Conflict of Interest

- WL, DV, LG, and ML have served as consultants to Genentech
- WW and TT are employees of Genentech

Modeling Approaches to Estimate Realized Real Option Value of Ipilimumab in Metastatic Melanoma

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What is Real Option Value (ROV)?

- One of the novel elements of value[1]
- Generated when a medical technology extends the life of patients thereby creating opportunities to take advantage of future medical advances[2]

Source: Towse A, Li M. Real option value drugs: is it really an option? 2019 ISPOR, New Orleans, Breakout session 6, May 2019

[1]Li M, Garrison LP. The ABCs of Real Option Value of Medical Technologies. Value and Outcomes Spotlight, January/February 2020

[2]Lakdawalla DN, Doshi JA, Garrison Jr LP, Phelps CE, Basu A, Danzon PM. Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force report [3]. Value in Health. 2018 Feb 1;21(2):131-9.

How to Quantify ROV?

Ex ante perspective[1]

- Uses the information that is available at the time of product's launch
- Helps to inform potential additional value of a newly approved drug at the time of launch

Ex post perspective[2]

- Treats the arrivals of the subsequent innovations with certainty since that they are known
- Illustrates the realized ROV which is observed in the real world (*ex post* ROV is the same as realized ROV)

[1]Li M, Basu A, Bennette C, et al. How does option value affect the potential cost-effectiveness of a treatment? The case of ipilimumab for metastatic melanoma. Value in Health. 2019; 22: 777-84.
[2]Snider JT, Seabury S, Tebeka MG, et al. The option value of innovative treatments for metastatic melanoma. Forum for Health Economics & Policy: De Gruyter, 2018.

Rationale

Several methodological limitations in previous *ex post* ROV studies:

1. Distinction between the eligibility for future innovations and the actual receipt of them
2. The additional health gains due to the subsequent innovations in the comparator arm
3. The use of data primarily from clinical trials

Objective

To develop a new methodological approach for estimating *ex post* ROV using real-world data (RWD) and to apply this approach to quantify the *ex post* ROV of ipilimumab in advanced melanoma

Overall Framework

We adapted existing frameworks for quantifying *ex post* ROV and developed a new framework to incorporate:

1. The uptake of next innovative therapies
2. The additional health gain due to the next innovation in the standard of care arm
3. The real-world effectiveness of treatments

