Supplementary Online Content

Zhang X, Wang J, Shi J, Jia X, Dang S, Wang W. Cost-effectiveness of atezolizumab plus bevacizumab vs sorafenib for patients with unresectable or metastatic hepatocellular carcinoma. *JAMA Netw Open*. 2021;4(4):e214846. doi:10.1001/jamanetworkopen.2021.4846

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Model Parameters: Baseline Values, Ranges, and Distributions for Sensitivity Analyses

Variable	Baseline value	Range	Distribution	Ref.
HR of atezolizumab-bevacizumab vs sorafenib for OS	0.58	0.42-0.79	LogNormal (-0.544727175, 0.157655532)	1
HR of atezolizumab-bevacizumab vs sorafenib for PFS	0.59	0.47-0.76	LogNormal (-0.527632742, 0.12918158)	1
Weibull OS survival model with atezolizumab-bevacizumab	λ 0.013401, γ 1.349788			1
Weibull OS survival model with sorafenib	λ 0.033685, γ 1.240405			1
Weibull PFS survival model with atezolizumab-bevacizumab	λ 0.065646, γ 1.172345			1
Weibull PFS survival model with sorafenib	λ 0.083910, γ 1.338220			1
Rate of treatment discontinuation due to adverse events				
Atezolizumab	0.085	0.057-0.118	Beta (28, 301)	1
Bevacizumab	0.146	0.110-0.186	Beta (48, 281)	1
Sorafenib	0.103	0.060-0.186	Beta (16, 140)	1
Incidence of 3-4 grade adverse events with atezolizumab-bevacizumab				
Hypertension	0.152	0.115-0.193	Beta (50, 279)	1
Fatigue	0.024	0.011-0.043	Beta (8, 321)	1
Proteinuria	0.030	0.015-0.051	Beta (10, 319)	1
Hepatitis	0.213	0.170-0.259	Beta (70, 259)	1
Diarrhea	0.018	0.007-0.035	Beta (6, 323)	1
Decreased appetite	0.012	0.003-0.026	Beta (4, 325)	1
Rash	0	0-0	-	1
Abdominal pain	0.012	0.003-0.026	Beta (4, 325)	1
Infusion-related reaction	0.024	0.011-0.043	Beta (8, 321)	1
Platelet count decrease	0.033	0.017-0.055	Beta (11, 318)	1
Asthenia	0.003	0.000-0.011	Beta (1, 328)	1
Palmar–plantar erythrodysesthesia syndrome	0	0-0	-	1
Upper gastrointestinal bleeding	0.070	0.045-0.100	Beta (23, 306)	1
Incidence of 3-4 grade adverse events with sorafenib				
Hypertension	0.122	0.075-0.177	Beta (19, 137)	1
Fatigue	0.032	0.011-0.065	Beta (5, 151)	1
Proteinuria	0.006	0.000-0.024	Beta (1, 155)	1
Hepatitis	0.167	0.113-0.229	Beta (26, 130)	1
Diarrhea	0.051	0.023-0.091	Beta (8, 148)	1
Decreased appetite	0.038	0.014-0.074	Beta (6, 150)	1
Rash	0.026	0.007-0.056	Beta (4, 152)	1
Abdominal pain	0.026	0.007-0.056	Beta (4, 152)	1
Infusion-related reaction	0	0-0	-	1
Platelet count decrease	0.013	0.002-0.035	Beta (2, 154)	1
Asthenia	0.026	0.007-0.056	Beta (4, 152)	1
Palmar–plantar erythrodysesthesia syndrome	0.083	0.045-0.131	Beta (13, 143)	1
Upper gastrointestinal bleeding	0.045	0.018-0.082	Beta (7, 149)	1

