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Pharmacokinetic study of osimertinib in cancer patients with mild or moderate hepatic impairment

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Supplementary Material

Child-Pugh and NCI-ODWG criteria

The Child-Pugh Classification system is a universal scoring system originally used to predict mortality for liver cirrhosis surgery but is now used to determine prognosis of chronic liver disease, and is based on the following variables: serum bilirubin and albumin levels, prothrombin time, and presence or absence of ascites or hepatic encephalopathy (Pugh et al. 1973). Patients' liver disease is graded (A, B, or C) according to the combined sum of scores of each variable (Supplementary Table S1). The Child-Pugh grading system can be used in PK studies to categorize patients into groups based on their degree of hepatic impairment; if the PK of a drug is affected in a particular group, this can then be used to provide recommendations for dose adjustments (Spray et al. 2007). Other ways of classifying liver dysfunction can be used; for example, in oncology, National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria are used to evaluate the impact of hepatic impairment on PK exposure (Supplementary Table S1) (National Cancer Institute 2017) . Similarly to the Child-Pugh criteria, the NCI-ODWG classification system also uses total bilirubin as a parameter to categorize patients. Aspartate aminotransferase (AST) is the only other parameter measured in the NCI-ODWG system. Although NCI-ODWG criteria are now being used to evaluate the impact of hepatic impairment in oncology, Child-Pugh classification is still considered the regulatory standard for hepatic impairment evaluation.

Supplementary Methods

Inclusion criteria: previous anti-cancer treatments

Treatment with another EGFR-TKI had to be completed 8 days or ~5x half-life, whichever was the longer, before entering; any cytotoxic chemotherapy or other anticancer drugs had to be completed within 14 days of study treatment; major surgery had to be completed within 4 weeks of study treatment; radiotherapy had to be completed within 1 week of study treatment.

Excluded patients

Eight patients were initially enrolled into the mild hepatic impairment group and received osimertinib treatment in Part A. However, further medical review of the eligibility of these patients revealed that there was insufficient substantiation of stable global chronic liver impairment. The following medical conditions were reported for these eight patients: medical history of obesity (1 patient), alcoholism (1 patient), hepatic steatosis (4 patients; none of whom had evidence of chronic liver damage), transient liver impairment due to previous anti-cancer agent (1 patient), and underlying cholangiocarcinoma and liver metastasis (1 patient). These patients were not included in the cohort of patients with liver impairment, nor with those with normal liver function, and were excluded from the PK analysis set.

Demographic and safety data are summarized for these patients under “other”.

Results

Safety

In Part A, 3 patients (10%) reported a total of 5 SAEs (acute kidney injury, hypokalemia, lower respiratory tract infection, sepsis, and sepsis that resulted in death). In Part B, 6 patients (25%) had a total of 11 SAEs (acute kidney injury that resulted in death; meningitis; pneumonia aspiration that resulted in death; neck pain; systemic inflammatory response syndrome; anemia; sepsis [2 patients]; chronic obstructive pulmonary disease; device-related infection; multiple organ dysfunction syndrome).

Table S1. Description of studies included in the population PK dataset

Study Number	Study Description	Number of patients with PK information	PK sampling schedule*
D5160C00001 (AURA)	Phase I component in EGFR mutation positive advanced NSCLC patients. Doses: 20, 40, 80, 160 and 240 mg (capsule) 80 mg (tablet) Note: capsule and tablets provided similar exposure and formulation has no impact on osimertinib exposure.	402**	Following a single dose: pre-dose, (0.5), 1, 1.5, 2, (3), 4, 6, 8, 10, 12, 24, 48, (72) and (120) hours post dosing Following multiple doses: Cycle 1 Day 8: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hours post dosing, or Cycle 2 Day 1: predose, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hours post dosing and predose on Cycle 1 day 15.
D5160C00001 (AURA extension)	Phase II in EGFR T790M positive advanced NSCLC patients who have progressed following either 1 prior therapy with an EGFR TKI agent or following treatment with at least 1 EGFR TKI and at least 1 prior platinum-based doublet chemotherapy. Dose: 80 mg (tablet)	201	Cycle 2 Day 1: predose, 1, 1.5, 2, 4, 6, 8, 10, 12 and 24 hours post dosing and predose on Cycle 1 days 1, 8 and 15.
D5160C00002 (AURA2)	Phase II component in EGFR T790M positive advanced NSCLC patients who have progressed following either 1 prior therapy with an EGFR TKI agent or following treatment with both EGFR TKI and at least 1 other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy. Dose: 80 mg (tablet)	210	Following a single dose: predose, 1, 2, 4, 6 and 8 hours post dosing. Following multiple doses on Cycle 2 Day 1 : predose and on Cycle 3 Day 1: predose, 1, 2, 4, 6, 8, 10, 12 and 24 hours post dosing. Dose reductions were allowed.

