Osimertinib in patients with EGFRmutated NSCLC and leptomeningeal or brain metastases: results of the IFCT-1804 ORBITAL trial

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Background

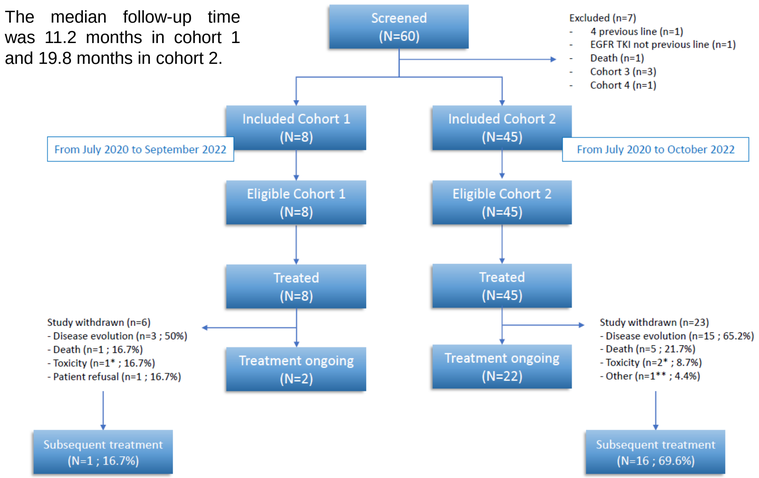
Advanced Non small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations are at an increased risk of developing central nervous system (CNS) metastases, which can lead to significant morbidity and mortality. Although osimertinib is the recommended first line treatment in this population, its efficacy in treating CNS metastases has been poorly studied.

Methods and Objectives

ORBITAL is a multicenter phase II trial investigating the efficacy and safety of osimertinib 80 mg/d in EGFR mutated NSCLC patients with leptomeningeal metastases (cohort 1) or patients with brain metastases who have not received prior EGFR Tyrosine kinase inhibitor or radiation therapy (cohort 2). The primary endpoint was objective response rate (ORR) at 6 months, secondary endpoints included progression free survival (PFS), overall survival (OS), CNS ORR and CNS PFS,.
Brain magnetic resonance imaging (MRI) was performed every 6 weeks during first year and then every 8 weeks.

Study flowchart

The median follow-up time was 11.2 months in cohort 1 and 19.8 months in cohort 2.



Toxicities that led to discontinuation of treatment (*)
- Cohort 1: Lyell syndrome (n=1)
- Cohort 2: Interstitial pneumonitis (n=2)

Other cause that led to discontinuation of treatment (**)
- Cohort 2: Patient decision (n=1)

Baseline characteristics

		Cohort 1 (N=8)	Cohort 2 (N=45)
Female	N (%)	7 (87.5)	30 (66.7)
Age	Median	73.4	67.0
Smoking status			
Never	N (%)	5 (62.5)	28 (62.2)
Former		3 (37.5)	12 (26.7)
Current		0 (0)	5 (11.1)
Histology			
Adenocarcinoma	N (%)	8 (100)	39 (86.7)
Non-small cell carcinoma		0 (0)	5 (11.1)
Non-squamous NSCLC		0 (0)	1 (2.2)
Number of previous lines			
0	N (%)	2 (25)	40 (88.9)
1		4 (50)	4 (8.9)
2		2 (25)	1 (2.2)
Activating EGFR mutations			
Exon 19 deletion	N (%)	6 (75)	26 (57.8)
L858R		1 (12.5)	15 (33.3)
Exon 19 insertion		1 (12.5)	1 (2.2)
G719X		0 (0)	1 (2.2)
L861Q		0 (0)	1 (2.2)
Other		0 (0)	1 (2.2)

Study Treatment-Related Adverse Events

Treatment-related adverse events observed in ≥ 15% of patients :

	Cohort 1 (N= 8)				Cohort 2 (N= 45)			
	Any Grade	Grade 1 – 2	Grade 3 – 4	Grade 5	Any Grade	Grade 1 – 2	Grade 3 – 4	Grade 5
Any adverse event	6 (75%)	5 (63%)	1 (13%)	0 (0%)	42 (93%)	34 (76%)	6 (13%)	2 (4%)
Serious adverse event	1 (13%)	0 (0%)	1 (13%)	0 (0%)	3 (7%)	0 (0%)	1 (2%)	0 (0%)
Dry skin	2 (25%)	2 (25%)	0 (0%)	0 (0%)	13 (29%)	13 (29%)	0 (0%)	0 (0%)
Dermatitis acneiform	1 (13%)	1 (13%)	0 (0%)	0 (0%)	8 (18%)	8 (18%)	0 (0%)	0 (0%)
Nail disorder	1 (13%)	1 (13%)	0 (0%)	0 (0%)	8 (18%)	8 (18%)	0 (0%)	0 (0%)
Alopecia	2 (25%)	2 (25%)	0 (0%)	0 (0%)	5 (11%)	5 (11%)	0 (0%)	0 (0%)
Erythema multiforme	2 (25%)	2 (25%)	0 (0%)	0 (0%)	3 (7%)	3 (7%)	0 (0%)	0 (0%)
Diarrhoea	1 (13%)	1 (13%)	0 (0%)	0 (0%)	24 (53%)	23 (51%)	1 (2%)	0 (0%)
ALT increased	2 (25%)	2 (25%)	0 (0%)	0 (0%)	8 (18%)	8 (18%)	0 (0%)	0 (0%)
AST increased	1 (13%)	1 (13%)	0 (0%)	0 (0%)	8 (18%)	8 (18%)	0 (0%)	0 (0%)
CPK increase	2 (25%)	2 (25%)	0 (0%)	0 (0%)	5 (11%)	4 (9%)	1 (2%)	0 (0%)
Fatigue	3 (38%)	3 (38%)	0 (0%)	0 (0%)	13 (29%)	13 (29%)	0 (0%)	0 (0%)
Paronychia	2 (25%)	2 (25%)	0 (0%)	0 (0%)	7 (16%)	7 (16%)	0 (0%)	0 (0%)
Muscle spasms	1 (13%)	1 (13%)	0 (0%)	0 (0%)	7 (16%)	7 (16%)	0 (0%)	0 (0%)
Pneumonitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (9%)	2 (4%)	0 (0%)	2 (4%)
Renal failure	2 (25%)	2 (25%)	0 (0%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)

