Conflict-of-interest Disclosures

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- No other disclosures were reported.

Cost-Effectiveness of Atezolizumab Plus Cobimetinib and Vemurafenib in the Treatment of *BRAF V600* Mutation-Positive Metastatic Melanoma

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Session: Cost Effectiveness Analysis In Oncology Studies

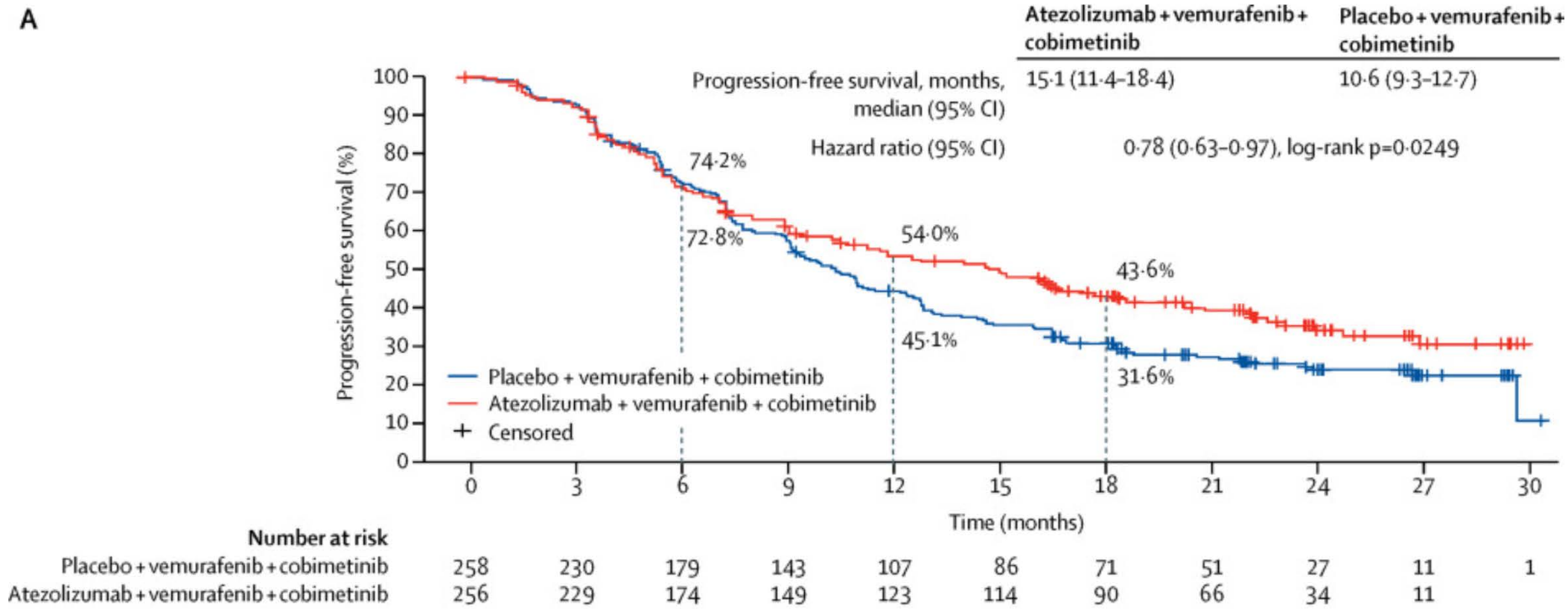
Significance and Motivation

In July 2020, FDA approved the **triplet** combination of PD-L1 inhibitor **atezolizumab** plus *BRAF* inhibitor **vemurafenib** plus *MEK* inhibitor **cobimetinib** as the first triplet regimen for treating advanced melanoma patients with *BRAF V600* mutation.

