



# Lung-specific response to atezolizumab plus bevacizumab is associated with overall survival in patients with lung metastasis from hepatocellular carcinoma

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# Background

- Atezolizumab plus Bevacizumab (Atezo/Bev) has been established as a standard first-line systemic treatment for advanced hepatocellular carcinoma (HCC).
- Tumor immune microenvironment is heterogenous and influences the effect of immunotherapy and/or targeted molecular agents in solid cancers.
  - Recently, some studies showed differential organ specific responses to combined immune checkpoint inhibitor and/or tyrosine kinase inhibitor in advanced HCC.
  - Especially, **lung-specific responses** were better than those of other metastatic lesions.
- However, there was no studies exploring **differential organ-specific responses** and its association with **overall survival** in patients with **advanced HCC treated by first-line Atezo/Bev.**

## Aim

- To investigate overall and organ-specific responses and their impact on survival in a specific group of patients with HCC and pulmonary metastases receiving first-line Atezo/Bev.

# Methods

- Single center, retrospective cohort study of consecutive 59 patients with lung metastasis and preserved liver function who received at least three 3-weekly cycles of first-line Atezo/Bev.
- Responses assessment was based on RECIST v1.1
  - All metastatic lung lesions in 9 cases were not considered measurable
  - **“Initial responder”** as patient who achieved complete remission (CR) or partial remission (PR) after the first cycle of treatment
  - **“Initial progressor”** as patient with progressive disease (PD) at an initial evaluation after the first cycle of treatment.
- Primary outcome
  - Lung-specific response and its association with overall survival in advanced HCC with pulmonary metastasis.

# Results

- **Baseline characteristics**

Variables	Entire study population (n=59)
Age	59.9 [51.7-67.5]
Sex	
Female	14 (23.7)
Male	45 (76.3)
Etiology	
Hepatitis B	44 (74.6)
Others	15 (25.4)
Diabetes	19 (32.2)
Family history of HCC	22 (37.3)
ECOG PS	
0	7 (11.9)
1	51 (86.4)
2	1 (1.7)
Child-Pugh class and score	
A4-6	55 (93.2)
B7	4 (6.8)
Alpha-fetoprotein	
AFP < 200	24 (40.7)
AFP ≥ 200	35 (59.3)
Neutrophil-to-lymphocyte ratio	
ratio < 3	25 (49.0)
ratio ≥ 3	26 (51.0)
Missing value	8 (13.6)
Intrahepatic metastasis	50 (84.7)
Lung metastasis alone	36 (61.0)
Multiple organ metastases	23 (39.0)
Macrovascular invasion	26 (44.1)
Previous anti-HCC treatment	
None	11(18.6)
Locoregional treatment	29 (49.2)
Surgery	9 (15.3)
Locoregional treatment and surgery	10 (16.9)

Data are presented as n (%) or median (IQR) as appropriate

Abbreviation: HCC; hepatocellular carcinoma; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status

