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Osimertinib plus platinum-pemetrexed in newly-diagnosed EGFR mutation (EGFRm)-positive advanced NSCLC: safety run-in results from the FLAURA2 study

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Introduction

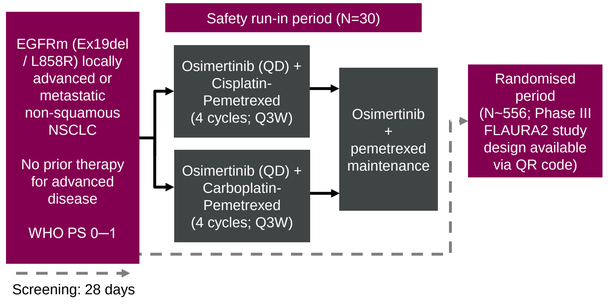
- Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the preferred first-line therapy for patients with EGFR-mutation positive (EGFRm) advanced or metastatic non-small cell lung cancer (NSCLC).[1,2]
- Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFRm and EGFR T790M and has demonstrated efficacy in NSCLC central nervous system metastases.[3,4]
- Osimertinib has previously shown efficacy vs the comparator EGFR-TKIs erlotinib and gefitinib in patients with previously untreated, advanced EGFRm NSCLC (median overall survival [OS] 38.6 vs 31.8 months; median progression-free survival [PFS] 18.9 vs 10.2 months).[5]
- First-generation EGFR-TKIs, such as gefitinib, have shown improved overall response rate (ORR) and PFS when combined with carboplatin-pemetrexed chemotherapy vs gefitinib alone in patients with advanced EGFRm NSCLC.[6]
- Combining osimertinib with platinum-pemetrexed chemotherapy may further improve patient outcomes in this setting.
- This safety run-in period, conducted to inform on the randomised evaluation period of FLAURA2, aimed to assess the safety and tolerability of osimertinib in combination with platinum-pemetrexed chemotherapy in patients with treatment-naïve, locally advanced/metastatic, EGFRm NSCLC.

Methods

Study design

- FLAURA2 is a global, phase 3, open-label, randomised study of osimertinib, with or without platinum plus pemetrexed chemotherapy, in patients with locally-advanced or metastatic EGFRm (exon 19 deletion [Ex19del] and/or L858R) NSCLC who have not received prior therapy for advanced disease (NCT04035486).
- In the safety run-in period (prior to the phase 3, randomised study period), 30 patients were allocated to receive osimertinib 80 mg once daily (QD) in combination with either cisplatin 75 mg/m^2 (n=15) or carboplatin AUC5 (n=15), plus pemetrexed 500 mg/m^2 every 3 weeks (Q3W) for 4 cycles, followed by osimertinib 80 mg QD with pemetrexed 500 mg/m^2 maintenance Q3W, until Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 defined progression or discontinuation (**Figure 1**).
- Safety run-in primary endpoints: adverse events (AEs; graded by Common Terminology Criteria for Adverse Events [CTCAE] version 5.0); laboratory evaluations of clinical chemistry, haematology/urinalysis, vital signs and physical examination (including the assessment of cardiac [LVEF and ECG] parameters; WHO performance status [PS]).

Figure 1. FLAURA2 safety run-in study design



EGFRm, epidermal growth factor receptor mutation; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; PS, performance status; QD, once daily; Q3W, every 3 weeks; WHO, World Health Organisation.

- All AEs occurring after the first dose and within 28 days of discontinuation (i.e. the last dose of study treatment) but prior to start of a new anti-cancer treatment are included in the AE summaries presented.
- Data cut-off (DCO) of the safety run-in period was 19 February 2020.

Results

Patients

- Of the 43 patients recruited to the safety run-in, 13 patients did not receive treatment due to screening failure, resulting in 30 patients enrolled across 5 countries (South Korea, Russia, Japan, Taiwan and Australia) who received at least one dose of study treatment.
- Patient demographics and clinical characteristics are summarised in **Table 1**.
- All patients (100%) had metastatic disease and adenocarcinoma histology.

