995P - Effectiveness of combination of Osimertinib with other targeted therapies in non-small-cell lung cancer with EGFR mutation and other oncogenic drivers : The real world COMPOSIT study

C. Mehlman[1], A. Swalduz[2], I. Monnet[3], J. Mazières[4], F. Guisier[5], H. Curcio[6], P. Du Rusquec[7], A. Cortot[8], V. Gounant[9], B.Abbar[10], B. Duchemann[11], E. Giroux-Leprieur[12], T. Pierret[13], F-M. Quilot[14], J. Cadranel[1], V. Fallet[1]

1 Department of Pneumology and Thoracic Oncology, Tenon Hospital, Assistance Publique Hôpitaux de Paris and GRC 4, Theranoscan, Sorbonne Université, Paris, France, 2 Department of Pneumology, Comprehensive Cancer Centre Léon Bérard, Lyon, France, 3 Department of Pneumology, CH Intercommunal de Créteil, Creteil, France, 4 Thoracic Oncology, Toulouse University Hospital, Toulouse, France, 5 Service de Pneumologie, Oncologie Thoracique et Soins Intensifs Respiratoires, CHU Rouen Normandie, Rouen, France, 6 Oncology Department, Centre Francois Baclesse, Caen, France, 7 Oncology Department, Institut Curie, Paris, France, 8 Thoracic Oncology Department, Univ. Lille, CHU Lille, CNRS, Inserm, Institut Pasteur de Lille, UMR9020 – UMR-S 1277 - Canther, Lille, France, 9 Thoracic Oncology, Hopital Bichat Claude Bernard, Paris, France, 10 Medical Oncology, Hopital Pitié Salpetrière - Hopitaux Universitaires Pitié Salpetrière - Charles Foix AP-HP, Paris, France, 11 Department of Pneumology and Thoracic Oncology, Hôpital Avicenne, Bobigny, France, 12 Respiratory Diseases and Thoracic Oncology Department, Hopital Ambroise Pare AP-HP, Boulogne-Billancourt, France, 13 Department of Pneumology, Groupement Hospitalier Sud, Hospices Civils de Lyon, Lyon, France, 14 Department of Pneumology, CHU Dijon, Dijon, France

BACKGROUND

Somatic activating mutations in *Epidermal Growth Factor Receptor* (*EGFR*) is detected in approximately 15% of lung adenocarcinoma. Osimertinib is a third-generation, irreversible EGFR tyrosine kinase inhibitors with greater potency and selectivity against both the *EGFR*-activating mutations and the T790M-resistance mutation. Actually, Osimertinib is the standard-of-care first-line therapy for patients with advanced-stage EGFR-mutant non small cell lung cancer (NSCLC).

Identification of resistance mechanisms is crucial to guide therapeutic approaches in patients progressing beyond Osimertinib. Resistance mechanisms can be divided into two categories: on-target (involving *EGFR*) and off-targets (through activation of bypass oncogenic mutation) resistance mechanisms.

MET amplification represents the most common mechanism of off target resistance (up to 25% of patients progressing on Osimertinib). Other infrequent but potentially druggable mechanisms include *ERBB2* amplification, *BRAF* mutations and oncogenic fusions involving *RET*, *ALK*, *ROS1*, *BRAF*….

The last guidelines by **European Society of Medical Oncology** (released in May 2022) on the management of *EGFR*-mutant NSCLC recommend performing a biopsy at progression to determine if new targetable mutation is present. In such cases, treatment with the relevant targeted agent is appropriate however there are no targeted agents approved for patients who have progressed on Osimertinib. Strategies are evaluated in clinical trial or use off label.

The COMPOSIT study is a French national cohort reporting the effectiveness and tolerance of Osimertinib in combination with another targeted therapy in patients with advanced *EGFR* mutated NSCLC harboring other oncogenic drivers.

METHODS

Patients treated with Osimertinib between 01.01.2017 and 04.30.2021 who received a combination of Osimertinib with another targeted treatment were included.
Clinical and histomolecular data were retrospectively collected.

The main efficacy outcomes of therapies combinations assessed were objective response rate (ORR), disease control rate (DCR), real worl progression free survival (rwPFS) and overall survival (OS).
The adverse events were reported according to Common Terminology Criteria for Adverse Events (CTCAE).

We presented here, the preliminary data from 14 french centers.

RESULTS

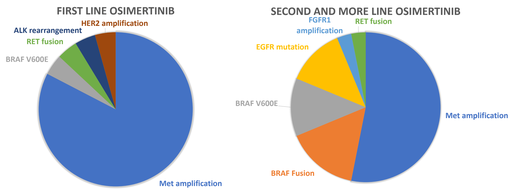
Patients and histomolecular characteristics

From 14 centers in France, 55 patients were included.

Characteristics	Total N (%)
Gender	
Sex Female	31 (56,3%)
Age (years)	
Median (range)	59 (29-83)
Smoking history	
Smoker	22 (40%)
Non-smoker	33 (60%)
TNM stage at diagnosis	
I or II	3 (5.4%)
IV	52 (94.6%)
Histological subtypes	
Adenocarcinoma	54 (98.2%)
EGFR mutation type at diagnosis	
19 deletion	37 (67.3%)
L858R	14 (25.5%)
others	4 (7.2%)
First line treatment	
Osimertinib	23 (41.8%)
Other EGFR TKI*	26 (47.3%)
Chemotherapy	6 (10.9%)
Combination Line	
Second line	20 (36.4%)
Third line	13 (23.6%)
Fourth line	10 (18.2%)
Fifth line	10 (18.2%)
Sixth line	3 (5.4%)

* Erlotinib n=8; Gefinitib n=10; Afatinib n=6

Figure 1 : Histomolecular alterations according to osimertinib line



MET pathway was the most targeted mechanism by combination therapies (66.1%).