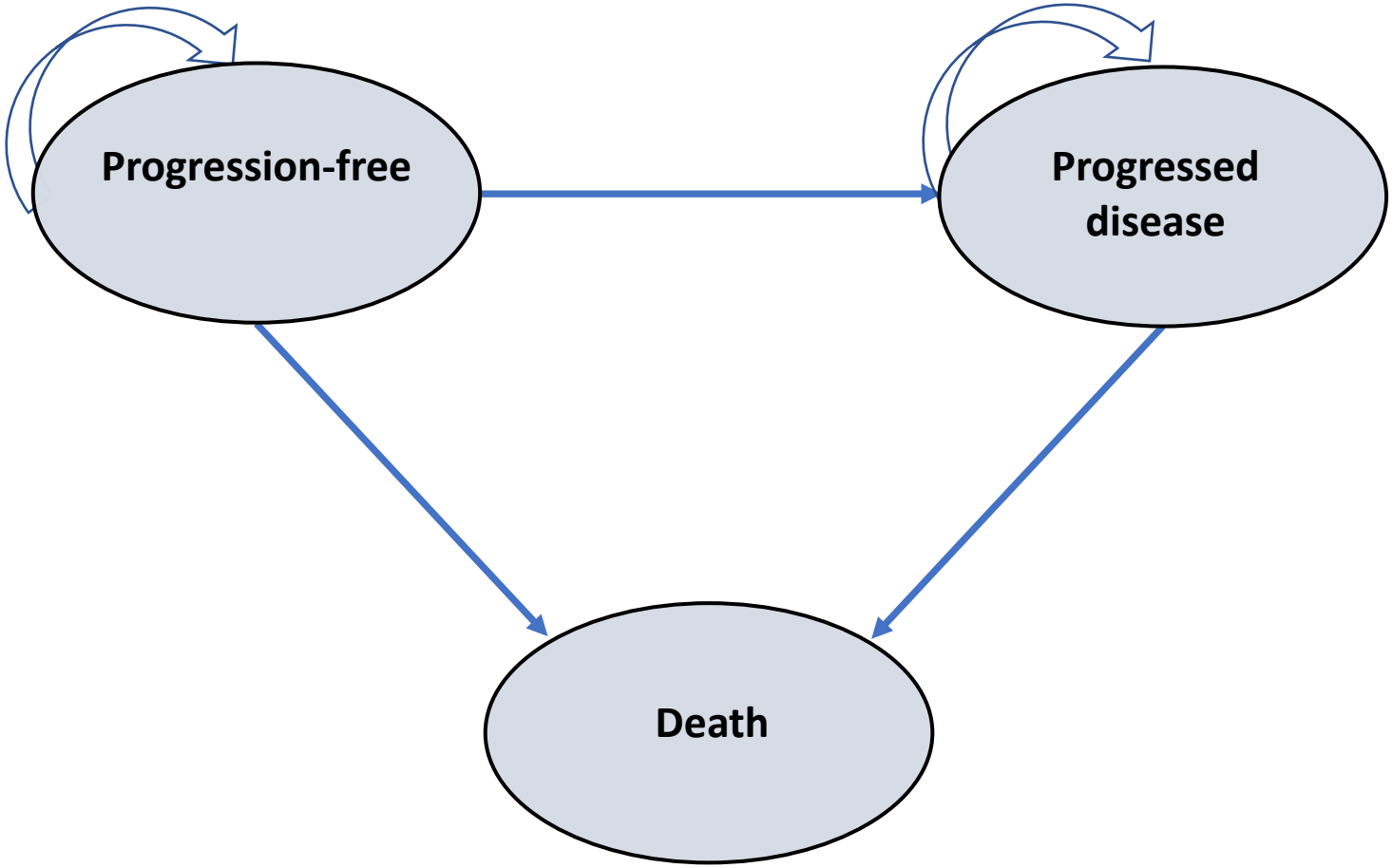
IMspire 150 (Phase III)

Progression free survival (PFS) was improved by 4.5 months with triple therapy vs. doublet.

