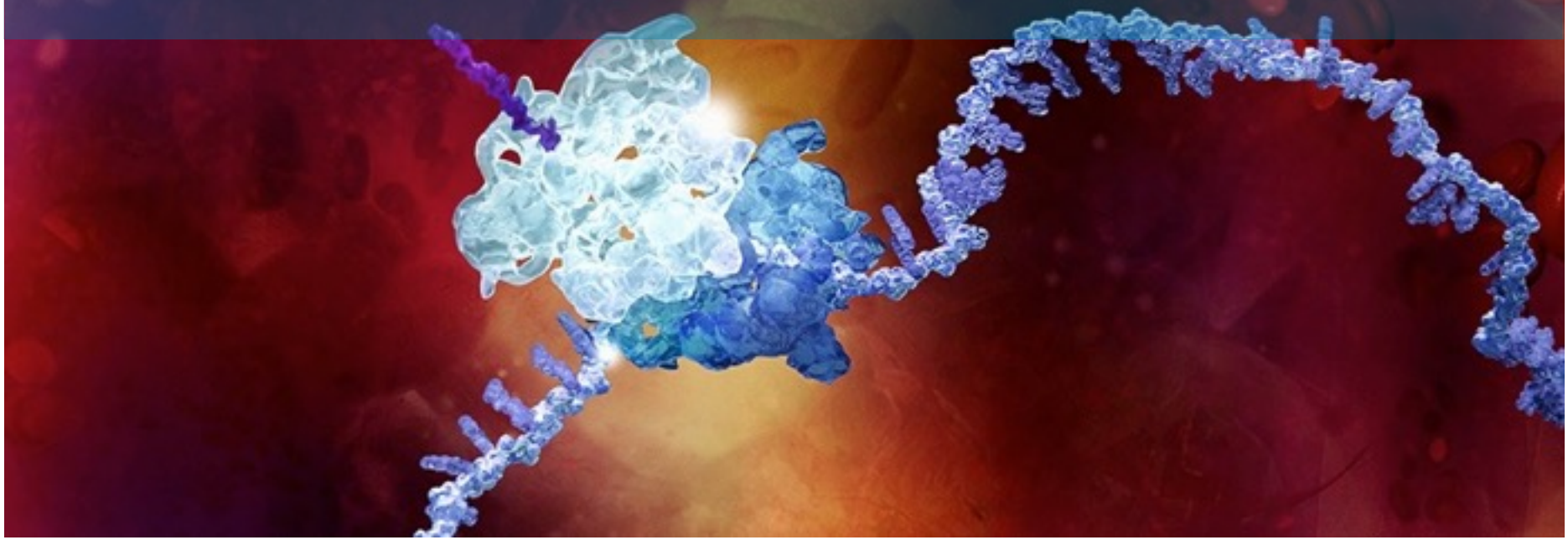


Disclosure

Dr Sarit Rabbie is currently Post doc - clinical pharmacology scientist, Quantitative Clinical Pharmacology, iMed, AstraZeneca, Cambridge, UK.

Background

- EGFR TKI is now the standard care in frontline treatment of patients harbouring EGFR mutation, however majority of the patients will eventually progress. CNS failure, i.e. brain metastases (BM) is one of the major issues.

- There are reports[1] of TKIs providing benefit in treatment of EGFR mutant NSCLC patients with BM, regardless currently approved TKIs are generally believed to have poor properties for penetrating the blood brain barrier[1-4]

- AZD3759 is being developed as an oral EGFR inhibitor for the treatment of BM and leptomeningeal disease (LM).

- AZD3759 is an oral, CNS-penetrable, potent inhibitor of EGFR with L858R and exon19Del mutations.