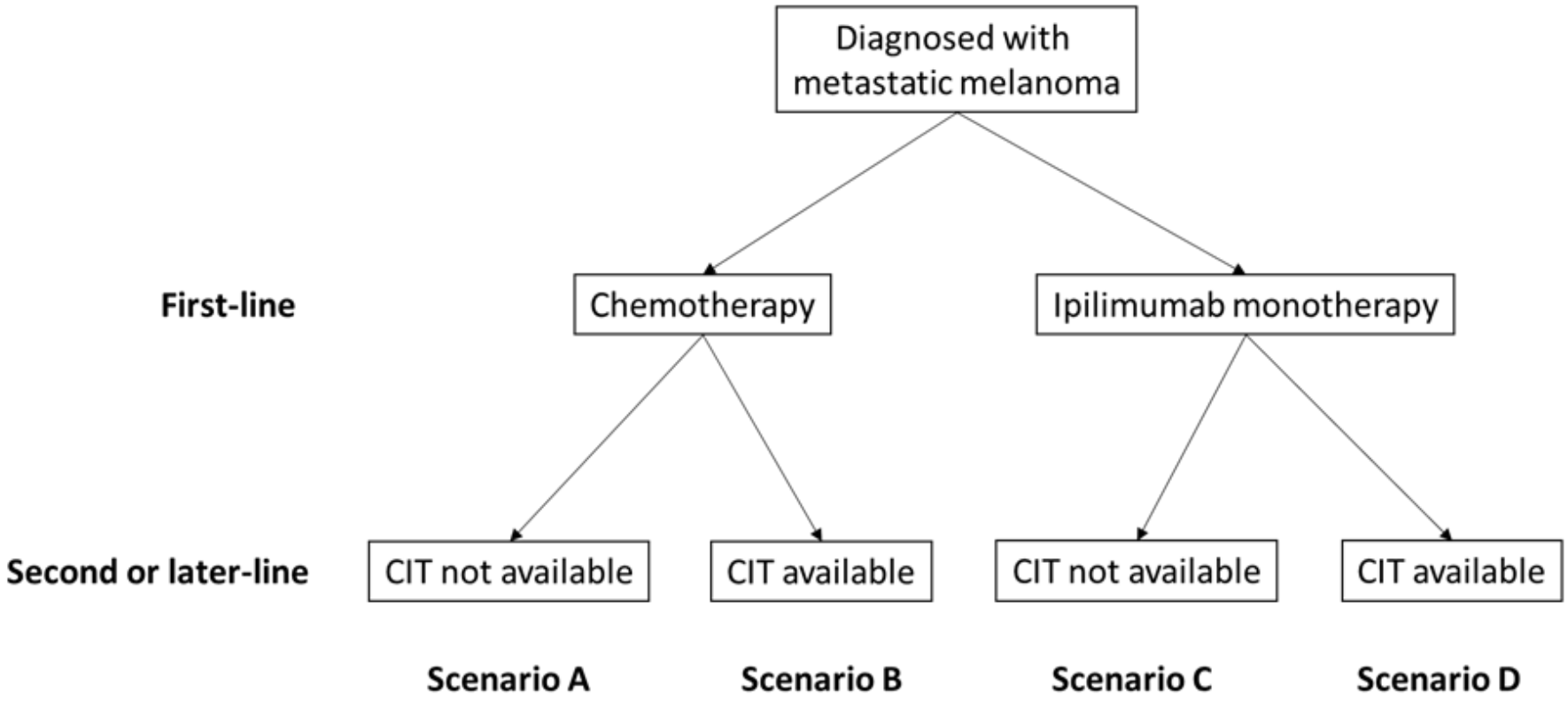
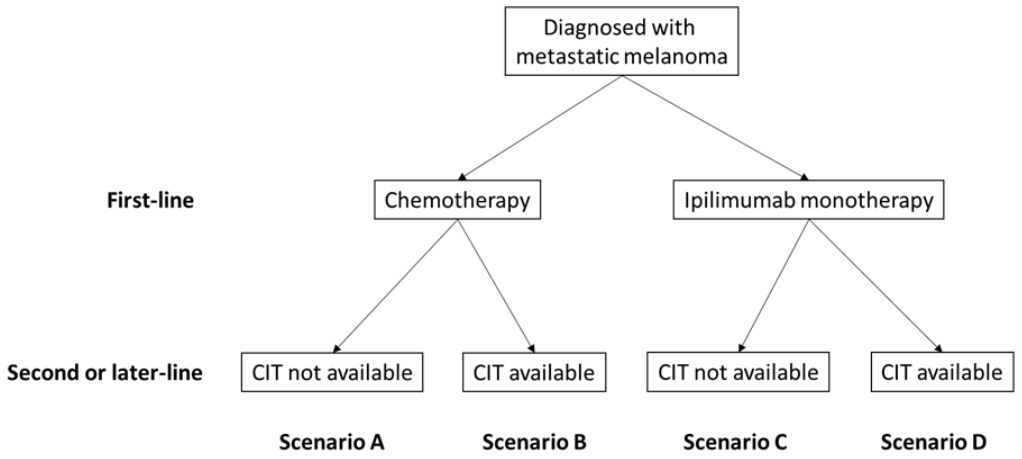


Figure. Scenarios of comparison.
CIT=cancer immunotherapies (i.e. the next innovations such as pembrolizumab and nivolumab)



QALYs gained in each scenario:

Scenario A: $QALY_{c\_com}$

Scenario B: $p_{\_com} \cdot QALY_{o\_com} + (1\text{-}p_{\_com}) \cdot QALY_{c\_com}$

Scenario C: $QALY_{c\_int}$

Scenario D: $p_{\_int} \cdot QALY_{o\_int} + (1\text{-}p_{\_int}) \cdot QALY_{c\_int}$