In patients with *BRAF V600* mutated advanced melanoma, are the incremental costs of triplet therapy of atezolizumab, vemurafenib plus cobimetinib vs vemurafenib plus cobimetinib alone cost-effective for the survival gains?



3-state partitioned survival model



Methods

Analytic Overview

CHEERS; hēRo3

- US Second Panel on Cost-Effectiveness in Health and Medicine
- Reports followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)
- All modeling analyses were performed in R version 4.1.1. and hēRo3 platform.

Data Source

Digitized survival curves

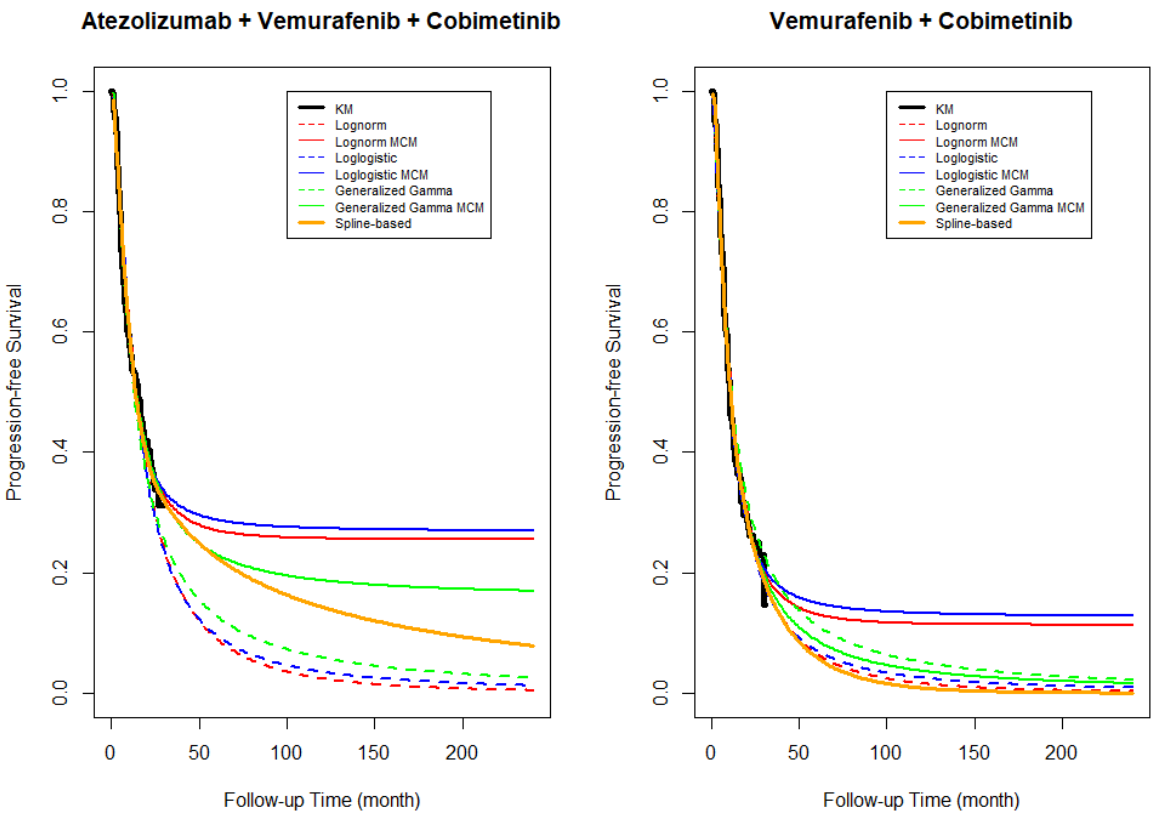
- Individual patient data for IMspire150 is not publicly available.
- Overall survival (OS) and progression free survival (PFS) curves from the IMspire150 trial were **digitized** using digit software (WebPlotDigitizer, version 4.4).