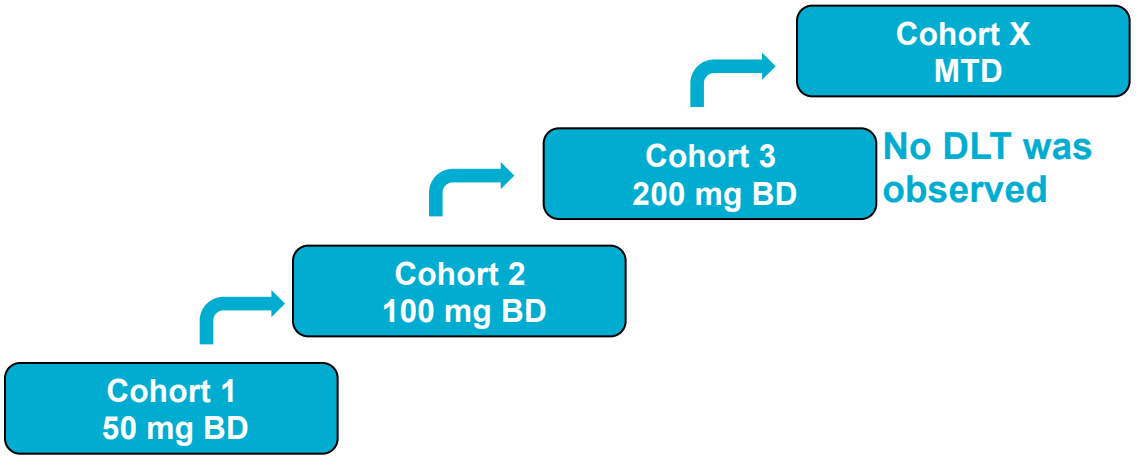
- *Trial is ongoing, the presentation only contains an overview of clinical data to the cut off date 12 September 2015.*

References
1. Bartolloti et al. Expert Rev Anticancer Ther 2012;12:1429–1435; 2. Lee et al. Cancer 2010;116:1336–1343;
3. Omuro et al. Cancer 2005;103:2344–2348; 4. Hoffknecht et al. Thorac Oncol 2015;10:156–163

Clinical trial design and status

- Phase I, multicenter, first-in-human study to assess the safety, tolerability, PK and Preliminary Anti-Tumour Activity of AZD3759 in patients with EGFRm+ non-small cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM) [NCT02228369]

- Part A of this trial is the dose escalation and planned part B is the expansion of selected dose/ schedule in BM /LM EGFRm+ NSCLC patients.



PK Sampling Times

Time relative to dose	Single dose	Multiple dose	
	Day 1	Day 8 plasma	Day 8 CSF
Pre dose	X	X	
0.5	X	X	
1	X	X	
1.5	X	X	
2	X	X	
3	X	X	
4	X	X	
6	X	X	
8	X	X	
10	X	X	
12	X	X	X
24	X		
48	X		

Site activation

- Part A (dose escalation)
  - Korea: 2 sites, active and recruiting.
  - Taiwan: 1 site, active and recruiting.

Preliminary PK data presented that were calculated using nominal sampling times are draft, unvalidated and subject to changes

Key inclusion criteria

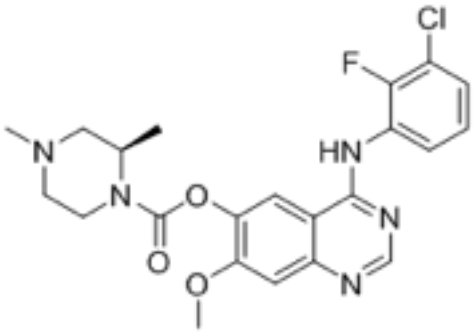
•Male or female aged at least 18 years.
•Histologically or cytologically confirmed diagnosis of NSCLC with activating EGFR mutations (L858R or Exon19Del).
•Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, or for patients with LM, 0 to 2.
•In Part A, patient must have had prior treatment with a single agent EGFR TKI (eg,gefitinib, erlotinib, afatinib, or AZD9291) and 1 line of chemotherapy (doublet or single agent) and progressed either intracranially or extracranially.

Demography

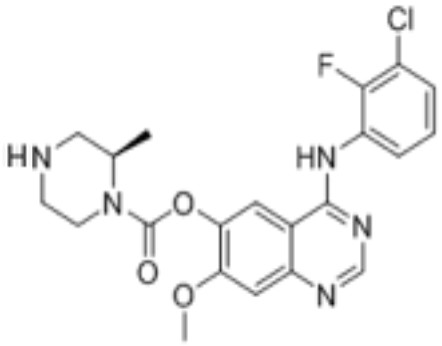
To the cut off date of 12 September 2015, 19 patients with advanced stage EGFRm+ NSCLC were enrolled into the study (5, 7 and 7 in 50, 100 and 200 mg BD, respectively).