Study Number	Study Description	Number of patients with PK information	PK sampling schedule*
D5160C00003 (AURA3)	A Phase III, Open Label, Randomized Study of AZD9291 versus Platinum-Based Doublet Chemotherapy for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene (AURA3). Dose: 80 mg (tablet)	279**	Plasma samples were collected at pre-dose, between 0.5 to 1.5 hours and between 2 and 4 hours after dosing on first day of dosing in cycle 1, 3, 5, 7, 9, 11, and 13. Dose reductions were allowed.
D5160C00007 (FLAURA)	A Phase III, Double-Blind, Randomised Study to Assess the Efficacy and Safety of AZD9291 versus a Standard of Care Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor as First-Line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer. Dose: 80mg (tablet)	279	Plasma samples were collected at pre-dose, between 0.5 to 2 hours and between 3 and 5 hours after dosing at Day 1 cycle 1 and every other cycle thereafter up to and including Cycle 13. Dose reductions were allowed.

*In AURA the PK sampling scheme was updated based on emerging PK data and hence single dose samples in brackets were not collected in all patients and multiple dose samples were collected on either Cycle 1 Day 8 or Cycle 2 Day 1; multiple dose PK dosing was repeated once daily oral dosing.
** Two patients from each of these studies were not included in the master dataset.

Table S2. Statistical assessment of the relationship between hepatic function variables and key osimertinib PK parameters (PK analysis set)

Parameter (units)	Variable	n	Slope				
			Estimate	SE	90% CI	*P*-value	Coefficient of determination
AUC nM·h	Albumin	21	-0.003532	0.008645	(-0.0185, 0.0114)	0.6874	0.0087
	Total bilirubin	21	-0.007980	0.003782	(-0.0145, -0.0014)	0.0484	0.1898
C_{max} (nM)	Albumin	22	-0.002697	0.01093	(-0.0215, 0.0161)	0.8076	0.0030
	Total bilirubin	22	-0.01070	0.004762	(-0.0189, -0.0025)	0.0361	0.2015

AUC, area under plasma concentration-time curve from time zero to infinity; CI, confidence interval; C_{max}, maximum plasma drug concentration; SE, standard error

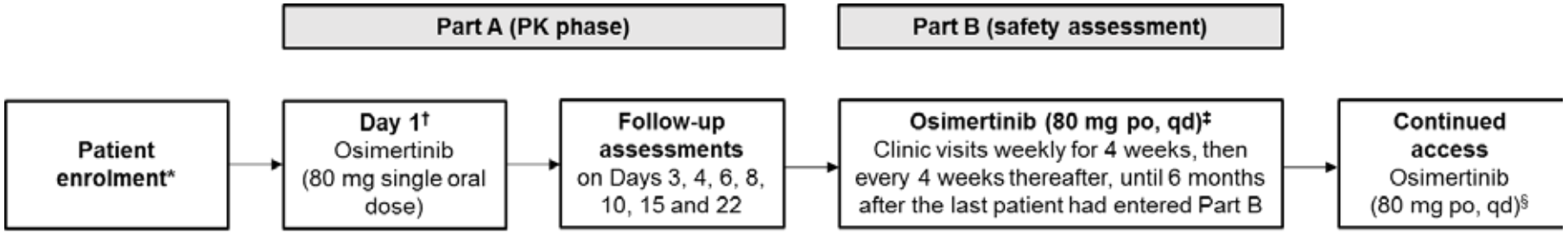
Table S3. Summary of adverse events (safety analysis set)