Table 1. Patient demographics and clinical characteristics

Characteristic	Osimertinib + carboplatin + Pemetrexed (n=15)	Osimertinib + cisplatin + pemetrexed (n=15)	Total (N=30)
Sex, %			
Female	60	67	63
Age (years), median (min, max)	61 (45–84)	60 (48–72)	61 (45–84)
Race, %			
Asian	87	60	73
Smoking status, %			
Never smoker	80	47	63
Former smoker	20	53	37
WHO performance status, %			
0	40	47	43
1	60	53	57
EGFR mutation*, %			
Ex19del	67	67	67
L858R	33	33	33

*EGFR test used for enrolment: 27 patients (90%) enrolled using local EGFR test, 3 patients (10%) enrolled using central Cobas EGFR test. 1 patient's local Ex19del was not confirmed by the central test and 1 patient was not tested centrally due to an insufficient sample. Ex19del (n=10) and L858R (n=5) were divided equally per treatment.
EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion.

Safety

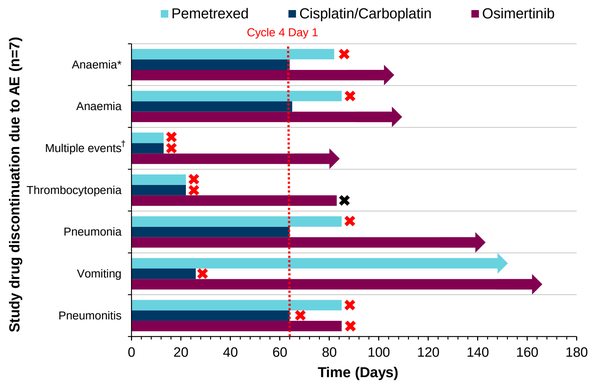
- At DCO, the majority of patients (90%) were ongoing with study treatment.
- 23 patients (77%) had completed 4 cycles of carboplatin or cisplatin chemotherapy by DCO; total exposure time was similar for both carboplatin (2.76 months) and cisplatin (2.79 months).
- Total exposure time for osimertinib (3.81 months) was similar to pemetrexed (4.14 months).
- AEs were reported by 27/30 patients (90%); the majority were not serious and mild to moderate in severity (**Table 2**).
- Most common AEs in all treatment groups were constipation (13/30, 43%), nausea (12/30, 40%) and diarrhoea (11/30, 37%; **Table 2**).
- Seven patients (23%) permanently discontinued any study drug: four patients (27%) in the osimertinib + carboplatin + pemetrexed cohort and three patients (20%) in the osimertinib + cisplatin + pemetrexed cohort (**Table 2, Figure 2**).
- The majority of AEs leading to discontinuation were single events and consistent with the known safety profile of osimertinib and chemotherapy (e.g. diarrhoea, laboratory-related toxicities; **Figure 2**).
- Two patients (7%) discontinued all study treatment due to AEs or disease under study.
  - One AE, which lead to the permanent discontinuation of osimertinib and chemotherapy, was a case of interstitial lung disease (pneumonitis; CTCAE grade 2) in the osimertinib + carboplatin + pemetrexed cohort (fulfilled a study-specific discontinuation criterion); the reported AE was considered moderate in severity and the patient recovered 24 days later.
  - One discontinuation was a fatal AE (haemoptysis) attributed to NSCLC, but not considered causally related to treatment by the investigator.
- Acute decreases in key haematological parameters were noted, but these stabilised under continued study treatment and appropriate management.

