Conflicts of interest

- MP, HS, JM, PD, and CJ are employees of Parexel International, funded by Bristol Myers Squibb to conduct the analysis
- YY, MAC, NV, AL, SJL, and JRP are employees of Bristol Myers Squibb

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A cost-effectiveness analysis of nivolumab plus ipilimumab plus two cycles of platinum doublet chemotherapy versus platinum doublet chemotherapy in the first-line treatment of stage IV or recurrent non-small cell lung cancer in the United States

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Introduction

- Lung cancer is the leading cause of cancer mortality worldwide, causing an estimated 1.8 million deaths in 2020[1]
  - NSCLC accounts for approximately 85% of all lung cancers[2]
- Despite recent advances in treatments for newly diagnosed NSCLC, there is a need for more durable and reduced chemotherapy-based treatment options that offer more patients the chance to survive long term
- Nivolumab and ipilimumab are immune checkpoint inhibitors with distinct but complementary mechanisms of action, targeting programmed cell death receptor-1 and cytotoxic T-lymphocyte antigen 4, respectively[3-6]
  - In combination, they have demonstrated durable and long-term survival benefits compared with chemotherapy

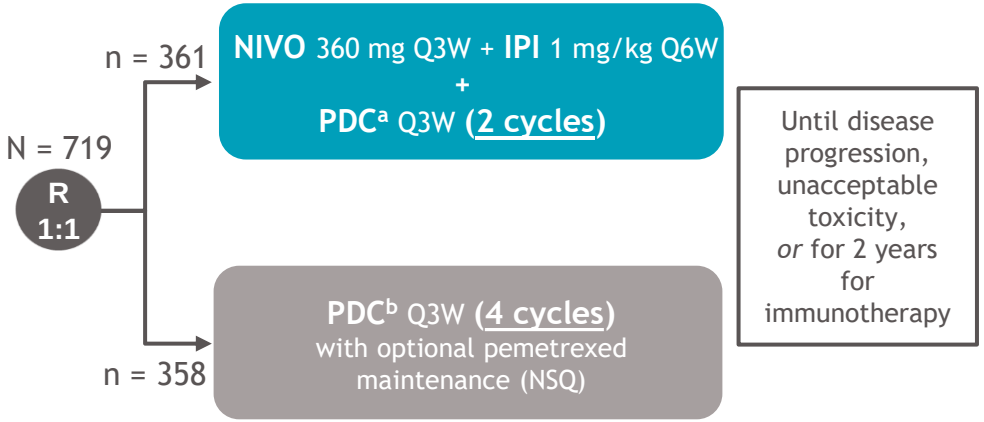
NSCLC, non-small cell lung cancer. 1. Sung H et al. *CA Cancer J Clin* 2021 Feb 4. doi: 10.3322/caac.21660. Online ahead of print. 2. Ahmadzada T et al. *J Clin Med* 2018;7:153. 3. Wei SC, et al. Cancer Discov 2018; 8:1069–1086; 4. Das R, et al. J Immunol 2015;194:950–959; 5. Wang C, et al. Cancer Immunol Res 2014;2:846–856; 6. Brahmer JR, et al. J Clin Oncol 2010;28:3167–3175;

Introduction: CheckMate 9LA

- CheckMate 9LA (NCT03215706) is a randomized, open-label, phase 3 trial[1]
  - The results from CheckMate 9LA indicate that NIVO+IPI+PDC significantly improved OS, PFS and ORR, with no new safety signals

Key Eligibility Criteria
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0–1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

	NIVO+IPI+PDC (n = 361)	PDC (n = 358)
ORR, %	38	25
Best overall response		
Complete response, n (%)	8 (2)	4 (1)
Partial response, n (%)	130 (36)	85 (24)
Stable disease, n (%)	164 (45	185 (52)
Progressive disease, n (%)	32 (9)	45 (13)
Unable to determine, n (%)	27 (7.5)	39 (10.9)
Median duration of response, months (95% CI)	11.30 (8.51, not estimable)	5.59 (4.37, 7.46)
Median PFS, months (95% CI)	6.7 (5.6, 7.8)	5.0 (4.3, 5.6)
Median OS, months (95% CI)	15.6 (13.9, 20.0)	10.9 (9.5, 12.6)

