Abstract #632
Poster #307

A phase II study of atezolizumab in combination with bevacizumab, carboplatin or cisplatin, and pemetrexed for *EGFR*-mutant metastatic NSCLC patients after failure of EGFR TKIs (ML41701).

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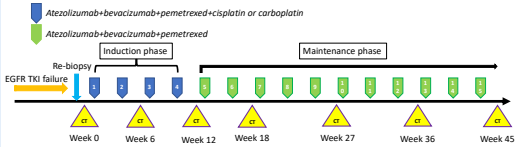
BACKGROUND

- Acquired resistance to EGFR TKI remains a significant barrier for patients with *EGFR*-mutated lung cancer, especially for those without acquired *EGFR*^{T790M}.[1]
- The phase III trial, IMpower150, reveals that atezolizumab in combination with bevacizumab, carboplatin, and paclitaxel (ABCP) as a first-line treatment for patients with metastatic non-squamous NSCLC provides clinical benefit. According to an exploratory analysis of the IMpower150, both OS and PFS benefit were observed in those *EGFR*-mutant patients treated with prior EGFR TKIs.[2]
- **Evidence gap**
  - Small (Asia/Chinese) patient number recruited from IMpower150 *EGFR*- mutant subgroup data.
  - IMpower150 subgroup data is mixed with non-T790M and T790M of *EGFR*.
  - Chemotherapy choice: current clinical practice regimen is pemetrexed + cisplatin/carboplatin.
  - Taiwan daily clinical practice use of bevacizumab is 7.5 mg/kg instead of 15 mg/kg.
- The current study explored the efficacy and safety of combinational treatment with VEGF inhibitor, immune check point inhibitor, and platinum-based chemotherapy in patients with *EGFR*-mutated lung cancer who progressed with standard EGFR targeted therapies.

METHODS

- An open-labelled, single arm, phase II study (ML41701) was conducted in NSCLC patients with activated *EGFR* mutations after failure of EGFR TKIs, and patients with acquired *EGFR*^{T790M} were excluded.
- The proposed experimental treatment is to combine atezolizumab (1200 mg), bevacizumab (7.5 mg/kg), pemetrexed (500 mg/m2) and cisplatin or carboplatin, once every 3 weeks until progression.
- ClinicalTrials.gov Identifier: NCT04147351



Major Inclusion criteria

- Stage IIIB~IV NSCLC
- *EGFR* mutation-positive tumor: Del-19, L858R, G719X, L861Q, or S768I
- PD after EGFR TKI (one or more lines)
- Re-biopsied tumor samples ➔*EGFR*^{T790M}: negative

Exclusion criteria (partial)

- Previous exposure to platinum-based C/T, VEGF inhibitor, I/O medications.
- Neo-adjuvant or adjuvant platinum-based ≦ 6 months.
- Re-biopsy tissue: T790M or exon20 insertion.
- Patients with untreated symptomatic brain metastases. Patients with treated brain metastases will be allowed if brain imaging obtained greater than 7 days from trial enrollment reveals stable disease. Patients with small (< 3mm) asymptomatic brain metastasis are allowed to enroll.
- Leptomeningeal disease
- **Primary endpoints: objective response rate (ORR)**
- Secondary endpoint: progression free survival (PFS) and overall survival (OS).

RESULTS

Patient distribution and baseline clinical characteristics

- From April 2020 to December 2021, 20 patients were enrolled. Median follow-up time was 15.6 months.
- Seven (35.0%) patients had exposure to osimertinib before enrollment. PD-L1 expression was ≧ 1% in 35.0%.

Table 1. Clinical characteristics of the enrolled NSCLC patients

	All patients
Total	20 (100.0%)
Age, median, years (range)	63.5 (49–72)
Sex	
Female	13 (65.0%)
Male	7 (35.0%)
Smoking status	
Non-smokers	14 (70.0%)
Smokers	6 (30.0%)
***EGFR* mutation**	
Del-19	8 (40.0%)
L858R	10 (50.0%)
Other	2 (10.0%)
Prior EGFR TKI	
Gefitinib/Erlotinib	9 (45.0%)
Afatinib	4 (20.0%)
Osimertinib	7 (35.0%)
PD-L1 IHC	
≧ 1%	7 (35.0%)
< 1%	13 (65.0%)