Efficacy of combinations

Real world PFS data was available for 54 combinations. Median follow-up was 16.7 months (95% CI; 13.3-19.1).

The median rwPFS was 4.1 months (95% CI; 3.2-5.5). Overall response rate (ORR) was 49.0% (95% CI; 35.3-62.7%). The median overall survival (OS) was 11.9 months (95% CI; 8.6-19.6).

In MET pathway alterations, rwPFS was 5.3 months (95 CI; 3.9-6.7), ORR 59.4% (95% CI; 42.4-76.4) and OS 14.8 months (95% CI; 7.4-33.2).

Figure 2 : Real World Progression Free Survival in global population and in MET population treated with combination

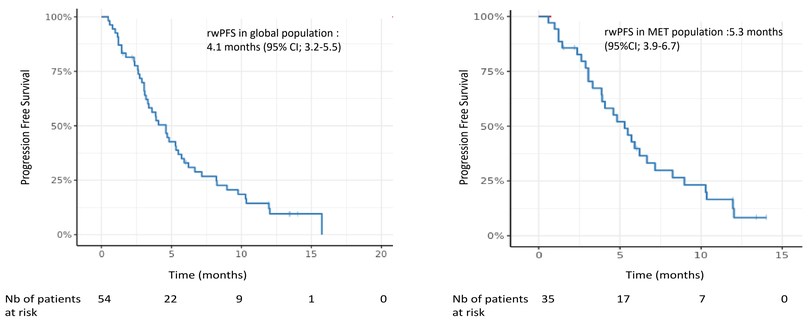
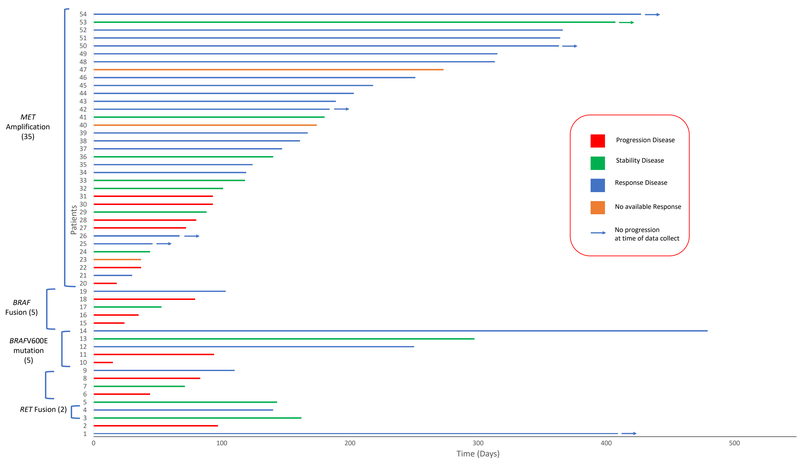


Figure 3: Duration of combination therapies



Molecular alterations and therapies combinations

Alteration targeted	Osimertinib (O) + Targeted therapy (number of patients)
MET amplification	O + crizotinib (19) O + capmatinib (7) O + savolitinib (4) O + tepotinib (5) O + crizotinib then O+ capmatinib (1)
BRAF fusion	O + trametinib (5)
BRAF V600E	O + trametinib (1) O + dabrafenib (2) O + dabrafenib Trametinib (2)
EGFR C797S + T790M	O + brigatinib (2)
EGFR C797S + T790M cis	O + gefitinib (1)
EGFR L861Q + G724S + T790M	O + afatinib (1)
RET rearrangement	O + praseltinib (2)
ALK rearrangement	O + crizotinib (1)
FGFR1 amplification	O + erdafitinib (1)
HER2 amplification	O + trastuzumab (1)

Tolerance

Adverse events (AE) were reported in 33 patients (60%). No death was related due to the therapies combinations. AE of grade >2 were reported in 13 patients (23.6%), mainly related to the associated targeted therapy and not to Osimertinib (93%).
The frequency of drug interruption due to AE was 12.7% (7 patients).

Associated therapy with osimertinib (number of patients)	Adverse event number of patients (%)	Grade >2 adverse event number of patients (%)	Discontinuation of treatment number of patients (%)	Reduction number of patients (%)
Crizotinib (22)	12 (54.5)	3 (13.6)	2 (9.0)	3 (13.6)
Capmatinib (7)	6 (85.7)	2 (28.6)	2 (28.6)	2 (28.6)
Trametinib (6)	5 (83.3)	0	0	2 (33.3)
Praseltinib (2)	2 (100.0)	2 (100.0)	1 (50.0)	1 (50.0)
Brigatinib (2)	1 (50.0)	0	0	0
Dabrafenib (2)	1 (50.0)	1 (50.0)	0	1 (50.0)
Dabrafenib-trametinib (2)	1 (50.0)	1 (50.0)	0	1 (50.0)
Afatinib (1)	1 (100.0)	1 (100.0)	1 (100.0)	0
Erdafitinib (1)	1 (100.0)	1 (100.0)	0	1 (100.0)
Gefitinib (1)	0	0	0	0
Trastuzumab (1)	1 (100.0)	1 (100.0)	1 (100.0)	0

* Data not available for tepotinib and savolitinib (clinical trial embargo)

CONCLUSION

To our knowledge, this is the largest real-world study of combination therapies in patients with advanced EGFR-mutated NSCLC harboring other oncogenic drivers. Combination approaches with oOsimertinib are already used to overcome resistance by clinicians.

Dr Camille Mehlman discloses no conflict of interest

Corespondance: vincent.fallet@aphp.fr