Age (years)	41- 79	
Gender	Male	6
	Female	13
Diagnosis	Measurable BM	12
	Non-measurable BM	3
	With LM	4
Immediate prior treatment	EGFR TKI	17
	Chemotherapy	12

AZD3759 and N-desmethyl metabolite (AZ'1168) activity in EGFRm+ and wild type cell lines



AZD3759



AZ'1168

AZ'1168 is the equi-active N-desmethyl metabolite of AZD3759

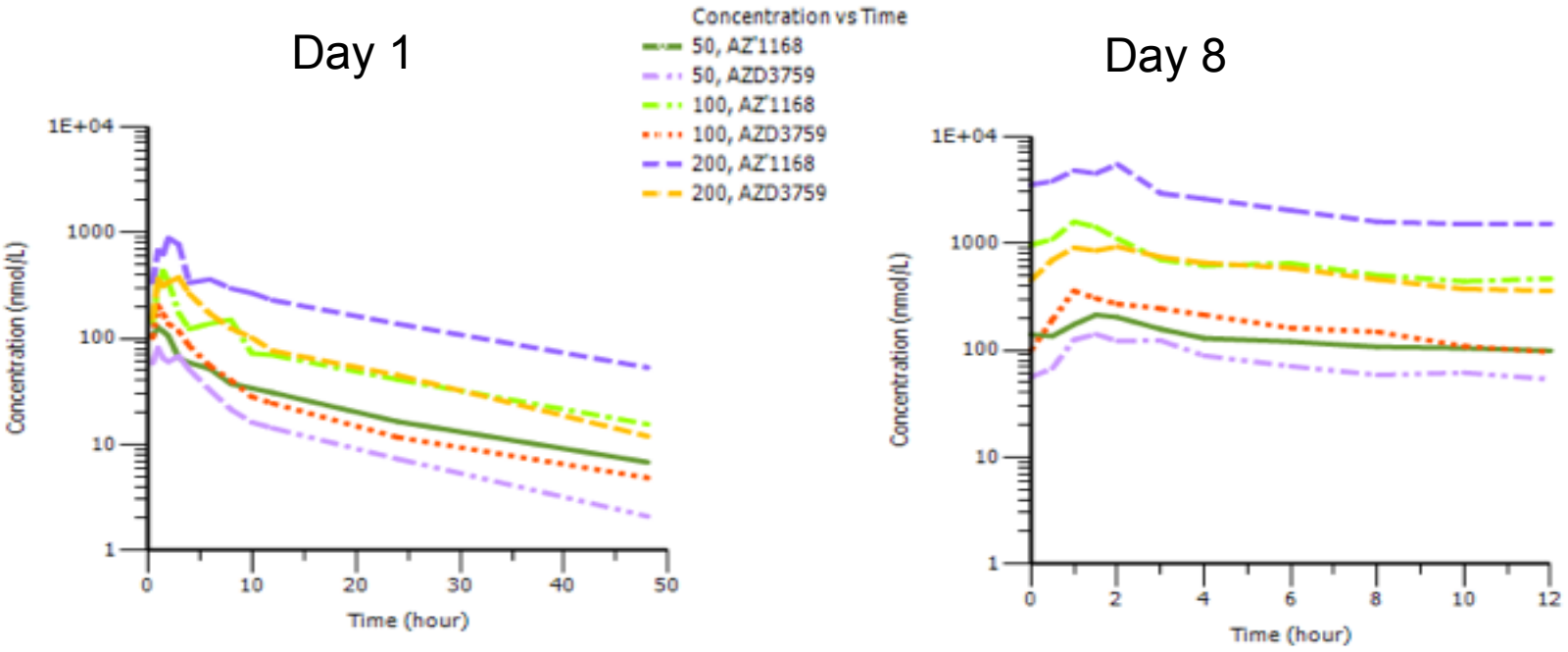
AZ #	MW	H838(wt) pEGFR IC_{50} (nM)	PC-9 pEGFR IC_{50} (nM)	H3255 pEGFR IC_{50} (nM)
AZD3759 (parent)	459.9	64.5	7.4	7.2
AZ'1168 (metabolite)	445.9	18.0	5.3	4.8

Plasma PK

Effective exposure in plasma after oral dosing

- Following a single oral dose of AZD3759, absorption appeared to be relatively fast with C_{max} achieved at a median t_{max} of 1 hour (individual range 0.5 to 3 hours).