- **$QALY_o$** = QALYs gained with accounting for survival benefits from the next innovations (option value scenario)
- **$QALY_c$** = QALYs gained without accounting for survival benefits from the next innovations (conventional scenario)
- **p** = The probability of receiving the next innovation among those who survive to the innovation date
- **Subscripts 'int'** = intervention (ipilimumab)
- **Subscript 'com'** = comparator (chemotherapy)

Conventional value	= (Scenario C) – (Scenario A)
***Ex post* ROV**	= (Scenario D – Scenario C) – (Scenario B – Scenario A)
Total value	= Conventional value + *Ex post* ROV

Estimating QALYs in Each of the Scenarios

- A Markov model with 4 health states
- Lifetime horizon
- Scenarios B and D, the option value scenarios, were stratified into six sub-categories
  - by the time from first-line (1L) initiation to the time of CIT availability
  - 0, 3, 6, 9, 12, and 24 months

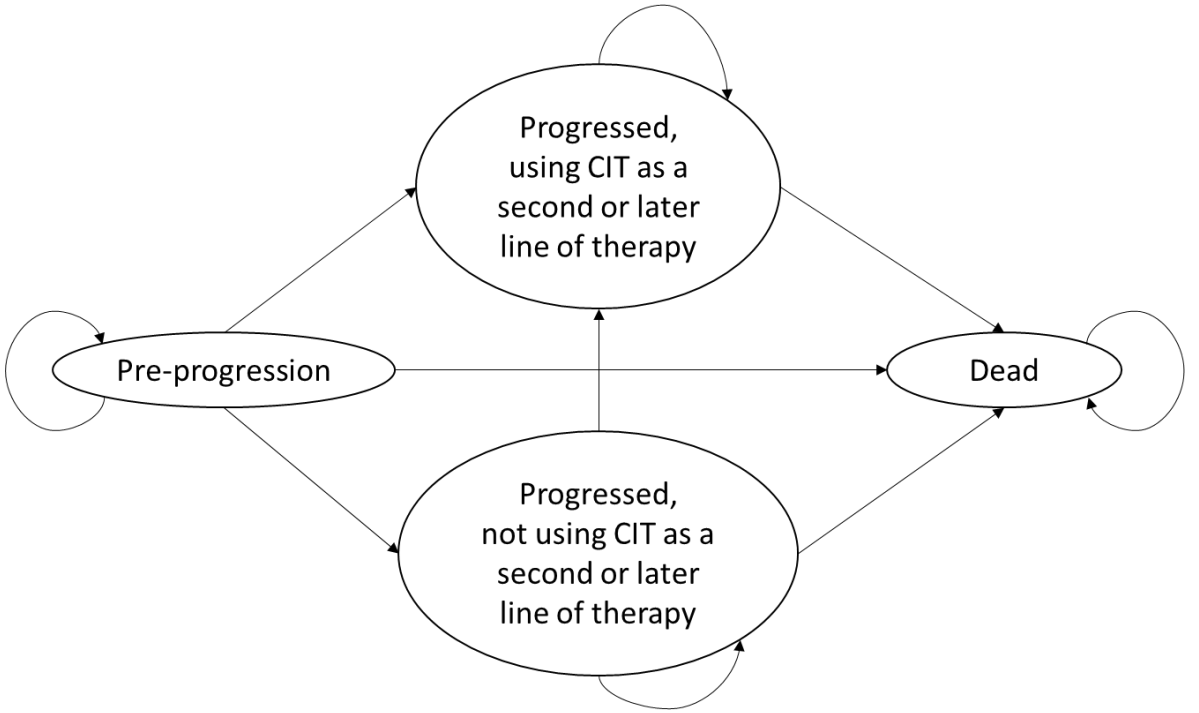


Figure. Model structure. CIT = cancer immunotherapies

Model Inputs

Real-world inputs were generated from a retrospective analysis of the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database[a]

Transition probabilities

- Those with advanced unresectable or metastatic melanoma who initiated either ipilimumab or chemotherapy as a 1L between 1/1/2011 and 4/19/15[b].
- Kaplan-Meier (KM) real-world progression-free survival (rwPFS) and overall survival (OS), stratified by 1L (ipilimumab or chemotherapy) and second-line or later (CITs or non-CITs)

[a] The Flatiron Health database is a longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction.