[a]NIVO (360 mg Q3W) + IPI (1 mg/kg Q6W) + histology-based PDC (intravenously Q3W for 2 cycles; NSQ: pemetrexed + cisplatin or carboplatin, Q3W for 2 cycles or SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for 2 cycles. [b]NSQ: pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles or SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles. ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IPI, ipilimumab; NIVO, nivolumab; NSQ, non-squamous; OS, overall survival; PDC, platinum doublet chemotherapy; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; Q6W, every 6 weeks; SQ, squamous. 1. Paz-Ares L et al. *Lancet Oncol* 2021;22:198–211.

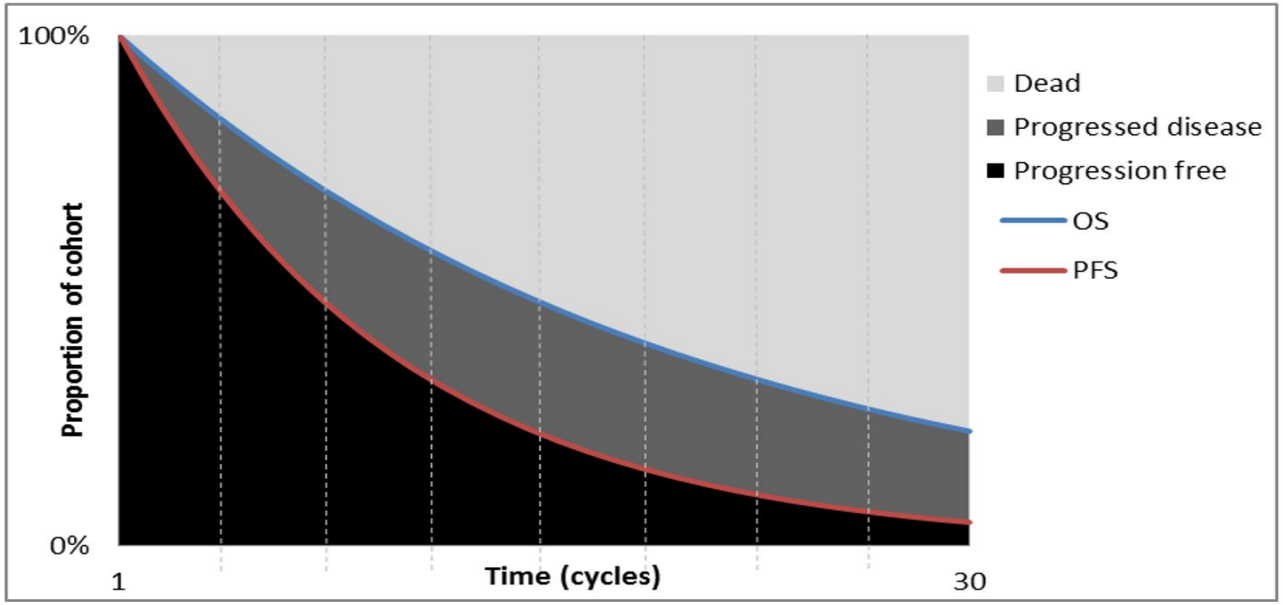
Objective

- To evaluate the cost-effectiveness of NIVO+IPI with **2 cycles** of platinum doublet chemotherapy[a] (NIVO+IPI+PDC) versus **4 cycles** of PDC[b] in the 1L treatment of stage IV or recurrent NSCLC from a health insurance perspective in the United States

[a]Carboplatin + paclitaxel in patients with squamous NSCLC; carboplatin + pemetrexed or cisplatin + pemetrexed in patients with non-squamous NSCLC. [b]Carboplatin + paclitaxel in patients with squamous NSCLC; carboplatin + pemetrexed or cisplatin + pemetrexed in patients with non-squamous NSCLC. After 4 cycles, patients with non-squamous NSCLC may receive optional maintenance therapy with pemetrexed until disease progression or unacceptable toxicity. 1L, first line.