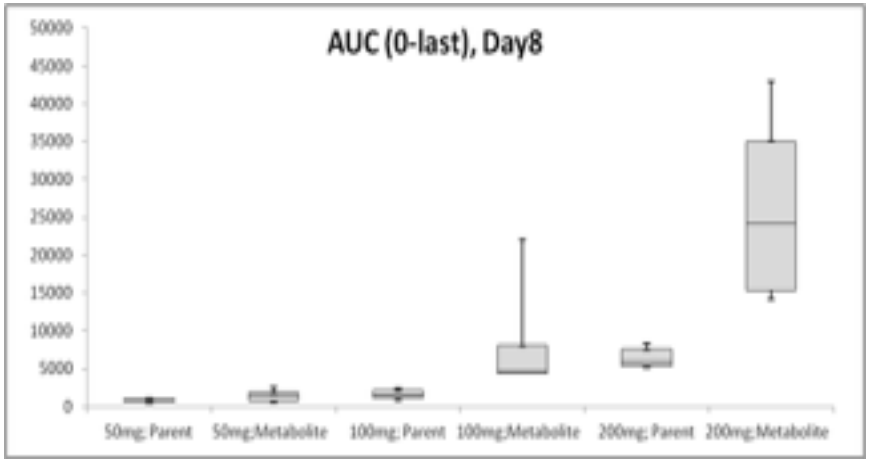
- Following the peak, plasma concentrations declined in a biphasic manner with mean half-lives in the range 12 to 14h, consistent with twice daily administration.

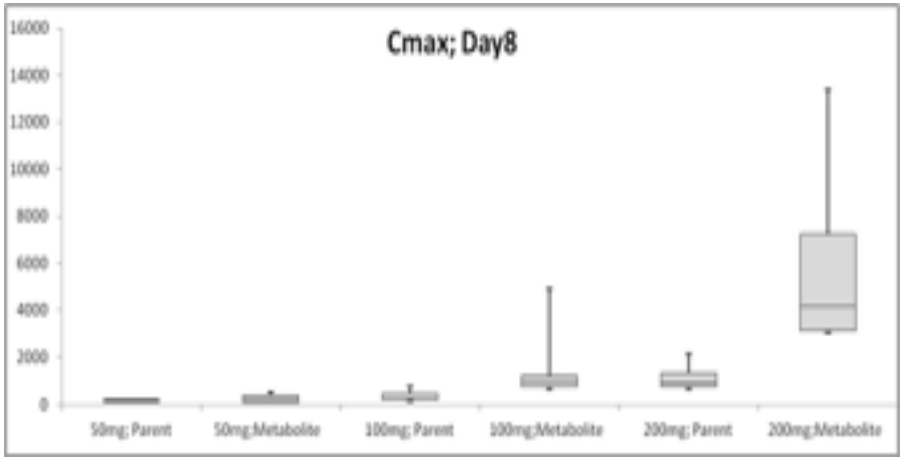


Clinical PK

Dose related changes with exposure

- With increasing dose, exposure is slightly higher than proportional for AZD3759 and for N-desmethyl.
- N-desmethyl concentrations were higher across all patients compared to AZD3759 and increase more than proportionately for dose.
- High –medium variability in AZD3759 AUC (CV ~30-50%) was observed and C_{max} CV ranged between 20-70%.