Objective Response Rate

- One patient were excluded from treatment response analysis due to patient was diagnosed as idiopathic thrombocytopenia purpura after first cycle treatment.
- ORR was 42.1%(8 of 19), and disease control rate (DCR) was 100%.
- Patients with PD-L1 expression ≧ 1% have a higher RR than those with PD-L1 expression < 1% (85.7% versus 16.7%; p = 0.006 by Fisher's exact test).(Table 2)

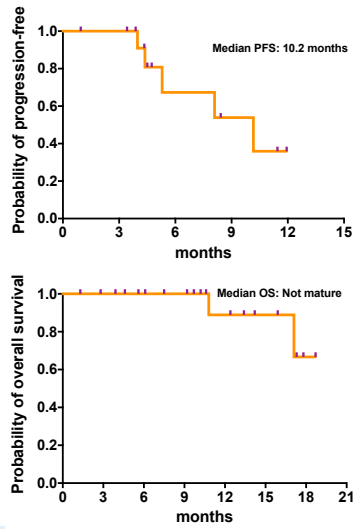
Table 2. Clinical characteristics of the patients enrolled for treatment efficacy analysis*

	All patients	Partial response	Stable disease	*P*#
Total	19	8 (42.1%)	11 (57.9%)	
Age, median, years (range)	63.5 (49–72)	60.5 (54–72)	64.0 (49–70)	0.968§
Sex				1.000
Female	12	5 (41.7%)	7 (58.3%)	
Male	7	3 (42.9%)	4 (57.1%)	
Smoking status				1.000
Non-smokers	13	6 (46.2%)	7 (53.8%)	
Smokers	6	2 (33.3%)	4 (66.7%)	
***EGFR* mutation**				0.212
Del-19	8	5 (62.5%)	3 (37.8%)	
L858R	9	3 (33.3%)	6 (66.7%)	
Other	2	0 (0.0%)	2 (100.0%)	
Prior EGFR TKI				0.856
Gefitinib/Erlotinib	9	4 (44.4%)	5 (55.6%)	
Afatinib	4	2 (50.0%)	2 (50.0%)	
Osimertinib	6	2 (33.3%)	4 (66.7%)	
PD-L1 IHC				0.006
≧ 1%	7	6 (85.7%)	1 (14.3%)	
< 1%	12	2 (16.7%)	10 (83.3%)	

#By Fisher's exact test §By Mann–Whitney U test
*one patient was excluded the efficacy analysis due to idiopathic thrombocytopenia purpura.

Progression-Free Survival (PFS) and Overall Survival (OS)

Figure 1. Kaplan–Meier survival curve of progression-free survival and overall survival in patients with *EGFR*-mutated NSCLC who received atezolizumab, bevacizumab, pemetrexed and cisplatin or carboplatin. (A) Median PFS was 10.2 (95% CI: 8.6–14.9)months. (B) OS was not mature yet.



Safety Analysis

	Any grade	(%)	Grade >=3
Abnormal liver function	7	35.0%	2
Pulmonary embolism/DVT	2	10.0%	2
Neutropenia	4	20.0%	1
Thrombocytopenia	3	15.0%	1(ITP)
UTI	2	10.0%	1(Renal abscess)
Anemia	2	10.0%	1
Hydrocephalus	1	5.0%	1
Constipation	4	20.0%	0
Rash acneiform	4	20.0%	0
Hypertension	2	10.0%	0
Dizziness	2	10.0%	0
Fever	2	10.0%	0
Insomnia	2	10.0%	0
URI	2	10.0%	0
Headache	2	10.0%	0
Gingivitis	1	5.0%	0
Malaise	1	5.0%	0
Dyspnea	1	5.0%	0
Muscle acne	1	5.0%	0
Leg edema	1	5.0%	0
Cellulitis	1	5.0%	0
Gout	1	5.0%	0
Diarrhea	1	5.0%	0
Anxiety	1	5.0%	0
Fatigue	1	5.0%	0
Epistaxis	1	5.0%	0
adrenal insufficiency	1	5.0%	0
Cough	1	5.0%	0
Back pain	1	5.0%	0
Eustachian tube obstruction	1	5.0%	0
Hyponatremia	1	5.0%	0
Oral mucositis	1	5.0%	0
Nausea	1	5.0%	0
Hemorrhoid	1	5.0%	0
Acute kidney injury	1	5.0%	0
Sore throat	1	5.0%	0
Hiccup	1	5.0%	0
Lower limb pain	1	5.0%	0
Rib pain	1	5.0%	0

DISCUSSION

Historical Control Comparison

- We collected 53 patients into the historical control group (Bev/Pem/Platin) from January 2009 to June 2020. (Table 3)

Table 3. Clinical characteristics of the patients enrolled as a historical control group.