Statistical Analysis

Long-term survival modeling; CEA; Sensitivity Analyses

- 7 survival models were used to extrapolate survivals
- Cost-effectiveness model construction
- Scenario and sensitivity analyses

Long-term Survival Modeling



Based on AIC and virtually inspection of fitted survival model, the following survival distributions were used for extrapolating long-term survival in base case analysis:

- **For triplet therapy**, generalized gamma MCM was used for PFS and lognormal MCM for OS.
- **For doublet therapy**, lognormal MCM was used for both PFS and OS.

Estimated Parameters and Goodness-of-fit AIC Values from Seven Survival Models

Strategy	Distribution	Parameter	PFS			OS		
			Estimate	SE	AIC	Estimate	SE	AIC
Atezolizumab+ Vemurafenib+ Cobimetinib (Triplet)	Log-normal	meanlog	2.69	0.09	1216.92	3.45	0.11	883.84
		sdlog	1.20	0.07		1.17	0.10	
	Log-logistic	shape	1.39	0.09	1225.32	1.49	0.13	889.68
		scale	14.45	1.23		30.35	3.02	
	Generalized Gamma	mu	2.25	0.19	1212.34	2.97	0.31	882.19
		sigma	1.26	0.08		1.39	0.11	
		Q	-0.88	0.32		-1.17	0.60	
	Log-logistic MCM	theta	0.33	NA	1181.30	0.60	NA	839.44
		shape	1.89	0.21		2.22	0.41	
		scale	8.80	1.16		13.55	3.15	
	Lognormal MCM	theta	0.31	NA	1177.10	0.55	NA	837.06
		meanlog	2.22	0.16		2.72	0.33	
		sdlog	0.92	0.10		0.82	0.17	
	Generalized Gamma MCM	theta	0.06	NA	1176.76	0.01	NA	837.62
		mu	2.18	0.25		3.00	0.46	
		sigma	1.22	0.35		1.52	0.34	
		Q	-1.11	0.94		-1.73	1.02	
	Spline-based Model	gamma0	-4.33	0.36	1219.36	-5.87	0.60	887.62
		gamma1	1.87	0.20		1.90	0.27	
		gamma2	-1.23	0.26		-4.12	1.44	
Vemurafenib +Cobimetinib (Doublet)	Log-normal	meanlog	2.44	0.07	1380.64	3.24	0.08	1035.64
		sdlog	0.99	0.05		1.00	0.07	
	Log-logistic	shape	1.72	0.10	1385.78	1.76	0.14	1039.24
		scale	11.23	0.74		24.99	1.87	
	Generalized Gamma	mu	2.21	0.13	1378.73	3.16	0.18	1037.36
		sigma	1.01	0.05		1.06	0.13	
		Q	-0.52	0.26		-0.25	0.47	
	Log-logistic MCM	theta	0.18	NA	1349.99	0.33	NA	996.31
		shape	2.12	0.20		2.13	0.34	
		scale	9.20	0.80		19.23	4.71	
	Lognormal MCM	theta	0.16	NA	1348.06	0.17	NA	994.48
		meanlog	2.24	0.11		3.20	0.46	
		sdlog	0.83	0.08		0.92	0.20	
	Generalized Gamma MCM	theta	0.12	NA	1349.75	0.00	NA	996.22
		mu	2.22	0.13		3.29	0.23	
		sigma	0.90	0.17		1.10	0.19	
		Q	-0.26	0.51		-0.37	0.61	
	Spline-based Model	gamma0	-5.74	0.58	1379.64	-7.68	1.16	1037.08
		gamma1	3.17	0.43		3.15	0.71	
		gamma2	0.41	0.08		5.77	2.36	

Cost-effectiveness Model Construction

Cost and Utility Input

Drug	Dose	Monthly cost, $	Source
Atezolizumab	840 mg for days 1& 15	15 909	[1]
Vemurafenib	720 mg BID for 28 days for triplet regimen	10 586	[1]
	960 mg BID for 28 days doublet regimen	14 115	
Cobimetinib	60 mg QD for 21 days	8 999	[1]