[b] To ensure robust estimates of survival outcomes for ipilimumab as an input to the ROV calculation, we expanded the patient pool for survival analyses to include patients treated up until April 19, 2015, —the date that 1L pembrolizumab data were presented at the 2015 American Association for Cancer Research (AACR) meeting.

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The level of uptake of next innovations (CIT)

- Real-world utilization for patients initiating treatment prior to 9/4/14.

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Utility and the prevalence of adverse drug events

- From phase 3 trials of ipilimumab and CITs

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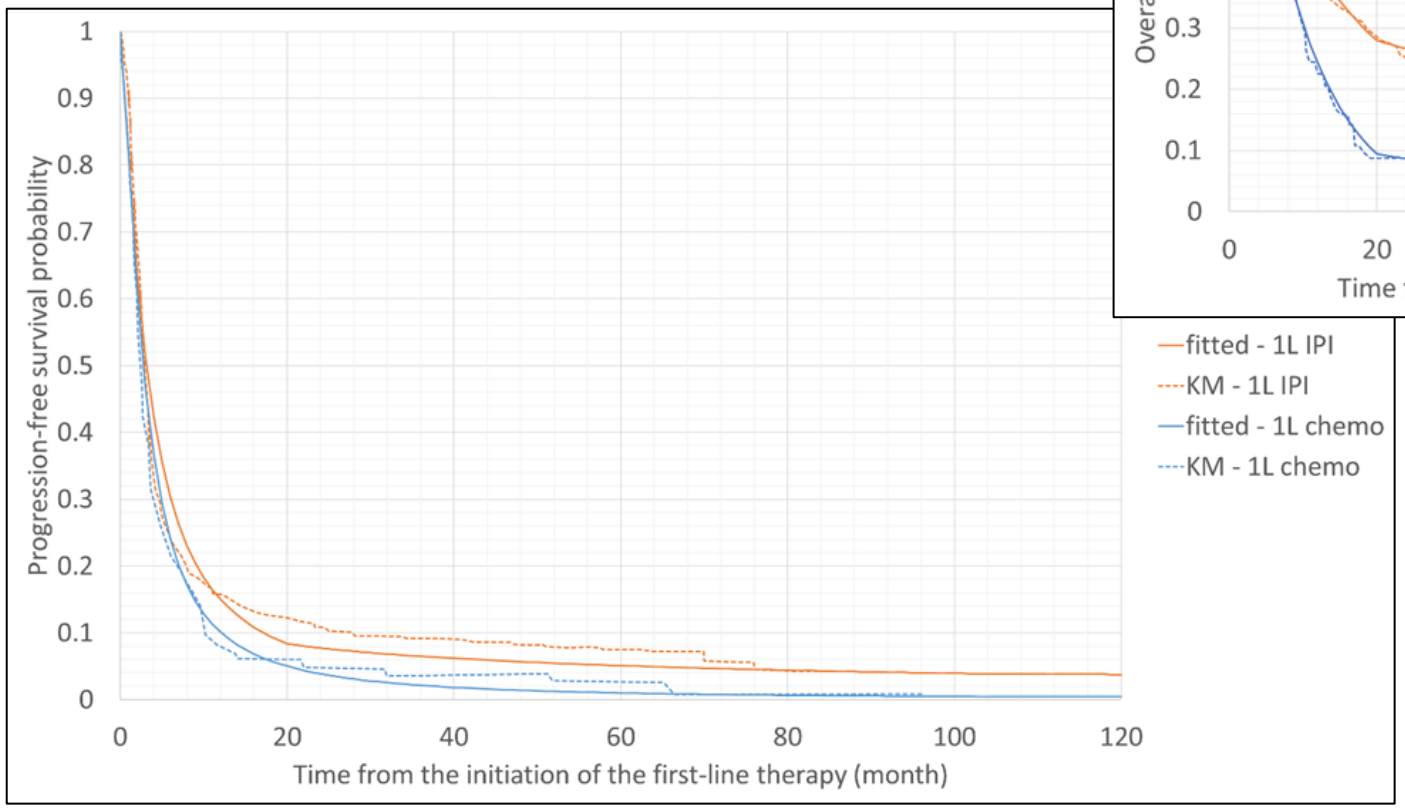