	ML41701 (Atezo/Bev/Pem/Platin)	Historical control (Bev/Pem/Platin)	*P*#
Total	20 (100.0%)	53 (100.0%)	
Age, median, years (range)	63.5 (49.0–72.0)	59.1 (32.3–80.7)	0.072§
Sex			0.812
Female	13 (65.0%)	36 (67.9%)	
Male	7 (35.0%)	17 (32.1%)	
Smoking status			0.405
Non-smokers	14 (70.0%)	42 (79.2%)	
Smokers	6 (30.0%)	11 (20.8%)	
***EGFR* mutation**			0.427
Del-19	8 (40.0%)	30 (56.6%)	
L858R	10 (50.0%)	20 (37.7%)	
Other	2 (10.0%)	3 (5.7%)	
Prior EGFR TKI			0.183
Gefitinib/Erlotinib	9 (45.0%)	30 (56.6%)	
Afatinib	4 (20.0%)	14 (26.4%)	
Osimertinib	7 (35.0%)	9* (17.0%)	

#By Fisher's exact test §By Mann–Whitney U test
*There were 5 osimertinib, 2 EGF816, one CO1686 and one HS-10296.

Comparison in Treatment Efficacy and Survival

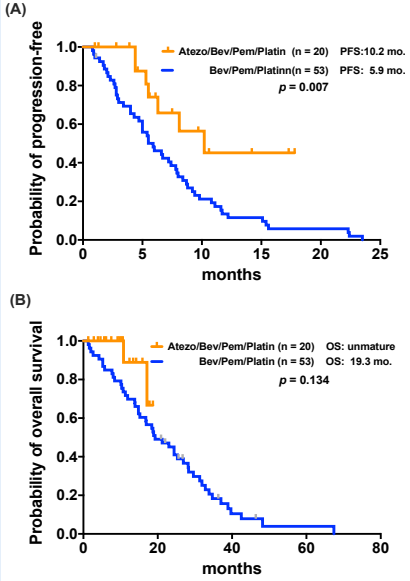
- Comparing with the 53 patients in the historical control group (Bev/Pem/Platin), the combination treatment (Atezo/Bev/Pem/Platin) of the current study showed significant benefits in DCR (100.0% vs. 64.2%; p = 0.002) and PFS (10.2 months vs. 5.9 months; p = 0.007).
- The differences in ORR (42.1% vs. 30.2%; p = 0.401) and OS (unmatured vs. 19.3 months; p = 0.134) did not reach the statistical significance between the two groups.

Table 4—Differences in treatment response between the current study(ML41701) and the historical control group.

Groups	PR	SD	PD	Total
ML41701(Atezo/Bev/Pem/Platin)*	8 (42.1%)	11 (57.9%)	0 (0.0%)	19
Historical control(Bev/Pem/Platin)	16 (30.2%)	18 (34.0%)	19 (35.8%)	53
Total	24 (33.3%)	29 (40.3%)	19 (26.4%)	72

Data are presented as n or n (%).
PR: partial response; SD: stable disease; PD: progressive disease
*one patient was excluded the response rate analysis due to idiopathic thrombocytopenia purpura.
p = 0.401 for response rates at ML41701 vs. historical control groups.
p = 0.009 for treatment responses at ML41701 vs. historical control groups.

Figure 2. (A) Differences in progression-free survival between patients with (ML41701) and without atezolizumab(Historical control group) was statistically significant (ML41701 [10.2 mo.] vs. Historical control [5.9 mo.]; p = 0.007, by the log-rank test). (B) The difference in OS did not reach a significant difference although there was a favorable trend of ML41701 (unmatured vs. 19.3 mo.; p = 0.134)



CONCLUSIONS

- **The combination treatment of atezolizumab, bevacizumab, pemetrexed and cisplatin/carboplatin provided favorable efficacy in *EGFR* mutation-positive NSCLC after TKI failure, and higher PD-L1 expression (≧ 1%) was associated with a higher ORR.**
- **The DCR and PFS of pemetrexed/platinum-based chemotherapy and bevacizumab could be improved by the addition of atezolizumab.**

References
1. Wu *et al.*, Mol. Can. 2018 17(1):38.
2. Reck *et al.*, Lancet Respir Med 2019; 7

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