Alanine transaminase (ALT), aspartate transaminase (AST), creatine phosphokinase (CPK)

↳ Safety / tolerability were as expected with no new safety signal.

ORR at 6 months

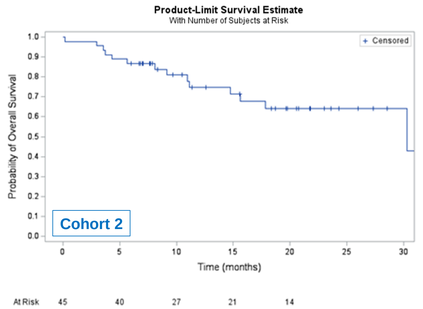
ORR

	Cohort 1 (N=8) N (%) [95% CI]	Cohort 2 (N=45) N (%) [95% CI]
Partial Response	3 (37.5%) [4.0-71.0]	27 (60%) [45.7-74.3]
Objective Response	**3 (37.5%) [4.0-71.0]**	**27 (60%) [45.7-74.3]**
Stable Disease	1 (12.5%) [0-35.4]	5 (11.1%) [1.9-20.3]
Disease Control	**4 (50%) [15.4-84.6]**	**32 (71.1%) [57.9-84.4]**
Progression Disease	0	5 (11.1%) [1.9-20.3]
Not Evaluable	4 (50%) [15.4-84.6]	8 (17.8%) [6.6-28.9]

CNS ORR

	Cohort 1 (N=8) N (%) [95% CI]	Cohort 2 (N=45) N (%) [95% CI]
Complete Response	0	5 (11.1%) [1.9-20.3]
Partial Response	1 (12.5%) [0-35.4]	21 (46.7%) [32.1-61.2]
Objective Response	**1 (12.5%) [0-35.4]**	**26 (57.8%) [43.3-72.2]**
Stable Disease	3 (37.5%) [4.0-71.0]	5 (11.1%) [1.9-20.3]
Disease Control	**4 (50%) [15.4-84.6]**	**31 (68.9%) [55.4-82.4]**
Progression Disease	0	3 (6.7%) [0-14.0]
Not Evaluable	4 (50%) [15.4-84.6]	11 (24.4%) [11.9-37.0]

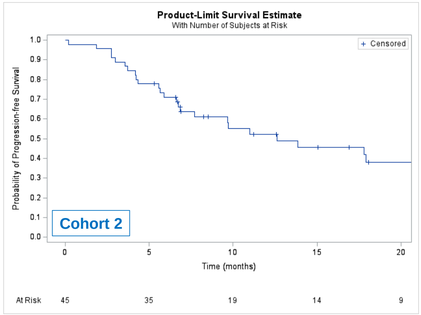
OS



	Cohort 1 (N=8)	Cohort 2 (N=45)
Event: N (%)	5 (62.5)	14 (31.1)
Median OS: months [95% CI]	7.4 [2.7NR]	30.3 [15.6-NR]
6m OS: % [95% CI]	62.5 [22.9-86.1]	86.7 [72.7-93.8]
12m OS: % [95% CI]	46.9 [12-76.3]	74.7 [57.7-85.7]

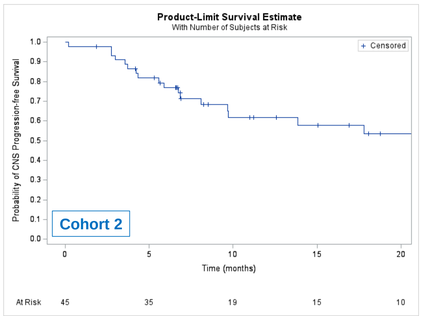
PFS

PFS



	Cohort 1 (N=8)	Cohort 2 (N=45)
Event: N (%)	5 (62.5)	25 (55.6)
Median PFS: months [95% CI]	7.4 [2.7-NR]	12.6 [6.92-6.2]
6m PFS: % [95% CI]	57.1 [17.2-83.7]	70.9 [55.2-82]
12m PFS: % [95% CI]	21.4 [1.2-58.6]	52.2 [35.8-66.3]

CNS PFS



	Cohort 1 (N=8)	Cohort 2 (N=45)
Event: N (%)	5 (62.5)	17 (37.8)
Median CNS PFS: months [95% CI]	7.4 [2.7-NR]	NR [9.7-NR]
6m CNS PFS: % [95% CI]	57.1 [17.2-83.7]	76.9 [61.2-86.8]
12m CNS PFS: % [95% CI]	21.4 [1.2-58.6]	61.8 [44.3-75.2]

Conclusions

Osimertinib demonstrated clinically meaningful responses in patients with EGFR mutated NSCLC against both leptomeningeal and brain metastases. Safety profile was acceptable and manageable. Tumour and blood samples will be analysed for exploratory biomarkers.

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