State	Utility	Source
PF	0.88	[2]
PP	0.52	[2]

1. Cost for drugs: mean wholesale price from the Red Book (Truven Health Analytics)
2. Utility: from published literature

Three Categories of Outcome Measures

1. Effectiveness: life-years [LYs] gained and quality-adjusted life-years [QALYs]
2. Costs
3. Cost-effectiveness: incremental cost-effectiveness ratios [ICERs], expressed as cost per LY and per QALY saved

Base Case Analysis

1. Willing-to-Pay (WTP) threshold=$150k/QALY
2. A lifetime horizon (30 years) used for the base case analysis

Scenario and Sensitivity Analyses

In practice, the length of immunotherapy could be 2 years, as supported by the KEYNOTE-006 phase 3 trial for pembrolizumab in metastatic melanoma

1. Both strategies stopped after 2 years of treatments
2. Only immunotherapy stopped after 2 years of treatment
3. Time horizons of 5, 10, 15, 20, and 30 years used to examine the robustness of the estimated long-term survival and cost-effectiveness model
4. Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA)

30-year time horizon

- Adding atezolizumab provided an additional 3.267 QALYs, with an incremental cost of $887 665, associated with a lifetime ICER of $271 669 per QALY.

Results of the Base Case Analysis

Outcome	Vemurafenib + Cobimetinib	Atezolizumab + Vemurafenib + Cobimetinib
Expected Cost, $US	1 205 321	2 092 986
Expected LYs	5.733	11.714
Expected QALYs	4.453	7.720
Incremental Cost		887 665
Incremental LYs		5.980
Incremental QALYs		3.267
ICER, Cost ($US) per QALYs		271 669

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years

Results of the Scenario Analyses

- When both strategies were stopped after 2 years
  - ❖ Triplet therapy could be cost-effective at a 20-year and 30-years time horizons.
- When only immunotherapy was stopped after 2 years
  - ❖ Triplet therapy could be cost-effective over a lifetime horizon ($122 220/QALY).

		Time Horizon				
		5 years	10 years	15 years	20 years	30 years
Immunotherapy and targeted therapy capped at 2 years	Total cost $					
	Atezolizumab+Vemurafenib +Cobimetinib	569 044	596 563	621 439	643 478	679 666
	Vemurafenib+Cobimetinib	334 644	343 937	349 244	353 206	359 160
	Incremental	234 400	252 626	272 195	290 272	320 505
	Discounted total LYs					
	Atezolizumab+Vemurafenib +Cobimetinib	3.279	5.521	7.430	9.074	11.714
	Vemurafenib+Cobimetinib	2.729	3.706	4.370	4.903	5.733
	Incremental	0.549	1.815	3.060	4.171	5.980
	Discounted total QALYs					
	Atezolizumab+Vemurafenib +Cobimetinib	2.462	3.932	5.129	6.135	7.720
	Vemurafenib+Cobimetinib	2.005	2.750	3.295	3.744	4.453
	Incremental	0.456	1.182	1.834	2.390	3.267
	ICER					
	$/LYs	426 587	139 187	88 947	69 595	53 593
	$/QALYs	513 544	213 645	148 448	**121 432**	**98 092**
Immunotherapy capped at 2 years	Total cost $					
	Atezolizumab+Vemurafenib +Cobimetinib	810 639	1 076 835	1 261 279	1 396 573	1 604 662
	Vemurafenib+Cobimetinib	487 124	681 854	843 866	982 723	1 205 321
	Incremental	323 515	394 981	417 413	419 235	399 341
	Discounted total LYs					
	Atezolizumab+Vemurafenib +Cobimetinib	3.279	5.521	7.430	9.074	11.714
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	Incremental	0.456	1.182	1.834	2.390	3.267
	ICER					
	$/LYs	588 768	217 619	136 401	100 515	66 775
	$/QALYs	708 784	334 035	227 646	175 383	**122 220**