Methods: model

- A partitioned survival (also known as AUC) model was developed for 3 health-state cohorts:
  - Progression free
  - Progressed disease
  - Dead



Schematic of the partitioned survival model

- The base case adopted a US payer perspective
- The analysis uses a 25-year lifetime horizon
- Weekly model cycles were used for the first 28 weeks, followed by 4-week cycles. Half-cycle correction was applied
- Costs and health outcomes were discounted at 3.0% annually
- Costs and benefits of treatments were calculated by combining the time spent in each health state with the costs and utilities associated with those states
- Model outcomes included incremental cost per LYG and incremental cost per QALY gained

AUC, area under the curve; LYG, life-year gained; PFS, progression-free survival; QALY, quality-adjusted life-year; US, United States.

Methods: survival analysis and safety

- OS and PFS data were derived from CheckMate 9LA (March 2020 DBL)
  - Minimum follow-up of 12.7 months for OS and 12.2 months for all PFS and DoT
- Data from a more mature trial involving NIVO+IPI in first line NSCLC, CheckMate 227 Part 1 (PD-L1>1% and <1%; February 2020 DBL; minimum FU of 37.7 months), were used to inform long-term OS and PFS over the 25-year (lifetime) horizon to capture the long-term survival effect observed from dual immuno-oncology therapy
- Given the similarities between the 2 trials in terms of patient population and treatment regimens, they are expected to have comparable long-term outcomes; therefore, it was considered appropriate to use survival data from CheckMate 227 Part 1 to extrapolate CheckMate 9LA survival, based on the methodology described by Jackson et al.[1]
- The extrapolations were validated against data from other BMS trials,[2,3] external registry data, estimates presented in health technology appraisals,[4-6] and other published literature[7,8]

DBL, database lock; DoT, duration of treatment. 1. Jackson C et al. *Med Decis Making* 2017;37:377-390. 2. Gettinger S et al. *J Thorac Oncol* 2019;14:S244-S245. 3. Bristol Myers Squibb, Data on file. 4. KEYTRUDA (pembrolizumab) [prescribing information]. Kenilworth, NJ: Merck and Co.; 2020. 5. National Institute for Health and Care Excellence (NICE) TA531. 2018. https://www.nice.org.uk/guidance/ta531. 6. National Institute for Health and Care Excellence TA683. 2021. https://www.nice.org.uk/guidance/TA683. 7. Insinga RP et al. *J Med Econ* 2018;21:1191-1205. 8. Healthcare Quality Improvement Partnership. National Lung Cancer Audit Report 2013. Accessed March 26, 2021. https://www.hqip.org.uk/resource/national-lung-cancer-audit-report-2013.