Table 2. Incidence of AEs

Incidence, n (%)	Osimertinib + carboplatin + pemetrexed (n=15)	Osimertinib + cisplatin + pemetrexed (n=15)	Total (N=30)
Any AE	15 (100)	12 (80)	27 (90)
Treatment-related AE	15 (100)	12 (80)	27 (90)
CTCAE grade ≥3	3 (20)	8 (53)	11 (37)
Serious AE	3 (20)	3 (20)	6 (20)
Death	1 (7)	0	1 (3)
Discontinuation of any study drug	4 (27)	3 (20)	7 (23)
Osimertinib	1* (7)	0	1 (3)
Carboplatin/cisplatin	2 (13)	2† (13)	4 (13)
Pemetrexed	3 (20)	3 (20)	6 (20)
Most common AEs (any grade)			
Constipation	9 (60)	4 (27)	13 (43)
Nausea	3 (20)	9 (60)	12 (40)
Diarrhoea	7 (47)	4 (27)	11 (37)
Rash	5 (33)	5 (33)	10 (33)
Stomatitis	6 (40)	3 (20)	9 (30)
Most common AEs (grade ≥3)			
Anaemia	1 (7)	4 (27)	5 (17)
Neutropenia	1 (7)	2 (13)	3 (10)
Thrombocytopenia	2 (13)	0	2 (7)
Nausea	0	1 (7)	1 (3)
Diarrhoea	0	1 (7)	1 (3)
Rash	0	1 (7)	1 (3)

*One patient discontinued all study treatments; due to fatal AE, osimertinib was discontinued but AE was not considered related to osimertinib treatment. †One patient switched from cisplatin to carboplatin after 1 cycle; patient completed 4 cycles of platinum chemotherapy.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

Figure 2. Study drug discontinuations due to AEs



* = patient switched to platinum chemotherapy after 1 cycle due to AE of inappropriate antidiuretic hormone secretion
† = pyrexia, rash, hyponatraemia
✖ = discontinuation due to AE ✖ = discontinuation due to patient death, not attributed to study treatment

Conclusions

- Osimertinib plus platinum-pemetrexed chemotherapy was generally well tolerated with no new safety signals identified.
- Most AEs identified were mild, manageable and consistent with the known safety profile of the respective treatments.
- No clear differences in safety were observed between chemotherapy regimens.
- These results support further assessment of this combination in the FLAURA2 phase 3, randomised study period.
  - FLAURA2 plans to enrol 556 patients across 163 sites.
  - The primary endpoint is PFS and secondary endpoints include OS, ORR, duration and depth of response, disease control rate, patient quality of life and safety.

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Conflicts of interest
DP: Honoraria (self and institution) and travel/accommodation expenses from AstraZeneca (AZ), Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME and Roche. TMK: Honoraria (institution) and advisory/consultancy from AZ, Boryung, Novartis, Regeneron, Sanofi, Takeda, and Voronoi. Research funding from AZ-KHID. CKL: Honoraria (self), advisory/consultancy, research funding and travel/accommodation expenses from AZ, Novartis, Pfizer, Roche, Boehringer Ingelheim, Novartis, Takeda. NY: Advisory/consultancy from Chugai Pharmaceutical Co., Ltd. SP: Employee of AZ. XH: Shareholder/Stock options and employee of AZ. PH: Employee of AZ. PJ: Advisory/consultancy from AZ, Boehringer Ingelheim, Pfizer, Roche/Genentech, Acea Biosciences, Ignyta, LOXO Oncology, Eli Lilly, Araxes pharmaceuticals, SFJ Pharmarceuticals, Voronoi, Daiichi Sankyo, Biocartis, Sanofi, Takeda Oncology; Mirati Therapeutics. Research funding from Astellas Pharmaceuticals, AZ, Daiichi Sankyo, PUMA, Eli Lilly, Boehringer Ingelheim, Revolution Medicines and Takeda Oncology. Shareholder/Stock options from Gatekeeper Pharmaceuticals and LOXO Oncology. Licensing/Royalties from LabCorp. KK: Speaker bureau/expert testimony from AZ, Bristol-Myers Squibb Japan, Ono Pharmaceutical, Boehringer Ingelheim, Taiho Pharmaceutical Co.

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