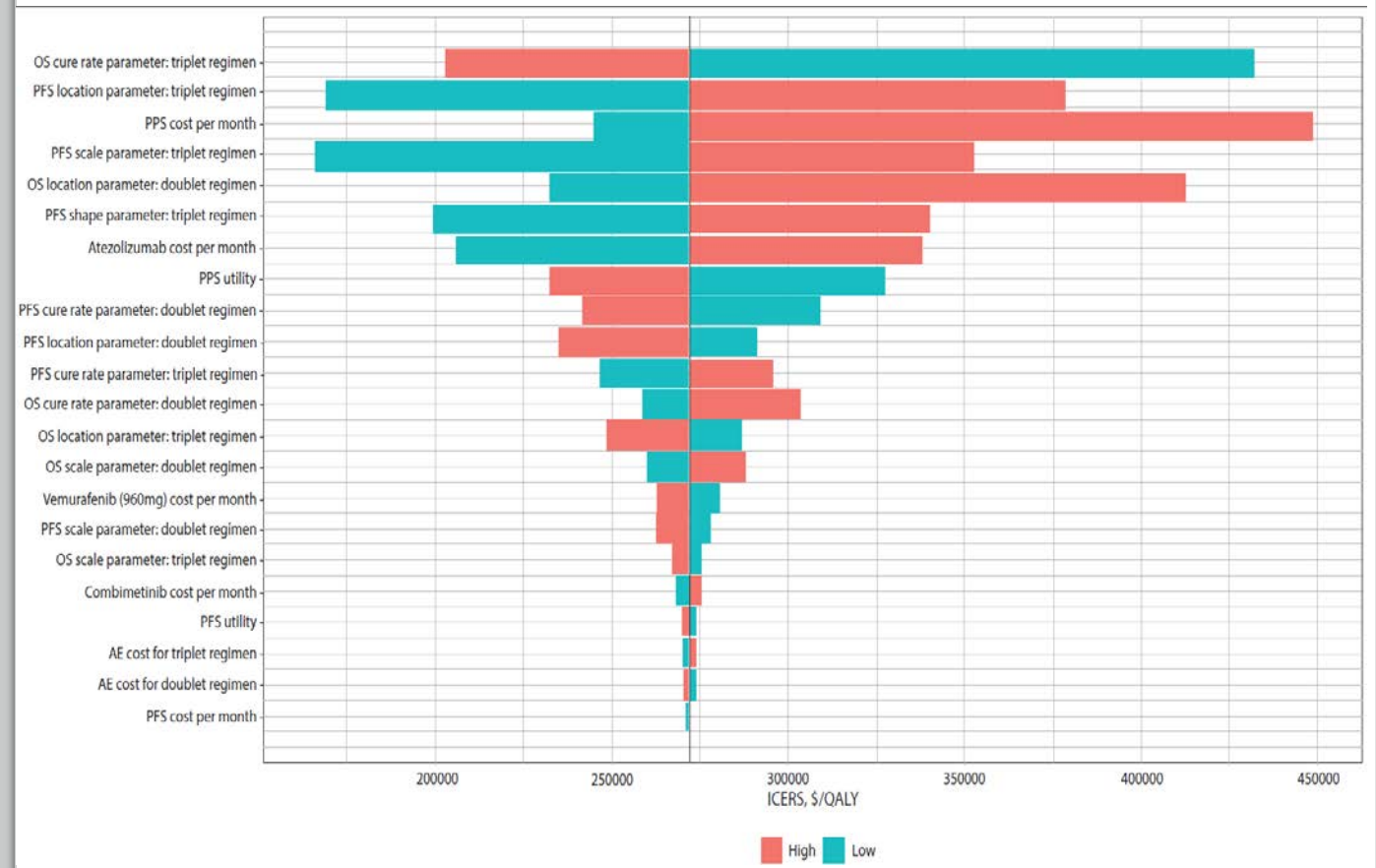
Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years