Methods: CheckMate 9LA and CheckMate 227 Part 1 baseline characteristics

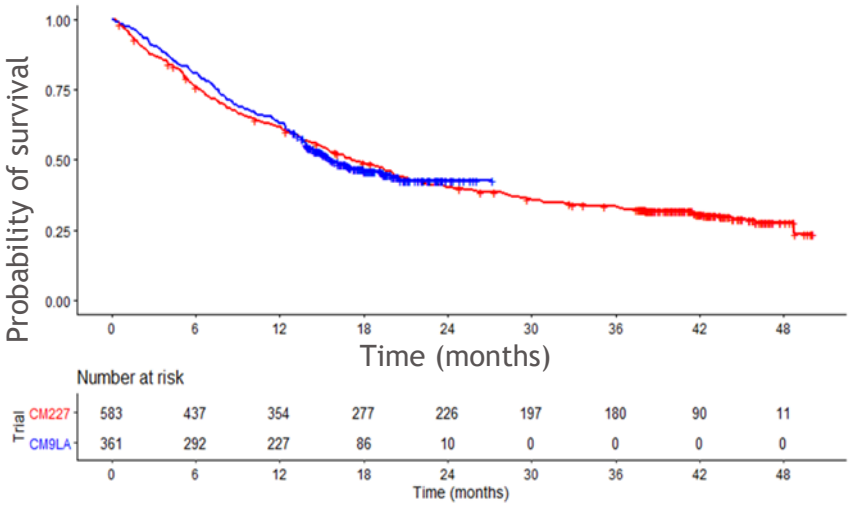
	CheckMate 9LA		CheckMate 227 Part 1	
	NIVO+IPI+PDC (n = 361)	PDC (n = 358)	NIVO+IPI (n = 583)	PDC (n = 583)
Median age, years	65.0	65.0	64.0	64.0
< 65, %	48.8	49.7	52.5	52.3
≥ 75, %	10.2	9.2	9.9	9.4
Male, %	69.8	70.4	67.4	66.0
Smoking status, %				
Current/former	87.3	85.2	85.2	85.6
Never smoked	12.7	14.8	13.6	13.4
ECOG PS, %				
0	31.3	31.3	35.0	32.8
1	68.4	68.4	64.7	66.2
Tumor histologic type, %				
Squamous	31.3	31.0	28.1	28.1
Non-squamous	68.7	69.0	71.9	71.9
PD-L1 expression level, %				
< 1%	37.4	36.0	32.1	31.9
≥ 1%	56.2	57.0	67.9	68.1

Methods: CheckMate 9LA and CheckMate 227 Part 1 OS and PFS

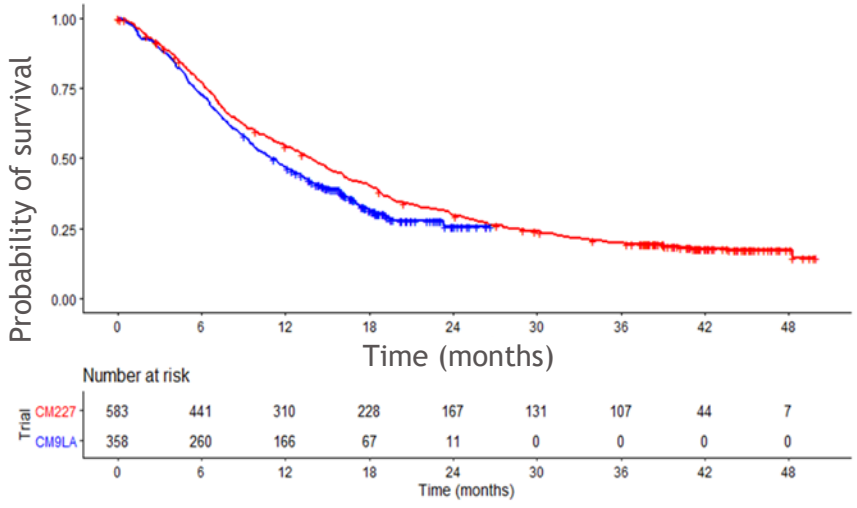
Overall survival

- CheckMate 227 Part 1
- CheckMate 9LA

NIVO+IPI+PDC (CM9LA) or NIVO+IPI (CM227)