Probability of receiving second-line therapy				
In atezolizumab-bevacizumab treated patients (tyrosine kinase inhibitors: cabozantinib or regorafenib)	0.259	0.209-0.314	Beta (69, 197)	1
In sorafenib treated patients	0.462	0.385-0.540	Beta (73, 85)	1
Proportion of those receiving immunotherapy as second-line therapy in sorafenib treated patients	0.419	0.310-0.532	Beta (31, 43)	1
Body weight, kg	73	42-113	Gamma (15.72845, 4.634364)	2
Drug costs and follow-up costs, $*				
Sorafenib, per month	14,767.65	13,220.42-22,034.12	Gamma (331, 44.615257)	3, 4
Atezolizumab, 10mg	78.493	58.870-98.116	Gamma (53.42, 1.469356)	5
Bevacizumab, 10mg	78.399	58.799-97.999	Gamma (53.42, 1.467596)	5
Pembrolizumab, 1mg#	50.927	38.195-63.659	Gamma (53.42, 0.953332)	5
Cabozantinib	12537.14	8774.85-16299.44	Gamma (35.75, 350.689231)	6, 7
Regorafenib	14481.47	10934.28-18028.66	Gamma (55.83, 259.385098)	8, 9
Physician visits: no progression, per month	149.71	75.04-249.73	Gamma (11.11, 13.475248)	10
Physician visits: post progression, per month	284.39	142.54-474.40	Gamma (11.11, 25.597660)	10
Laboratory tests, per month	285.64	143.17-476.49	Gamma (11.11, 25.710171)	10
CT scan, per month	783	548-1018	Gamma (35.86, 21.834914)	7, 11
Administration cost	147.44	119.54-178.22	Gamma (96.84044, 1.52253)	12
Costs of adverse events (3-4 grade), $*				
Hypertension	14704.23	11028.18-18380.29	Gamma (53, 277.438302)	4
Fatigue	2692.56	1723.03-3874.21	Gamma (24, 112.190000)	13
Proteinuria	3194.10	2395.58-3992.63	Gamma (53, 60.266038)	4
Hepatitis	13286.50	9964.88-16608.13	Gamma (53, 250.688679)	14
Diarrhea	1008.57	645.49-1427.62	Gamma (24, 42.023750)	13
Decreased appetite	12874.84	9646.28-16093.54	Gamma (53, 242.921509)	4
Rash	284.57	213.42-	Gamma (53, 5.369245)	15

		355.71		
Abdominal pain	2533.79	1621.53-3557.98	Gamma (24, 105.574583)	13
Infusion-related reaction	6932.44	5199.32-8665.54	Gamma (53, 130.800755)	16, 17
Platelet count decrease	1111.38	711.86-1552.55	Gamma (24, 46.307500)	13
Asthenia	2692.56	1723.03-3874.21	Gamma (24, 112.190000)	13
Palmar–plantar erythrodysesthesia syndrome	8382.19	6286.64-10477.74	Gamma (53, 158.154528)	4
Upper gastrointestinal bleeding	23233.79	15489.19-30978.39	Gamma (28, 829.778214)	18
End of life cost	34101.80	25576.35-42627.25	Gamma (53, 643.430189)	19, 20
Discount rate	0.03	0-0.05	Uniform (0-0.05)	21
Utility				
Progression-free state	0.837	0.532-0.988	Beta (8.837, 1.721)	7, 9, 22
Post-progression state	0.714	0.476-0.884	-	7, 9, 22
Utility ratio of post-progression state to progression-free state[§]	0.850	0.700-1.000	Triangle	Assumed

* All costs were converted to 2020 US dollars using the Medical component of the Consumer Price Index (ref. 23).

[#] For patients receiving first-line sorafenib, pembrolizumab was considered after disease progression or intolerance to sorafenib if they chose immunotherapy as second-line therapy.

[§] Utility ratio of post-progression state to progression-free state is only used in probabilistic sensitivity analysis.