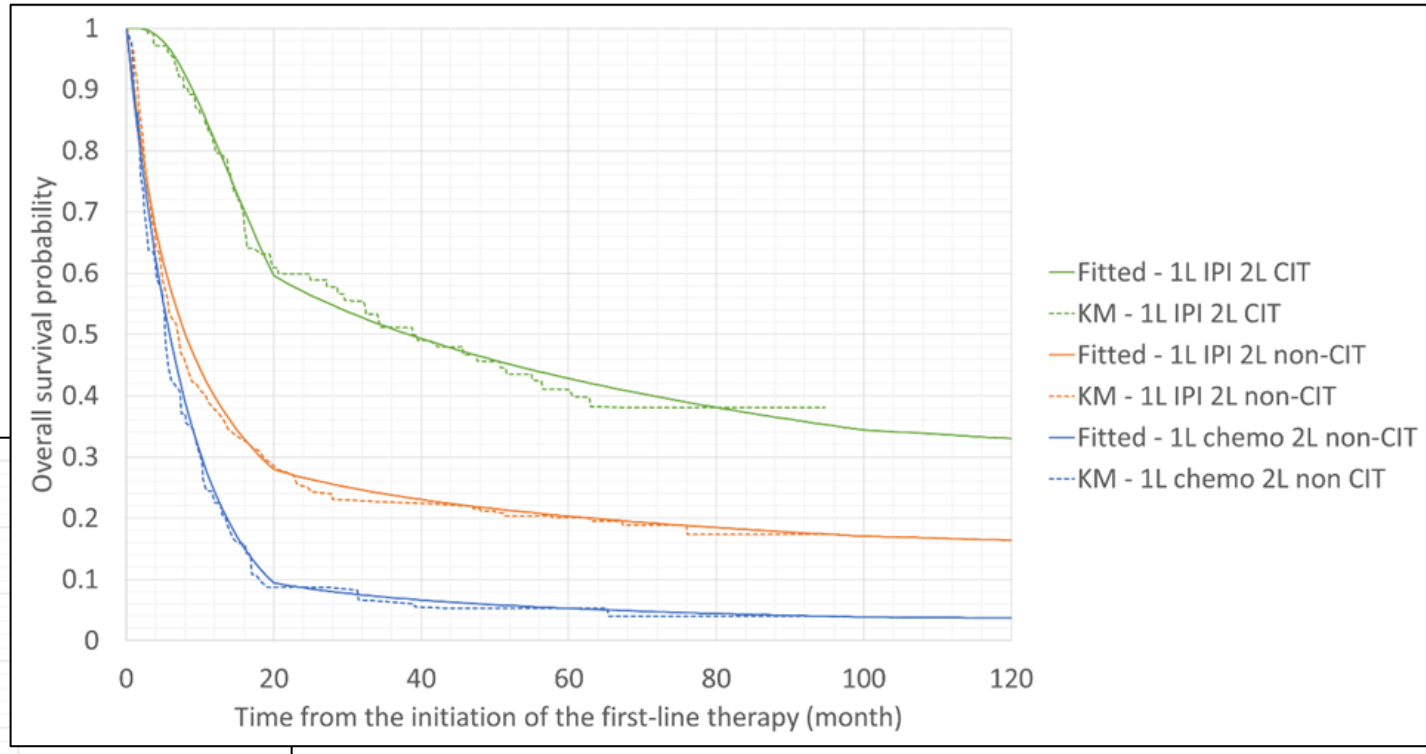


Figure. KM rwPFS curves stratified by 1L (ipilimumab and chemotherapy) (left) and KM OS curves stratified by 1L (ipilimumab and chemotherapy) and 2L (CIT and non-CIT) (right). IPI: ipilimumab; chemo: chemotherapy; CIT: cancer immunotherapies; 1L: first-line; 2L: second-line