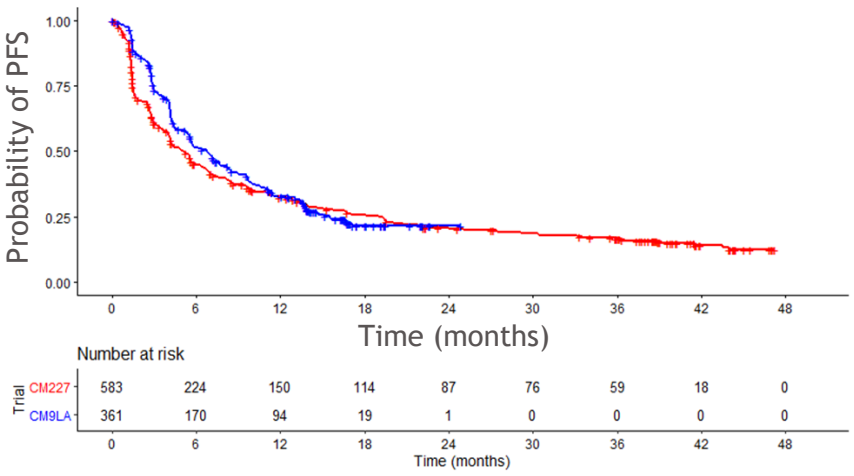


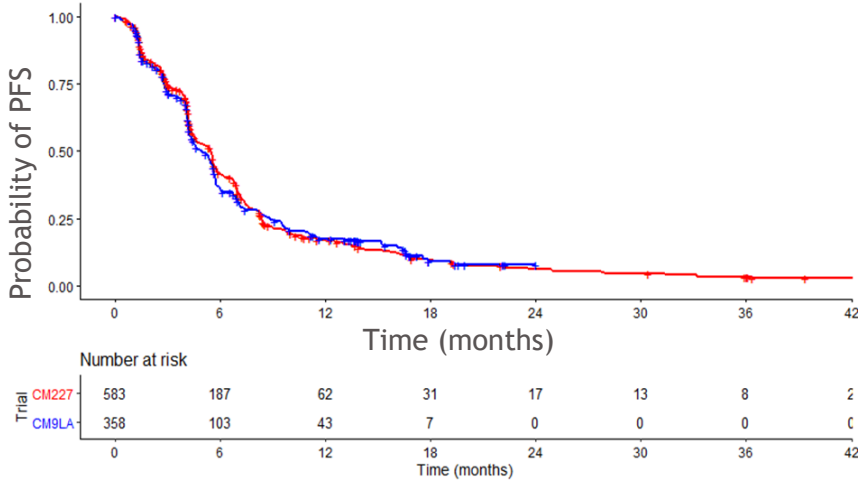
PDC



Progression-free survival

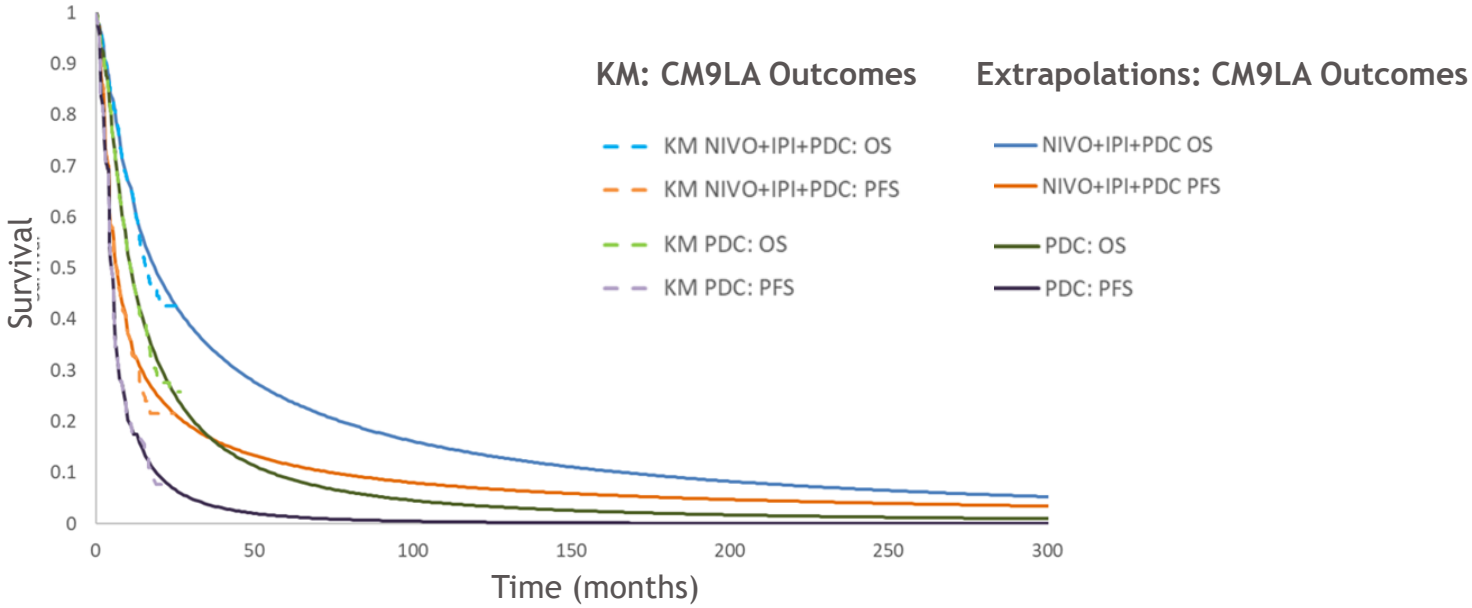
- CheckMate 227 Part 1
- CheckMate 9LA





Methods: survival analysis and safety

- OS and PFS were estimated based on CheckMate 9LA KM data up to 13 months then extrapolated using the conditional survival estimates from CheckMate 227 Part 1 extrapolation curves



- DoT data were derived from CheckMate 9LA (March 2020 DBL)
- AEs considered in the analysis included grade 3, 4, or 5 TRAEs experienced by ≥ 5% of patients in the NIVO+IPI+PDC or PDC arm of CheckMate 9LA (March 2020 DBL)

AE, adverse event; KM, Kaplan-Meier; TRAE, treatment-related adverse event.

Methods: utilities, disutilities and costs

- Treatment-specific progression-based utilities were derived from patient-level EQ-5D-3L questionnaire data from CheckMate 9LA
  - Analyses conducted to assess model fit using utilities based on models with or without treatment demonstrated a better fit for models with treatment (p=0.013)
- Disutilities associated with AEs were excluded in the base-case to avoid double-counting

	NIVO+IPI+PDC		PDC	
	Mean utility	95% CI	Mean utility	95% CI
Progression free	0.797	0.781–0.813	0.772	0.756–0.788
Progressed disease	0.738	0.719–0.757	0.696	0.677–0.716