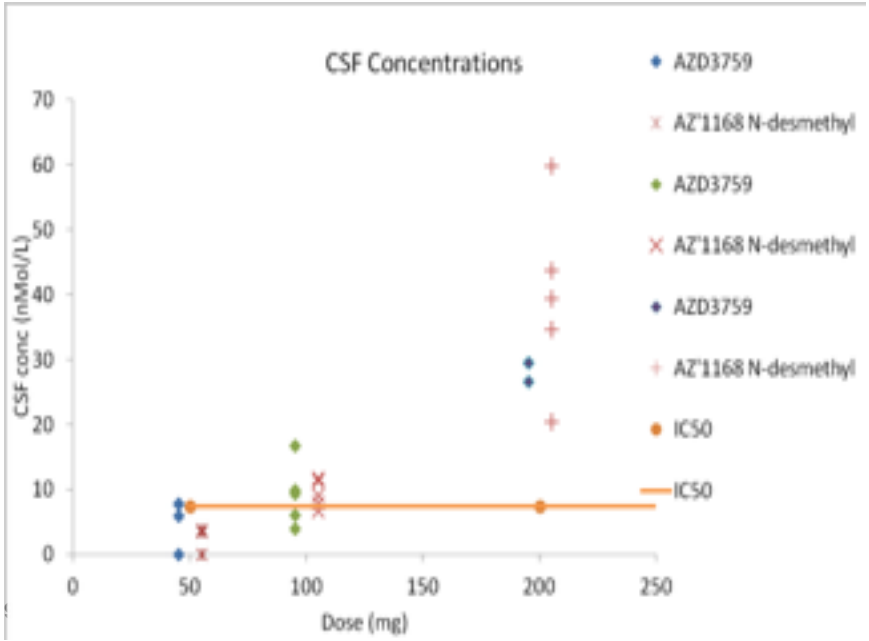


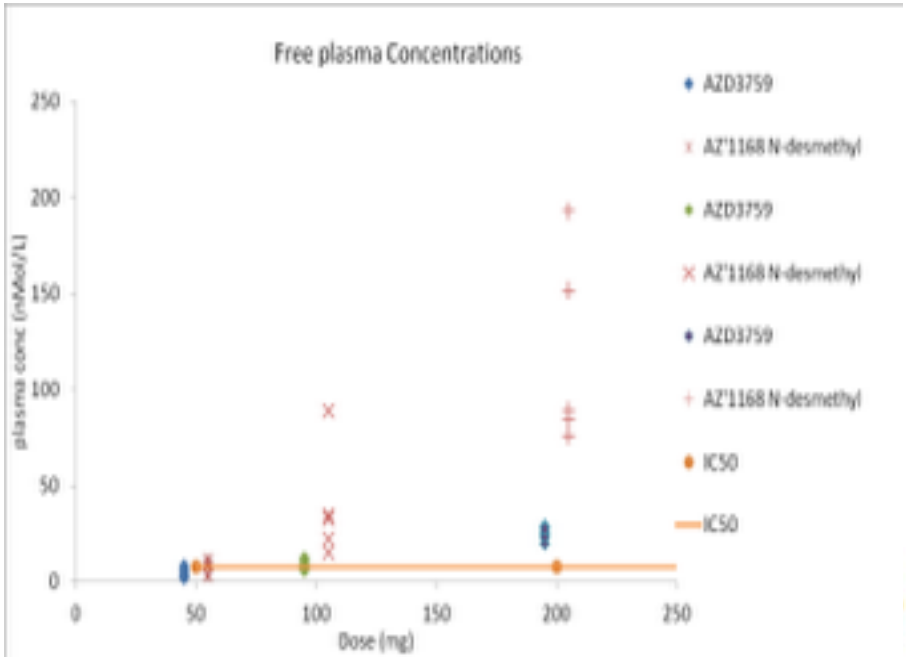


Free concentration in plasma and CSF

Confirmed exposure at target

- Therapeutic target is to obtain CSF exposure >EGFR IC50 for 24 hours. Parent and metabolite penetrate to the CSF at the same range of IC50.
- CSF concentrations of parent and metabolite increase with increasing the dose, non proportionally (3 times higher at 200 mg from 100 mg).
- CSF concentrations of parent and metabolite roughly at the same range as free concentrations in plasma at the same time point.
- Human $K_{p\ CSF}$ is 1.11 across 50-200 mg dose range.