Deterministic Sensitivity Analysis

- Tornado Diagram
  - ❖ Evaluated influence of each variable's uncertainty

- Variables influenced on ICER
  - ❖ OS cure rate parameter for triplet regimen
  - ❖ PFS location parameters for triplet regimen
  - ❖ PPS monthly cost

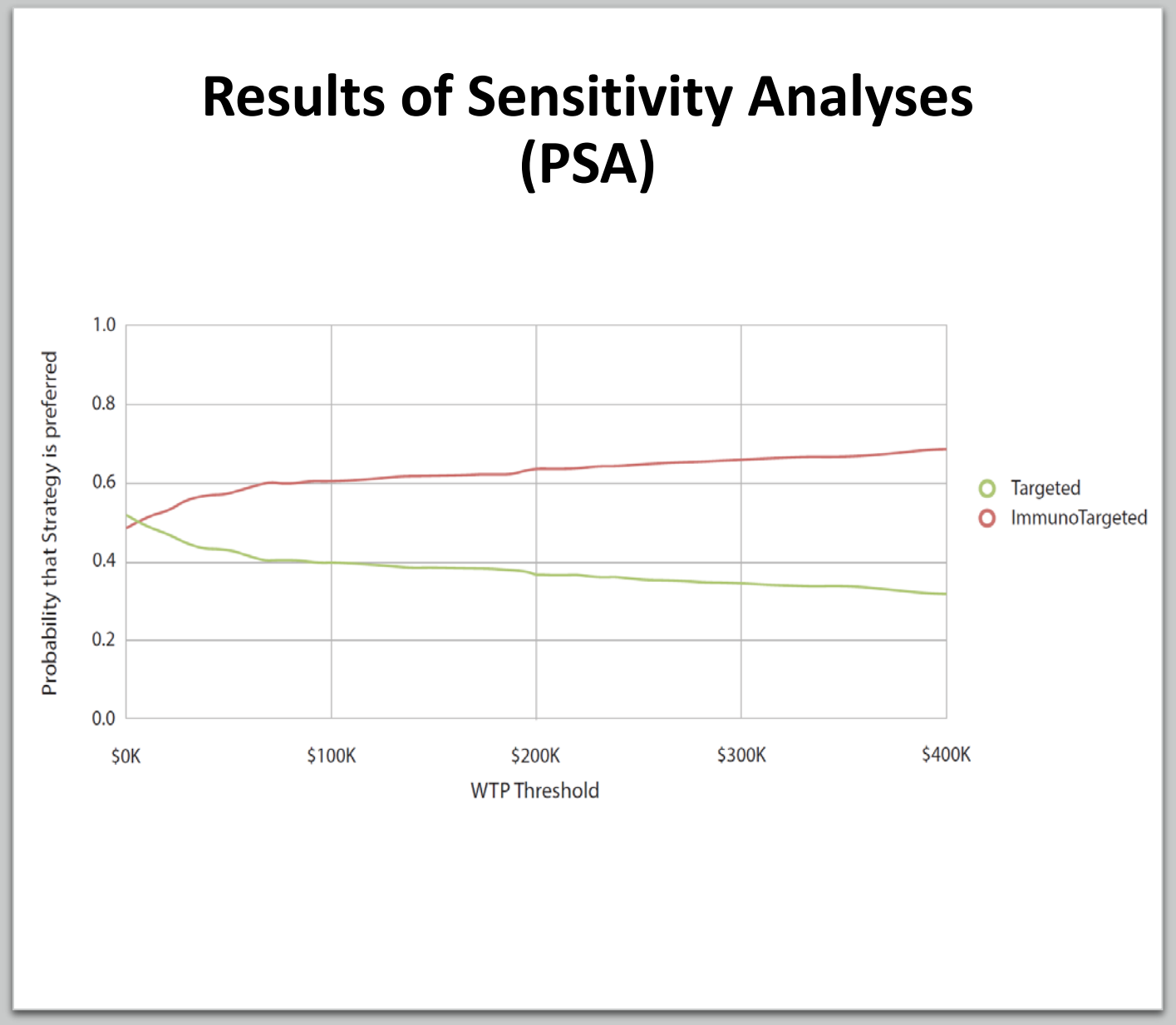
Results of Sensitivity Analyses (DSA)