- US-specific costs for disease management (PF and PD health states); end-of-life care; drug acquisition, administration, and monitoring; management of AEs; and subsequent treatments were included in the model

CI, confidence interval; EQ-5D-3L EuroQoL 5 dimensions 3 levels; PD, progressed disease; PF, progression free.

Methods: sensitivity analyses

- Deterministic sensitivity analyses were conducted by varying key parameters by their SE, 95% CI, or ±20% of the expected values (base case) based on data availability and included:
  - Discount rate: varied from 0% to 6% (SE)
  - Body weight and body surface area: varied by ±20%
  - Costs (including disease management, treatment acquisition, administration, and monitoring): varied by ±20%
  - Utilities (treatment-specific for PF and PD): varied by 95% CI
- Probabilistic sensitivity analyses were conducted to assess the variation in model results stemming from uncertainty in each individual parameter used in the model: clinical data, cost data, and utilities data

SE, standard error.

Results: base-case analysis

- NIVO+IPI+PDC provides substantial health benefits at a higher total cost compared with PDC

Base-case incremental results

Treatment	Total costs (US$)	Total LY	Total QALY	Incremental cost per LYG (US$)	Incremental cost per QALY (US$)	Interpretation of CE (CEP)
NIVO+IPI+PDC	317,581	3.71	2.86	108,928	132,960	NE quadrant
PDC	119,909	1.89	1.37			

