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Final results and biomarker analysis of a randomized phase II study of osimertinib plus bevacizumab versus osimertinib monotherapy for untreated patients with non-squamous non-small-cell lung cancer harboring EGFR mutations; WJOG9717L study

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Background

- Previous studies showed that the addition of anti-VEGF inhibitors to erlotinib prolonged progression-free survival in EGFR mutated non-squamous non-small-cell lung cancer (Ns-NSCLC) patients.
- The primary results of WJOG9717L study, open-label, randomized phase II trial comparing osimertinib plus bevacizumab with osimertinib monotherapy for untreated patients with advanced EGFR mutated Ns-NSCLC, were reported at ESMO2021.

Methods

WJOG9717L: Study Design

KEY ELIGIBILITY CRITERIA
- Non-squamous NSCLC harboring *EGFR* activating mutations
- Clinical stage IIIB, IIIC, IV, or recurrence after surgical resection
- Previously untreated
- ECOG PS 0-1
- Age 20- years
- Absence of symptomatic brain metastases

N=122 → RANDOMIZED 1:1
- **Osimertinib (80 mg, daily) + Bevacizumab (15 mg/kg, q3w)**
- **Osimertinib (80 mg , daily)**

Stratification factors
Sex (female vs. male)
Clinical stage (IIIB-IV vs. recurrence)
EGFR mutation (Del19 deletion vs. L858R)

Primary endpoint: PFS by the BICRs
Secondary endpoints: PFS by investigators, Overall response rate
Overall survival, Adverse events

Clinical trial information: UMIN000030206

Statistical Considerations

- The planned total sample size was 120 patients.
- We assumed the median PFS with osimertinib monotherapy as 18 months and expected as 27 months for osimertinib plus bevacizumab, with HR 0.67.
- One-sided α = 0.20, a power of 80%, an expected accrual period of 1.5 years, and a follow-up period of 2 years.
- This final analysis were performed at the data cut-off, 31th July 2021.

Results

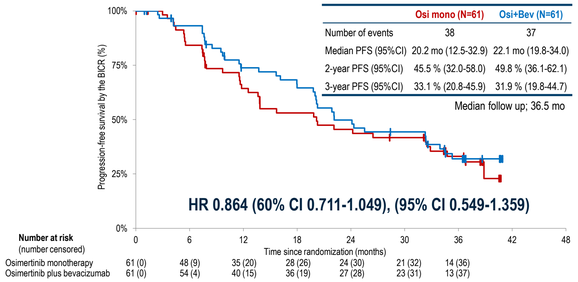
Disposition of Study Treatment

Between January 2018 and September 2018 at 21 institutions

122 assessed for eligibility and randomized

61 randomly assigned to receive osimertinb monotherapy (ITT population)	61 randomly assigned to receive osimertinb plus Bev (ITT population)
1 not receive study treatment due to symptomatic brain metastasis	
60 received osimertinb monotherapy (safety analysis population)	61 received osimertinb plus bevacizumab (safety analysis population)
2 not evaluable by BICRs	
58 without significant protocol deviations (PPS population)	61 without significant protocol deviations (PPS population)
47 discontinued study treatment 29 disease progression 10 pneumonitis 8 physician decision	47 discontinued study treatment 32 disease progression 2 adverse events, 3 pneumonitis 2 patient decision, 8 physician decision
13 completed study treatment	14 completed study treatment

Primary Endpoint: PFS (ITT), assessed by BICRs



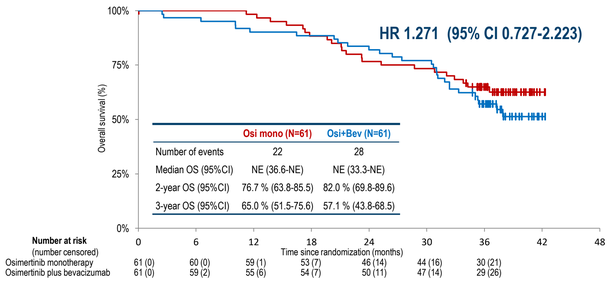
Safety summary

	Osimertinib monotherapy (N=60)		Osimertinib plus bevacizumab (N=61)	
Median duration of osimertinib (weeks)(range)	57.6	(1.4 – 183.6)	94.0	(1.6 – 183.6)
Median duration of bevacizumab (weeks)(range)	-		33.4	(3.0 – 159.0)
Grade 3-5 adverse events (AEs)	29	(48.3 %)	35	(57.4 %)
Serious adverse events (SAEs)	13	(21.7 %)	21	(34.4 %)
AEs leading to treatment discontinuation	16	(26.7 %)	37	(60.7 %)
SAEs leading to treatment discontinuation	4	(6.7 %)	8	(13.1 %)
AEs leading to dose modification	24	(40.0 %)	39	(63.9 %)
AEs leading to dose reduction	0	-	3	(4.9 %)
AEs leading to treatment-related death	0	-	1	(1.6 %)