Abbreviations: AE, adverse events; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; OS, overall survival; PFS, progression-free survival

Probabilistic Sensitivity Analyses

- Probability of vemurafenib plus cobimetinib alone being cost-effective compared with atezolizumab and vemurafenib plus cobimetinib was 38.3% at a WTP of $150 000/QALY.



Implication for Clinic

Combining immunotherapy with targeted therapies can lead to significant survival benefit for patients with *BRAF V600* mutated advanced melanoma.

Adding the immunotherapy to the targeted therapies could be cost-effective over a lifetime horizon if **long-lasting immunotherapeutic effect was sustainable** and **physicians would be willing to stop systematic immunotherapy after 2 years in the absence of disease progression**.

Discussion and Conclusions

- First study of a combination of an immunotherapeutic agent with a doublet targeted therapy in patients with advanced melanoma in the United States
- Assumed patients who were censored at the end of the follow-up in the IMspire150 trial are potential long-term survivors
- In clinical practice, it is safe to assume that patients and treating oncologists would be willing to stop systemic immunotherapy after 2 years in the absence of disease progression and the lack of data supporting the need for lifelong treatment continuation.
  (KEYNOTE-006 pembrolizumab)
- There is a need for a substantial reduction in price for this triplet regimen, which may be needed for its incremental cost to be worth the additional benefit.
- In practice where immunotherapies are often stopped after 2 years, adding atezolizumab to vemurafenib plus cobimetinib could be cost-effective.

JAMA Network Open

Original Investigation | Oncology

Estimated Cost-effectiveness of Atezolizumab Plus Cobimetinib and Vemurafenib for Treatment of *BRAF V600* Variation Metastatic Melanoma

Chao Cai, PhD; Ismaeel Yunusa, PharmD, PhD; Ahmad Tarhini, MD, PhD

Abstract

IMPORTANCE In the IMspire150 trial, triplet treatment with atezolizumab and vemurafenib plus cobimetinib significantly improved progression-free survival (PFS) compared with vemurafenib plus cobimetinib alone for treatment of *BRAF V600* variation metastatic melanoma. However, considering high cost of this combination, it is unclear if the incremental cost is worth the additional survival benefit.

OBJECTIVE To evaluate the cost-effectiveness of atezolizumab and vemurafenib plus cobimetinib vs vemurafenib plus cobimetinib alone in patients with newly diagnosed unresectable *BRAF V600* variation metastatic melanoma from the US health care perspective.

DESIGN, SETTING, AND PARTICIPANTS This economic evaluation study used a 3-state partitioned survival model to assess the cost-effectiveness of the combination of atezolizumab with vemurafenib

Key Points

Question In patients with *BRAF V600* altered metastatic melanoma, are the incremental costs of triplet therapy of atezolizumab, vemurafenib plus cobimetinib vs vemurafenib plus cobimetinib alone cost-effective for the survival gains?

Findings In this economic evaluation, the triplet combination therapy was not cost-effective if immunotherapy was continued over a lifetime horizon at a willingness-to-pay threshold of

Cai C*, Yunusa I, Tarhini A. Estimated Cost-effectiveness of Atezolizumab Plus Cobimetinib and Vemurafenib for Treatment of *BRAF V600* Variation Metastatic Melanoma. *JAMA Network Open.* 2021;4(11):e2132262.

Thank you!

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