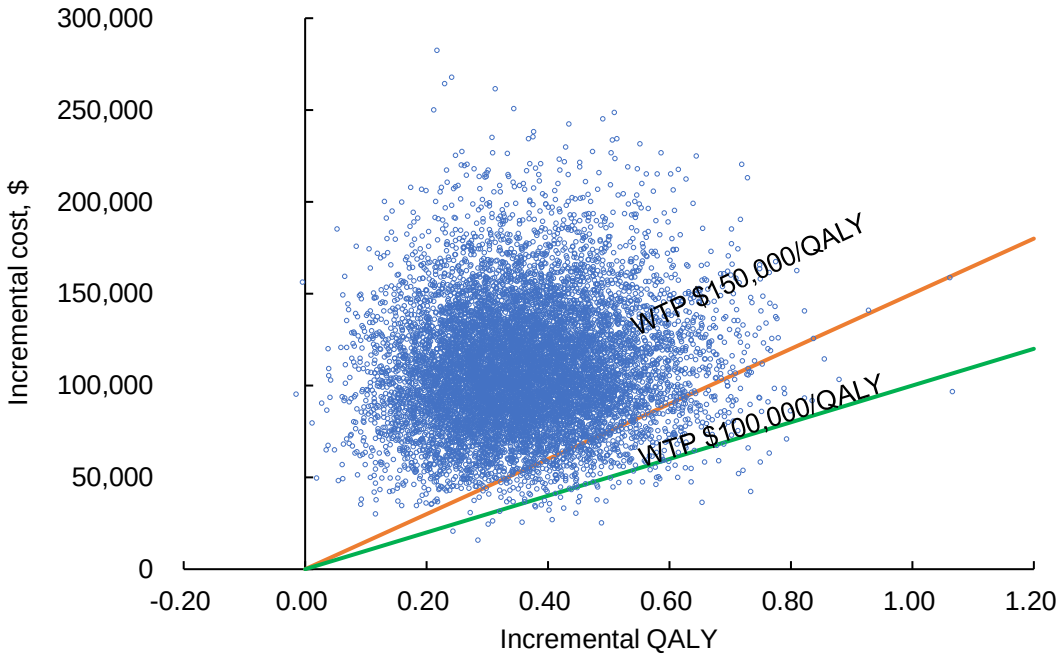
CT, computed tomography; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

eTable 2. Results for Subgroup Analyses

Subgroup	No. of patients	No. of events		HR for OS	HR for PFS	ICER ($ per QALY)
		Atezolizumab-bevacizumab	Sorafenib			
Age ≥65 years	252	39	32	0.58	0.63	289,023
Sex						
Male	414	86	53	0.66	0.59	405,799
Female	87	10	12	0.35	0.60	152,561
Geographic region						
Asia (excluding Japan)	201	34	27	0.53	0.46	321,628
Rest of the world	300	62	38	0.65	0.70	334,191
ECOG performance status score						
0	312	50	31	0.67	0.57	434,007
1	189	46	34	0.51	0.63	231,671
Barcelona Clinic liver cancer stage						
B	78	9	4	1.09	0.65	dominated
C	409	86	61	0.54	0.58	273,773
Alpha-fetoprotein category						
<400 ng/ml	314	45	36	0.52	0.49	296,599
≥400 ng/ml	187	51	29	0.68	0.79	331,997
Macrovascular invasion at study entry						
No	301	47	29	0.64	0.65	345,579
Yes	200	49	36	0.58	0.53	336,163
Extrahepatic spread at study entry						
No	196	29	20	0.77	0.61	633,622
Yes	305	67	45	0.50	0.54	257,520
Macrovascular invasion and/or extrahepatic spread at study entry						
No	123	12	9	0.69	0.72	380,106
Yes	378	84	56	0.55	0.53	305,247
Etiology						
Hepatitis B	240	44	31	0.51	0.47	297,463
Hepatitis C	108	18	15	0.43	0.69	168,240
Nonviral	153	34	19	0.91	0.71	1,647,858
Prior local therapy						
No	255	55	37	0.57	0.68	260,299
Yes	246	41	28	0.63	0.51	410,855

ECOG, Eastern Cooperative Oncology Group (ECOG scores range from 0 to 5, with higher numbers reflecting greater disability); HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

eFigure. Scatter Plot of Probabilistic Sensitivity Analysis



To explore the effect of parameter uncertainty on the cost-effectiveness analysis outcomes, a probabilistic sensitivity analysis was performed using 10,000 Monte Carlo simulations. Inputted parameters and their distributions are listed in eTable 1. Dots above the lines reflect simulations in which cost per QALY gained are above the WTP threshold of $100,000 or $150,000. Costs are expressed in 2020 US dollars ($). QALY, quality-adjusted life-year. WTP, willingness to pay.

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