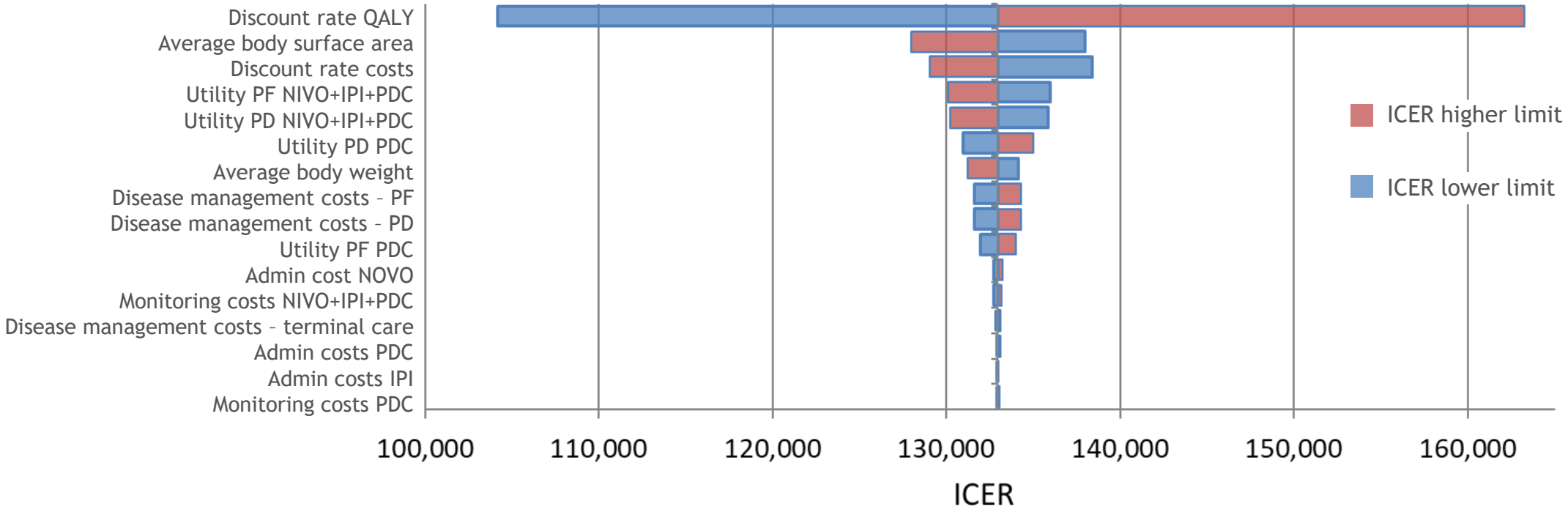
Disaggregated costs by treatment

Treatment	Total costs (US$)	Cost breakdown (US$)					
		Disease mgmt	Acquisition	Administration	Monitoring	AE	Subsequent treatment
NIVO+IPI+PDC	317,581	64,780	242,179	2672	1587	1881	4482
PDC	119,909	45,752	48,470	1405	587	2762	20,933

Incremental cost per QALY was calculated using the following incremental QALY: 1.4867. CE, cost effectiveness; CEP, cost-effectiveness plane; mgmt, management; NE, northeast.