The level of uptake of next innovations	
Variables	**Base-case value**
1L chemotherapy	
Less than 6 months	33%
6 – 12 months	25%
More than 12 months	25%
1L ipilimumab	
Less than 6 months	54%
6 – 12 months	48%
More than 12 months	50%

[a] Stratified by 1L therapy and the time from 1L initiation to the time of CIT availability (9/4/2014)

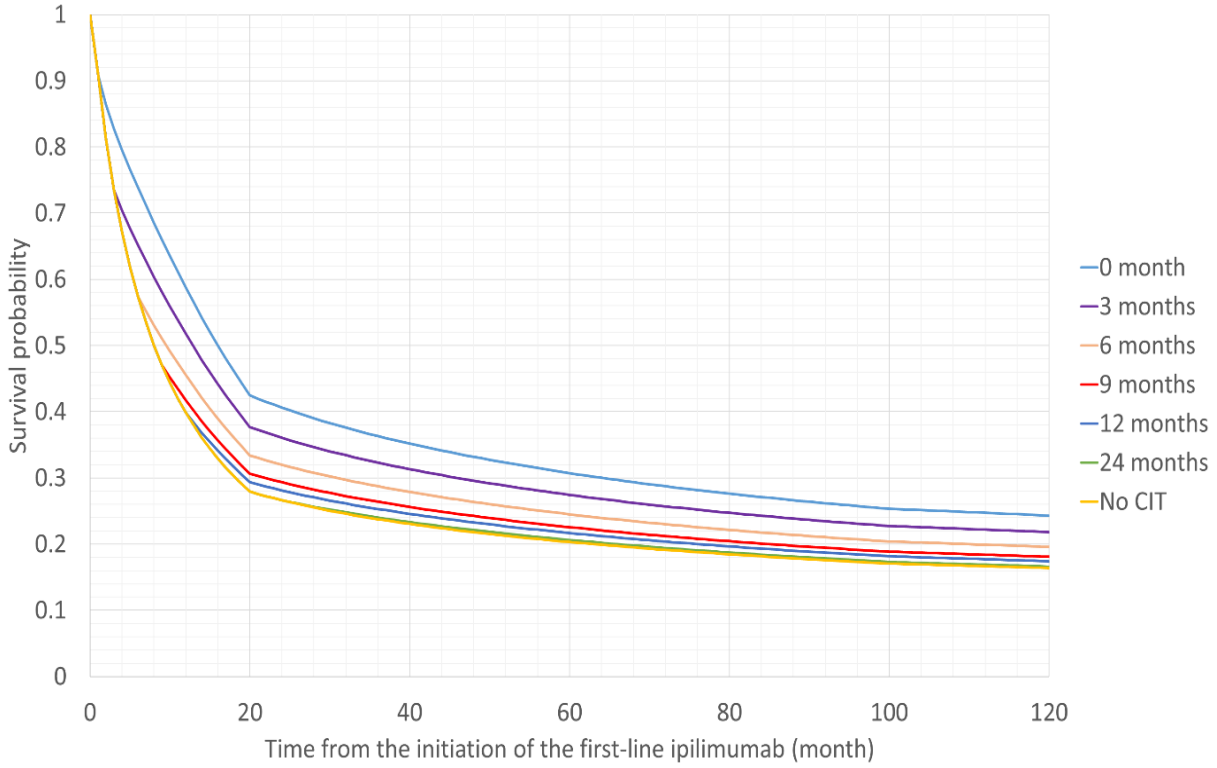
Sensitivity Analysis

- One-way sensitivity analysis
  - 95% confidence interval or standard errors
  - +/- 20% of the base case value
- Probabilistic sensitivity analysis (PSA)
  - 5,000 iterations of Monte Carlo simulation

Results

Conventional and *Ex post* Real Option Value of Ipilimumab			
	Chemotherapy	**Ipilimumab**	**Incremental**
Conventional value			
	1.06	2.80	1.74 (0.71, 2.36)[b]
Ex post real option value			
3 months[a]	0.21	0.81	**0.60** (0.33, 1.02)[b]
6 months[a]	0.13	0.46	**0.33** (0.16, 0.63)[b]
Total value = Conventional value + *Ex post* real option value			