Safety Summary

Adverse events assessed as AZD3759 related by investigators

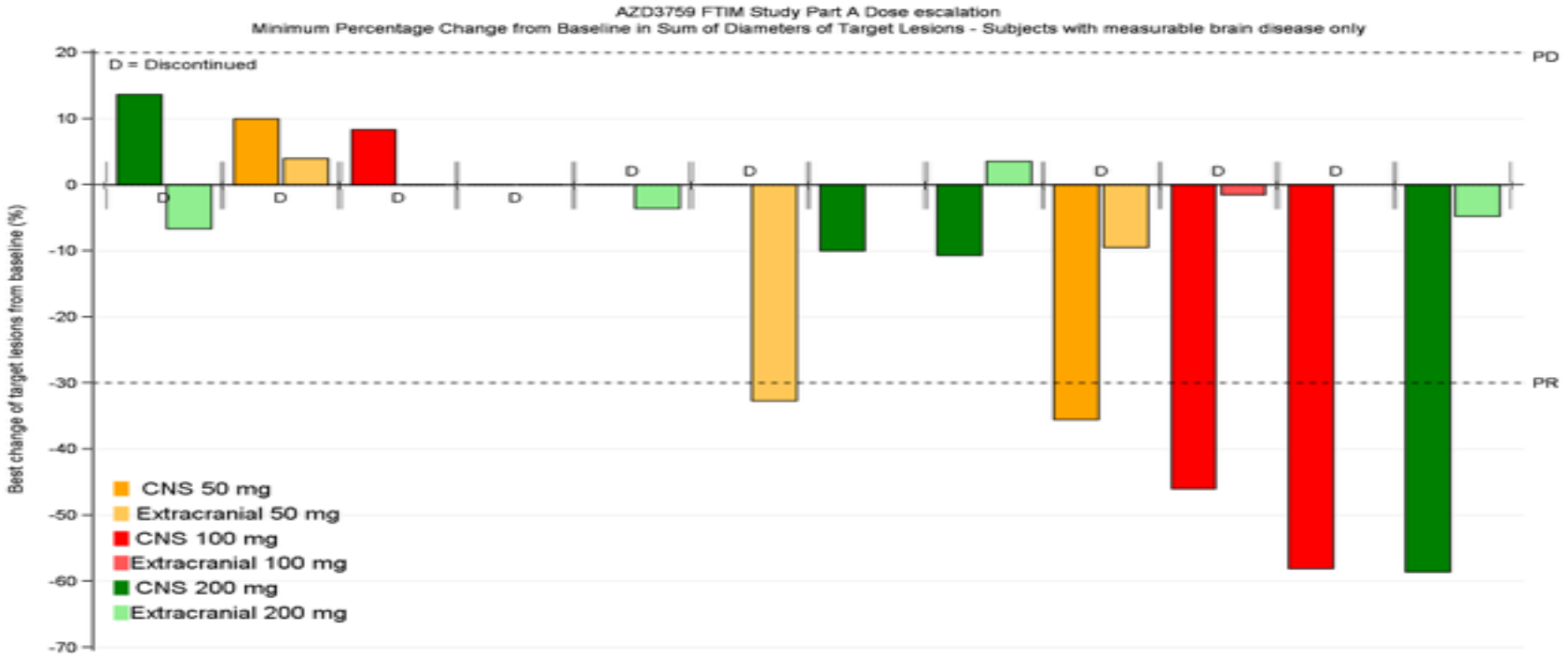
AZD3759 Dose (bid)							
	50mg (n=5)		100mg (n=7)		200mg (n=7)		
Grade	1	2	1	2	1	2	3
Skin reaction (acne, rash, pruritus, dry skin, etc)	1	0	0	2	4	3	0
Nail effect	0	0	0	0	3	0	0
Xerosis	0	0	0	0	2	0	0
Mucositis	0	0	0	0	2	1	0
Anorexia	0	0	0	0	1	0	0
Vomitting	0	0	0	0	0	1	0
Diarrhoea	0	0	1	0	2	0	1
Constipation	0	0	1	0	0	0	0
Fatigue	0	0	1	0	0	0	0

Cut off date 12 September 2015, data presented herein are unvalidated and subject to changes

- Drug-related adverse events are mainly skin rash and diarrhoea
- Adverse events reported related to AZD3759 are similar to these reported with approved EGFR TKI
- No dose limiting toxicities have been observed to date according to protocol criteria