Baseline Characteristics

		Osimertinib monotherapy (N=61)		Osimertinib plus bevacizumab (N=61)	
Age (years)	median (range)	66	(29 - 85)	67	(41 - 86)
Sex	Male	23	(37.7 %)	24	(39.3 %)
	Female	38	(62.3 %)	37	(60.7 %)
Smoking	Never	30	(49.2 %)	38	(62.3 %)
	Ever	31	(50.8 %)	23	(37.7 %)
ECOG performance status	0	34	(55.7 %)	32	(52.5 %)
	1	27	(44.3 %)	29	(47.5 %)
Histopathological diagnosis	Adenocarcinoma	60	(98.4 %)	61	(100 %)
	Others	1	(1.6 %)	0	-
Clinical stage	III	2	(3.3 %)	1	(1.6 %)
	IV	46	(75.4 %)	48	(78.7 %)
	Recurrence after surgical resection	13	(21.3 %)	12	(19.7 %)
EGFR mutation type	Deletion in exon 19	36	(59.0 %)	35	(57.4 %)
	Leu858Arg	25	(41.0 %)	26	(42.6 %)

Secondary Endpoint: Overall survival (ITT)



Summary

- This study did not show the efficacy of osimertinib plus bevacizumab against osimertinib monotherapy with respect to improving PFS in patients with non-squamous NSCLC harboring EGFR mutation.
- Regardless of TP53 mutation at baseline, there was also no significant difference in updated PFS between two arms.

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Biomarker study

Tissue samples (N=40) and plasma samples (N=94) at baseline were evaluable, and 197 genes were evaluated by targeted deep sequencing.

Tissue samples at baseline

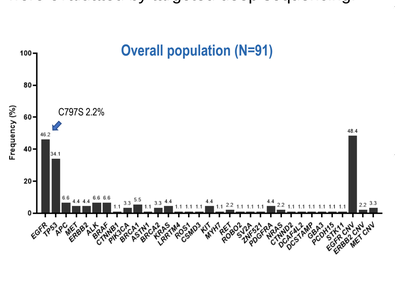
	All cases N=40 (%)		Osi mono N=22 (%)		Osi+Bev N=18 (%)	
EGFR	38	(95.0)	21	(95.5)	17	(94.4)
TP53	20	(50.0)	11	(50.0)	9	(50.0)
APC	3	(7.5)	2	(9.1)	1	(5.6)
ALK	1	(2.5)	1	(4.5)	0	(0.0)
BRAF	1	(2.5)	0	(0.0)	1	(5.6)
CTNNB1	2	(5.0)	1	(4.5)	1	(5.6)
KRAS	1	(2.5)	0	(0.0)	1	(5.6)
SLITRK1	1	(2.5)	1	(4.5)	0	(0.0)
PDGFRA	1	(2.5)	1	(4.5)	0	(0.0)
NRAS	1	(2.5)	1	(4.5)	0	(0.0)
LRRC7	1	(2.5)	0	(0.0)	1	(5.6)
EGFR CNV	8	(20.0)	4	(18.2)	4	(22.2)
ERBB2 CNV	3	(7.5)	2	(9.1)	1	(5.6)

Plasma samples at baseline

	All cases N=94 (%)		Osi mono N=46 (%)		Osi+Bev N=48 (%)	
EGFR	72	(76.6)	39	(84.8)	33	(68.8)
TP53	42	(44.7)	23	(50.0)	19	(39.6)
APC	11	(11.7)	4	(8.7)	7	(14.6)
MET	9	(9.6)	4	(8.7)	5	(10.4)
ERBB2	6	(6.4)	2	(4.3)	4	(8.3)
ALK	5	(5.3)	4	(8.7)	1	(2.1)
BRAF	5	(5.3)	2	(4.3)	3	(6.3)
CTNNB1	5	(5.3)	3	(6.5)	2	(4.2)
PIK3CA	5	(5.3)	3	(6.5)	2	(4.2)
BRCA1	4	(4.3)	2	(4.3)	2	(4.2)
ASTN1	2	(2.1)	1	(2.2)	1	(2.1)
BRCA2	2	(2.1)	1	(2.2)	1	(2.1)
KRAS	2	(2.1)	1	(2.2)	1	(2.1)
LRFN5	2	(2.1)	1	(2.2)	1	(2.1)
LRRTM4	2	(2.1)	2	(4.3)	0	(0.0)
ROS1	2	(2.1)	2	(4.3)	0	(0.0)
TRPS1	2	(2.1)	2	(4.3)	0	(0.0)
EGFR CNV	51	(54.3)	28	(60.9)	23	(47.9)
ERBB2 CNV	2	(2.1)	2	(4.3)	0	(0.0)
MET CNV	18	(19.1)	10	(21.7)	8	(16.7)

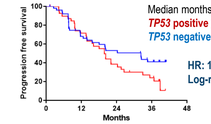
Gene alterations of plasma samples at PD or last dose

Plasma samples (N=91) at PD or last dose were evaluable, and 197 genes were evaluated by targeted deep sequencing.



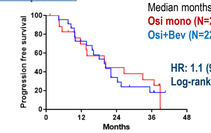
PFS assessed by BICRs, by *TP53* mutation in plasma at baseline

Patients with evaluable plasma samples at baseline



Variable		TP53 positive N (%)	TP53 negative N (%)	p value
Age	<65 yr	19 (45.2)	17 (32.7)	0.2862
	≥65 yr	23 (54.8)	35 (67.3)	
Sex	Male	19 (45.2)	20 (38.5)	0.5342
	Female	23 (54.8)	32 (61.5)	
Smoking	Ever	16 (38.1)	25 (48.1)	0.4044
	Never	26 (61.9)	27 (51.9)	

TP53 positive



TP53 negative