# Results

- Initial treatment responses of overall and individual organs

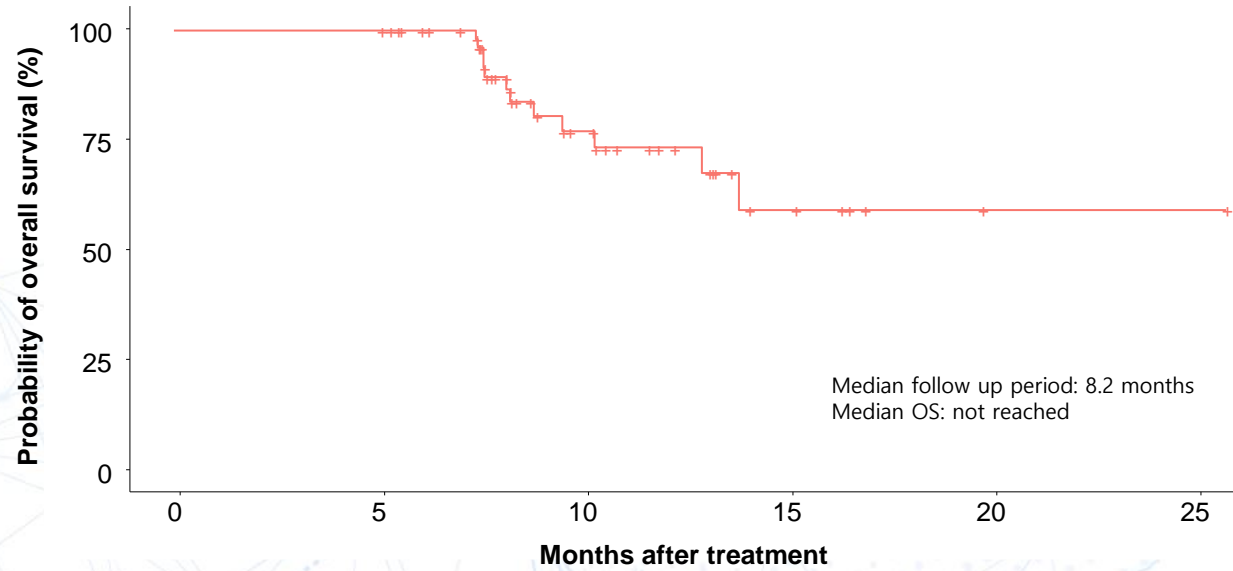
Response	Total (n=59)	Lung (n=59)	Intrahepatic (n=50)	MVI (n=26)
CR	1 (1.7)	2 (4.0)	1 (2.0)	1 (3.8)
PR	6 (10.2)	7 (14.0)	5 (10.0)	4 (15.4)
SD	37 (62.7)	25 (50.0)	34 (68.0)	18 (69.2)
PD	15 (25.4)	16 (32.0)	10 (20.0)	3 (11.6)
Responder (CR or PR)	7 (11.9)	9 (15.0)	6 (12.0)	5 (19.2)
Non-responder (PD or SD)	52 (88.1)	41 (82.0)	44 (88.0)	21 (80.8)
Non-progressor (CR, PR or SD)	44 (74.6)	34 (65.0)	40 (80.0)	23 (88.4)
Progressor (PD)	15 (25.4)	16 (32.0)	10 (20.0)	3 (11.6)
Number of non-measurable lesions	0	9	0	0

Data are presented as n (%)

Abbreviation: CR; complete response; PR, partial response; SD, stable disease; PD, progressive disease; MVI, macrovascular invasion

# Results

- Overall survival



Number at risk

Strata All

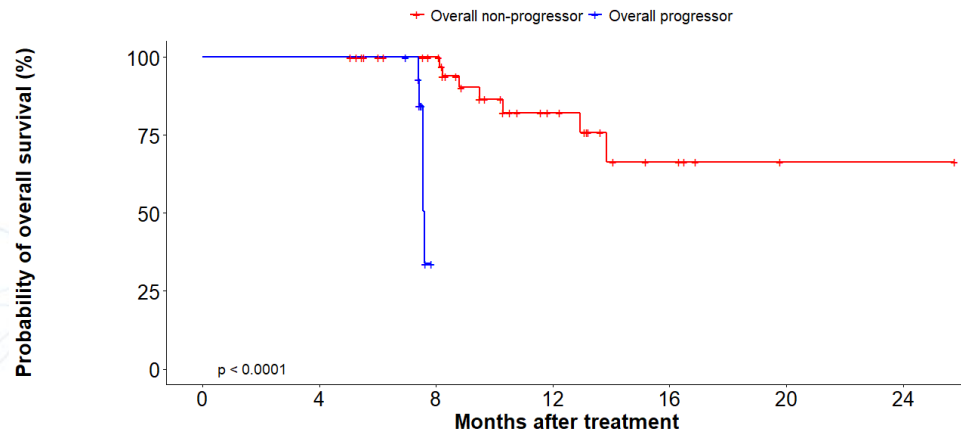
Months after treatment	5	10	15	20	25
All	59	21	6	1	1