[a] Time from 1L initiation from the time of CIT availability (9/4/2014); [b] 95% confidence interval



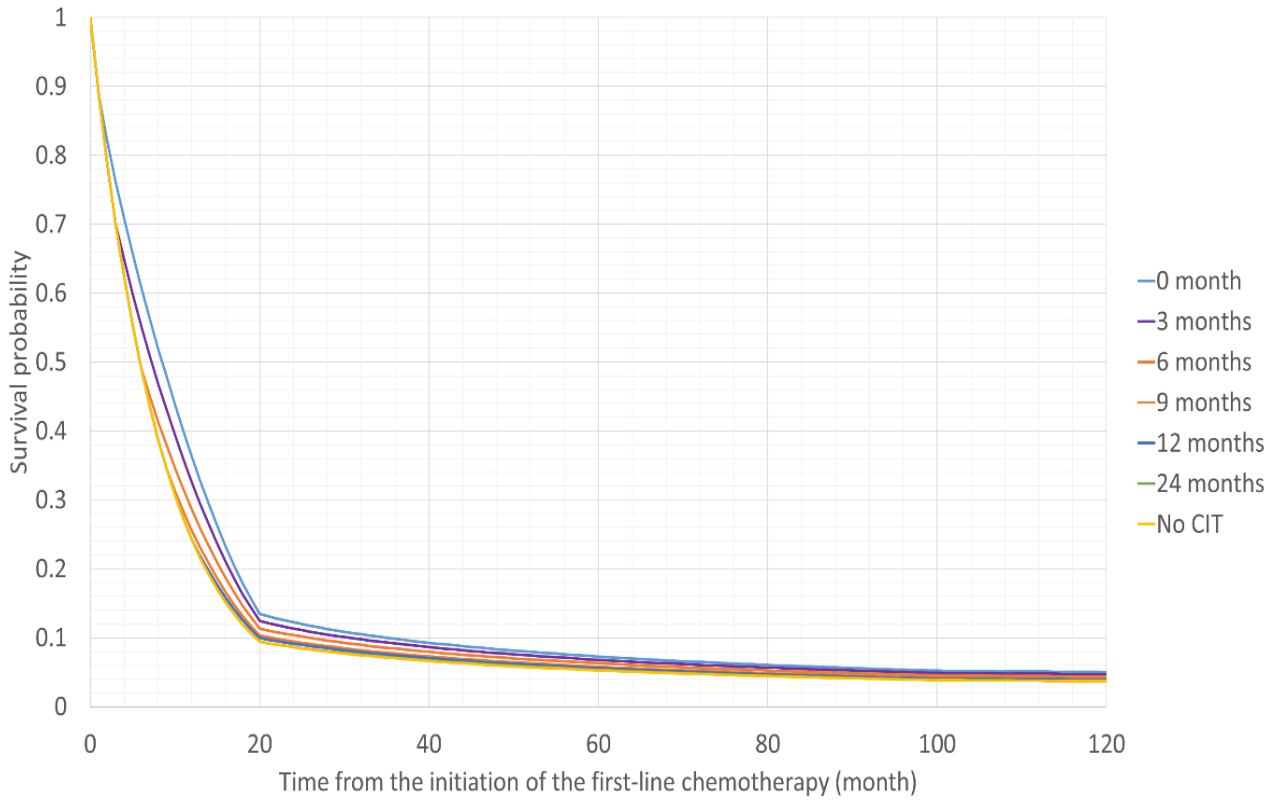


Figure. Overall survival of patients with metastatic melanoma stratified by the time from the 1L initiation to the date of CIT availability: Patients who received ipilimumab as a first-line therapy (left) and patients who received chemotherapy as a first-line therapy (right). Note: No CIT indicates a scenario where CIT was not available as a subsequent line of therapy. CIT: cancer immunotherapies

Results (cont’d)

- The total value of ipilimumab in QALYs ranged from 2.22 to 3.37.
- This represented an increase in total value of 53%, 34%, 19%, 10%, 6%, and 1% in scenarios where CIT becomes available in 0, 3, 6, 9, 12, and 24 months, respectively, compared to the conventional value.