Results: deterministic sensitivity analyses

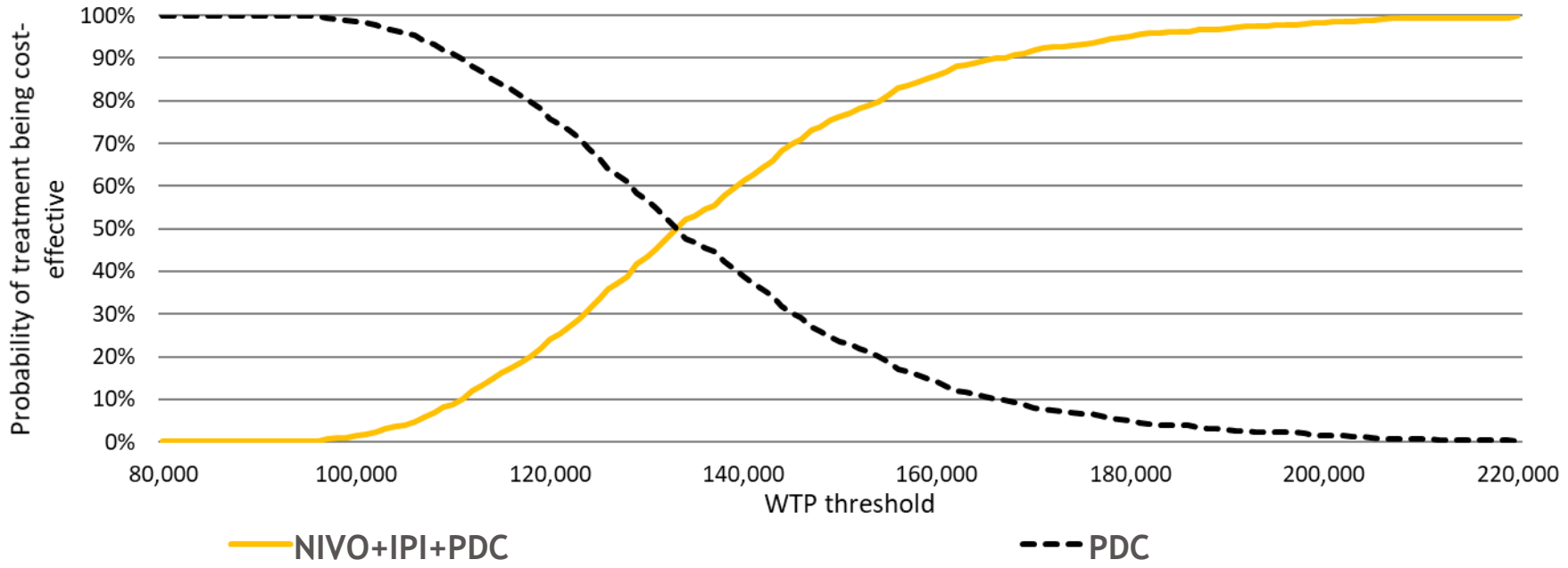
- Deterministic sensitivity analysis indicated the 5 most influential parameters affecting the results were discount rate applied to QALYs, followed by average surface body area, discount rate applied to costs and the utility values applied to PD and PF for NIVO+IPI+PDC



Body weight affects doses and treatment acquisition costs. ICER, incremental cost-effectiveness ratio.

Results: probabilistic sensitivity analyses

- Probabilistic sensitivity analysis based on 1000 iterations generated results consistent with the base case (incremental cost per QALY gained, $132,960 vs $131,410)
- Using a rather conservative willingness to pay threshold range of $150,000 to $250,000 per QALY, NIVO+IPI+PDC has a 77.7–100% probability of being cost-effective



WTP, willingness to pay.

Summary

- The current analysis indicates NIVO+IPI+PDC is a cost-effective option to treat patients with metastatic NSCLC regardless of histology with an incremental cost per QALY gained of $132,960 versus PDC
  - Although WTP threshold is not explicitly defined in the US, a review from 2003 concluded $200,000 or more per QALY was considered an acceptable cost-effectiveness threshold[1]. Adjusting this figure using the medical consumer price index[2] suggests $300,000 per QALY would be an acceptable cost-effectiveness threshold in the US
  - Some recent evidence suggests that acceptable threshold levels may be higher in a metastatic cancer end-of-life context[3,4]
- Deterministic sensitivity analysis indicated the most influential parameters were the discount rates for costs and outcomes, average surface body area, and the application of progression-based utilities
- Probabilistic sensitivity analyses confirmed the results are robust with a probabilistic ICER of $131,410

1. Ubel PA et al. *Arch Intern Med* 2003;163:1637-1641. 2. US Bureau of Labor Statistics. Consumer price index (CPI) databases, 2020. Accessed March 26, 2021. https://www.bls.gov/cpi/data.htm. 3. Becker G et al. National Bureau of Economic Research, 2010. Accessed March 26, 2021. https://www.nber.org/papers/w13333; 4. Nadler E et al. *Oncologist*, 2006;11:90-95.

Conclusion

NIVO+IPI+PDC offers a new cost-effective first-line treatment option for patients with metastatic first-line NSCLC with an ICER that is within the range of what is considered acceptable value for money in the US metastatic cancer setting

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