Evident clinical response

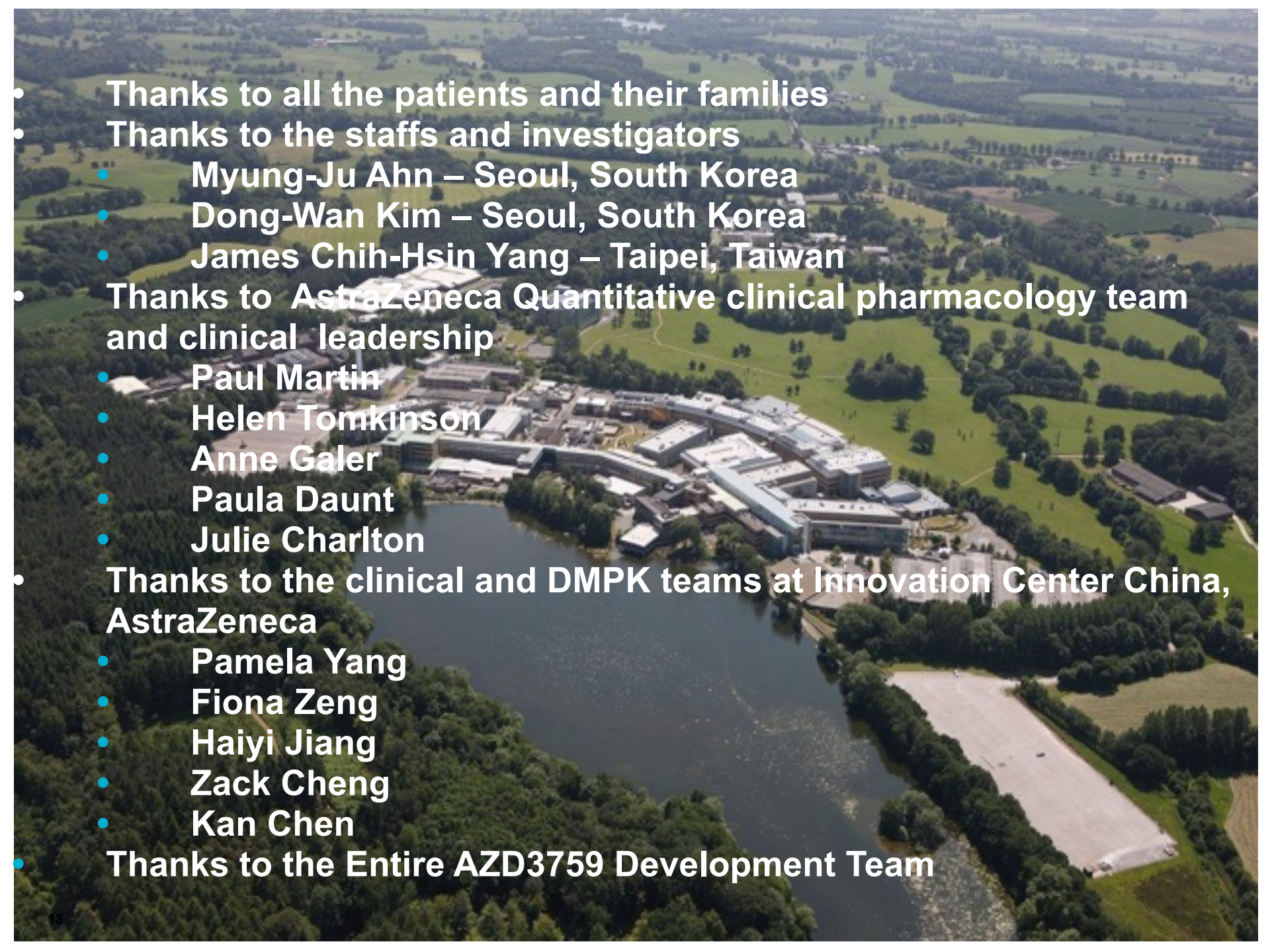
Among 19 dosed patients, 12 were evaluable for response (with measurable lesion and had went through 2 scan)



- Encouraging intracranial tumor shrinkage was observed after AZD3759 treatment in an ongoing phase I trial.
- For those patients with intracranial tumour shrinkage, all of them continue to have stable disease extracranially by RECIST.

Summary

- AZD3759 shows good BBB penetration in clinical settings with $k_{p\ CSF}$ close to 1
- At 200 mg BD at C_{trough} CSF exposure is higher than EGFRm+ IC50
- AZD3759 was well-tolerated, MTD not been reached at a dose of 200 mg BD
- Preliminary anti-tumor activity was observed in clinical setting



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Confidentiality Notice