One-way Sensitivity Analysis

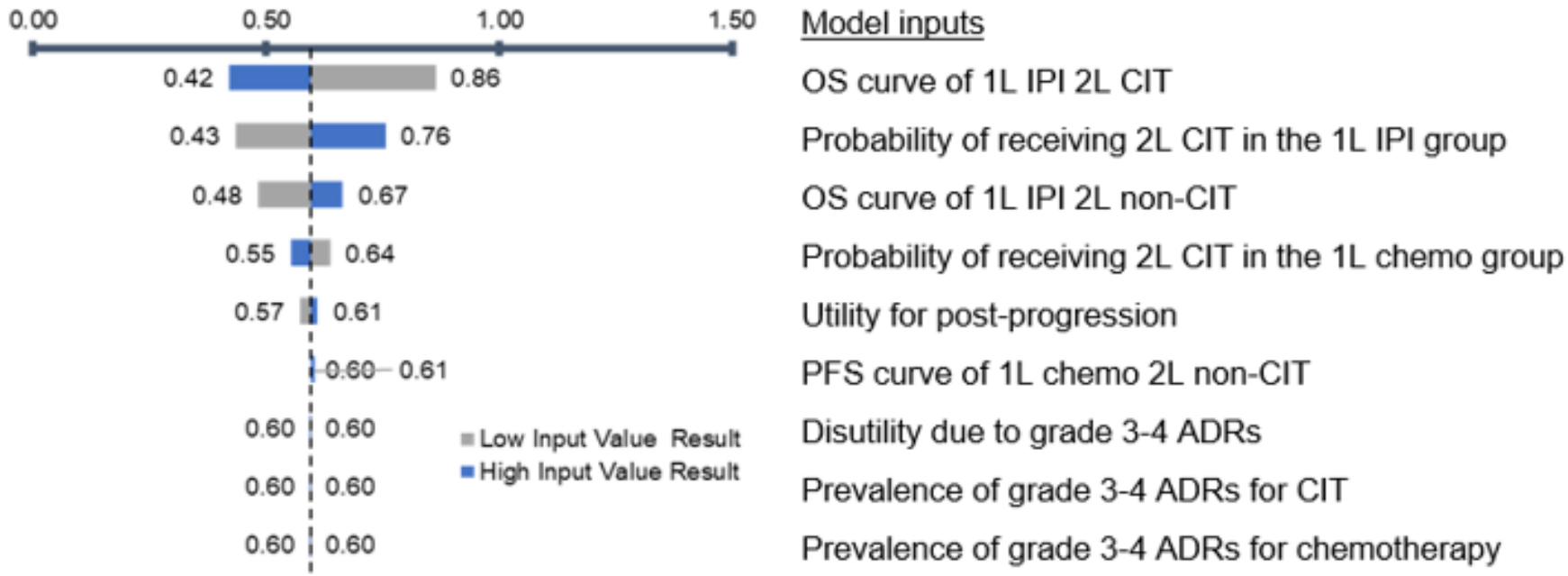


Figure. Tornado diagrams for one-way sensitivity analysis with an outcome being an option value of ipilimumab in QALYs among patients who had CIT available 3 months after the first-line initiation. OS = overall survival; IPI: ipilimumab, CIT: cancer immunotherapies; PFS: progression-free survival; ADR: adverse drug reaction; 1L: first-line; 2L: second-line

Limitations

- The estimation of survival probabilities using RWD is subject to selection bias and confounding.
- We did not capture other treatment pathways by which one could have gotten the ROV from ipilimumab (e.g., BRAF inhibitors).
- We did not consider the ROV due to any improvement in quality of life (e.g., daily functioning).

Conclusion

- We developed a new framework for *ex post* ROV to incorporate real-world data (RWD) into the ROV calculation.
- Not considering the level of uptake of the next innovations will lead to overestimation of ROV.
- Not considering the health gains due to the next innovations in the standard-of-care arm will lead to overestimation of ROV.
- ROV varies by the time to the arrival of the next innovative therapies.