	5-mon	10-mon	15-mon	20-mon	25-mon
OS rate (%)	100.0	77.2	59.2	59.2	59.2

# Results

- Overall and Lung-specific survival outcomes according to initial progression

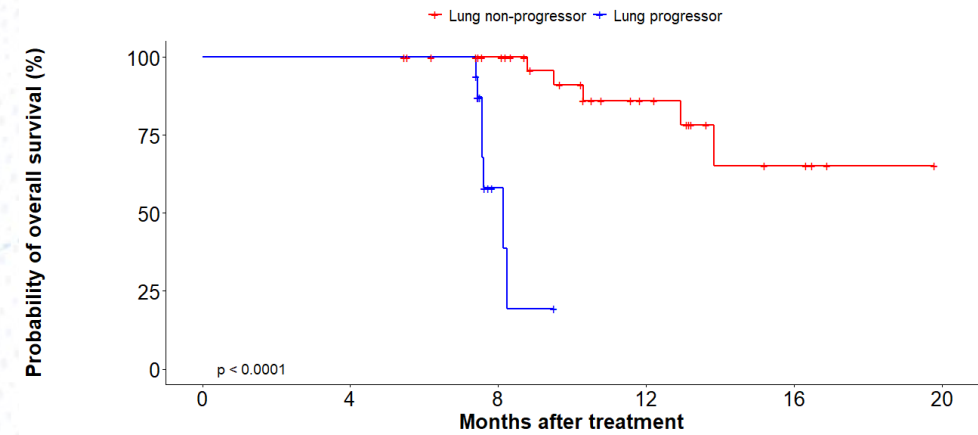
(A) Overall survival outcomes according to initial progression



	0	4	8	12	16	20	24
Overall non-progressor	44	44	35	14	5	1	1
Overall progressor	15	15	0	0	0	0	0

Overall non-progressor	4-mon	8-mon	12-mon	16-mon
OS rate (%)	100.0	100.0	82.1	66.4
Overall progressor	4-mon	8-mon	12-mon	16-mon
OS rate (%)	100.0	33.8	–	–

(B) Lung-specific survival outcomes according to initial progression



	0	4	8	12	16	20
Lung non-progressor	34	34	27	12	4	0
Lung progressor	16	16	3	0	0	0

Lung non-progressor	4-mon	8-mon	12-mon	16-mon
OS rate (%)	100.0	100.0	86.0	65.2
Lung progressor	4-mon	8-mon	12-mon	16-mon
OS rate (%)	100.0	58.0	19.3	–



# Results

- Univariate and multivariate analyses for predicting overall survival

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	aHR (95% CI)	P value
Non-progressor Initial lung progressor	1 (Reference) 29.5 (5.53-158)	<0.001	1 (Reference) <b>25.4 (4.38-148)</b>	<b>&lt;0.001</b>
Intrahepatic metastasis (Yes vs No)	3.36 (0.43-26.4)	0.2	–	–
Macrovascular invasion (Yes vs No)	2.57 (0.81-8.20)	0.11	–	–
Lung metastasis alone Multiple organ metastases	1 (Reference) 0.97 (0.31-3.09)	> 0.9	–	–
Age < 60 years Age ≥ 60 years	1 (Reference) 1.15 (0.37-3.59)	0.8	–	–
Female Male	1 (Reference) 0.23 (0.07-0.71)	0.01	1 (Reference) 0.37 (0.11-1.24)	0.11
Hepatitis B Other etiologies of chronic liver disease	1 (Reference) 0.47 (0.10-2.16)	0.3	–	–
Diabetes (Yes vs No)	1.19 (0.36-3.97)	0.8	–	–
Family history of HCC (Yes vs No)	0.89 (0.27-2.97)	0.9	–	–
Child-Pugh class A Child-Pugh class B	1 (Reference) 2.77 (0.33-23.4)	0.3	–	–
Neutrophil-to-lymphocyte ratio <3 Neutrophil-to-lymphocyte ratio ≥ 3	1 (Reference) 2.88 (0.69-12.0)	0.15	–	–
Alpha-fetoprotein < 200 Alpha-fetoprotein ≥ 200	1 (Reference) 1.67 (0.52-5.30)	0.4	–	–
Previous anti-HCC treatment (Yes vs No)	Not estimable	–	–	–

Abbreviation: HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma

# Conclusions

- Early phase of progression in lung metastasis was associated with overall survival in advanced HCC with pulmonary metastasis.
- Pulmonary response to Atezo/Bev could help clinicians decide whether to continue the drug or switch to second-lines at an early phase of the initial therapy for HCCs with pulmonary metastasis.