	Number (%) of patients[a]				
n (%)[a]	**Normal hepatic function**	**Mild hepatic impairment**	**Moderate hepatic impairment**	**Other[b]**	**Total**
Part B, n	n = 8	n = 6	n = 5	n = 5	n = 24
Any AE	8 (100)	6 (100)	4 (80)	5 (100)	23 (96)
Any AE causally related to osimertinib[c]	7 (88)	6 (100)	2 (40)	5 (100)	20 (83)
Any AE of CTCAE grade 3 or higher	2 (25)	3 (50)	1 (20)	2 (40)	8 (33)
Any AE of CTCAE grade 3 or higher causally related to osimertinib[c]	0	1 (17)	0	1 (20)	2 (8)
Any AE leading to death	0	1 (17)	1 (20)	0	2 (8)
Any SAE (including death)	2 (25)	2 (33)	1 (20)	1 (20)	6 (25)
Any SAE causing discontinuation of osimertinib	1 (13)	0	1 (20)	0	2 (8)
Any AE leading to discontinuation of osimertinib	1 (13)	0	1 (20)	0	2 (8)
Any other significant AE[d]	0	0	0	0	0
Adverse events of special interest					
n (%)					
Part A, n	n = 10	n = 7	n = 5	n = 8	n = 30
Diarrhea	0	3 (43)	0	0	3 (10)
Nail effects*	0	0	0	1 (13)	1 (3)
Conjunctival irritation	0	1 (14)	0	0	1 (3)
Eye pain	0	1 (14)	0	0	1 (3)
Dry skin*	0	0	0	1 (13)	1 (3)
Pruritus	0	1 (14)	0	0	1 (3)
Rashes and acnes*	0	1 (14)	0	0	1 (3)
Part B, n	n = 8	n = 6	n = 5	n = 5	n = 24
Diarrhea	1 (13)	2 (33)	1 (20)	4 (80)	8 (33)
Rashes and acnes*	2 (25)	2 (33)	2 (40)	0	6 (25)
Stomatitis	1 (13)	3 (50)	0	2 (40)	6 (25)
Dry skin*	0	1 (17)	0	1 (20)	2 (8)
Epistaxis	0	1 (17)	1 (20)	0	2 (8)
Syncope	0	0	0	1 (20)	1 (4)

Left ventricular failure	1 (13)	0	0	0	1 (4)
Nail effects*	0	1 (17)	0	1 (20)	2 (8)
Conjunctival edema	0	0	1 (20)	0	1 (4)
Lacrimation increased	0	0	0	1 (20)	1 (4)
Pruritus	0	0	0	1 (20)	1 (4)
Dysphagia	0	1 (17)	0	0	1 (4)
Odynophagia	1 (13)	0	0	0	1 (4)
Oral pain	0	1 (17)	0	0	1 (4)

*Grouped terms
[a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b]Patients not meeting inclusion criteria for a protocol-defined hepatic impairment group.
[c]As assessed by the Investigator.
[d]Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as other significant AEs (OAEs).
AE counted if onset was on or after the first dose date in Part B up to and including 30 days after the last dose date (of osimertinib) in Part B.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event

Figure S1. Study design



*The first patient was enrolled on 11 February 2015, and the last patient's last visit was on 16 May 2017.
†Patients fasted 1 hour before receiving osimertinib and continued to fast for 2 hours after dosing.
‡Patients were allowed to continue to receive osimertinib after completion of Part A if deemed clinically appropriate by the Investigator, until such time as the Investigator believed they no longer derived clinical benefit or if they stopped taking osimertinib for any other reason.
§Patients could continue on osimertinib if they and the Investigator deemed it appropriate, until such time as the Investigator believed they were no longer deriving clinical benefit or they stopped taking osimertinib for any other reason. During continued access to osimertinib, patients were to be seen as per their normal routine clinical schedule.
po, orally; qd, once daily.

References

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