
SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
sitc
Society for Immunotherapy of Cancer

November 8-12 • NATIONAL HARBOR, MD

SITC 2017

Report on Economics of Checkpoint Inhibitors Nivolumab and Ipiliumumab in Melanoma

Ahmad Tarhini, MD, PhD

Director, Melanoma and Skin Cancer Program
Director, Center for Immuno-Oncology Research
Cleveland Clinic Taussig Cancer Institute
Cleveland Clinic Lerner College of Medicine of Case Western Reserve

sitc
Society for Immunotherapy of Cancer

#SITC2017

Presenter Disclosure Information

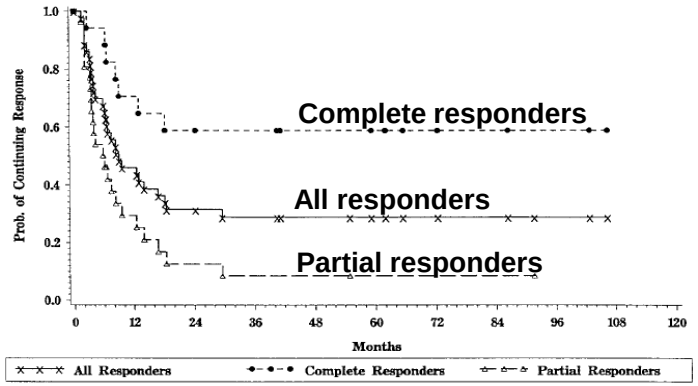
Ahmad Tarhini, MD. PhD

The following relationships exist related to this presentation:

Consultant role: BMS, Genentech, Incyte, Merck, Novartis, NewLink

Introduction

- A unique benefit of immunotherapies is the association with sustained clinical benefit beyond treatment discontinuation[1,2]
- The presence of treatment-free interval (TFI) and cost consequences of being in TFI require further study
- With the availability of multiple effective agents, lifetime costs and outcomes need to be considered, as influenced by:



- ➢Cost of treatment
- ➢Associated AEs
- ➢Management of condition
- ➢Sequence of treatments
- ➢Time on & off treatment
- ➢Duration of response
- ➢OS

1. Atkins MB et al. J Clin Oncol. 1999
2. Schadendorf D et al. *J Clin Oncol*. doi:10.1200/JCO.2017.73.2289

Introduction

- In Phase III CheckMate 067, NIVO+IPI showed improvement in OS compared to IPI (HR 0.55, P<0.0001) & numerically higher OS compared to NIVO (HR 0.85; 95% CI, 0.68 - 1.07)[1]
- Gr 3/4 related AEs reported in 59% of NIVO+IPI pts, 21% NIVO & 28% IPI[1]

➢ There was a need to assess net health benefits in terms of both quantity and quality of survival - accounting for:

- ➢ Duration and quality-of-life impact of AEs
- ➢ Length of time in relapse/progression
- ➢ Duration of "good survival" (Quality-adjusted OS)

1.Wolchok JD et al. N Engl J Med. 2017

Quality-adjusted Time without Symptoms or Toxicity (Q-TWiST) Analysis

- **Quality-adjusted OS** using a **Q-TWiST** approach with CheckMate 067 ITT population was evaluated for NIVO+IPI vs. IPI, NIVO+IPI vs. NIVO & NIVO vs. IPI
- Q-TWiST assesses **overall quantity and quality of survival** (PFS, OS) based on amount of time spent in the following health states:

Toxicity ("TOX" state)	**Time without symptoms of toxicity ("TWiST" state)**	**Relapse ("REL" state)**
Period of AEs grade ≥3 before progression or censoring	Period without symptoms or toxicities before progression	Period following disease progression until death or censoring

- Mean Q-TWiST values were calculated by taking the sum of the product of the time spent in each state by its respective utilities (U)

$$\text{Q-TWiST} = U_{TOX} \times TOX + U_{TWiST} \times TWiST + U_{REL} \times REL$$

- Botteman et al. ESMO 2017
- Goldhirsch et al. J Clin Oncol. 1989;7(1):36-44.
- Revicki et al. Qual Life Res. 2006;15(3):411-423

Q-TWiST Analysis of Treatment-naïve Patients with Advanced Melanoma in CheckMate 067

Restricted Mean Durations of Health States at Maximum Follow-up of 40 Months

Health State, months (95% CI)	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
TOX	0.8 (0.5, 1)	0.5 (0.2, 0.7)	0.2 (0.1, 0.3)
TWiST	19 (17.2, 20.9)	16.7 (14.9, 18.8)	8.3 (6.9, 9.6)
REL	8.2 (6.6, 9.6)	9.6 (8, 11.1)	13.8 (12.3, 15.4)
PFS	19.8 (17.9, 21.7)	17.2 (15.3, 19.2)	8.5 (7.1, 9.9)
OS	28 (26.3, 29.6)	26.8 (25.1, 28.4)	22.3 (20.6, 23.9)
Q-TWiST	23.5 (21.9, 25.2)	21.8 (20.2, 23.4)	15.3 (13.9 to 16.6)

- The mean Q-TWiST was highest for NIVO+IPI patients (23.5 months) as compared to NIVO (21.8 months) or IPI (15.3 months)

The utilities for the base case were assumed to be: U_{TWiST} =1, U_{TOX} =0.5, U_{REL} =0.5 and U_{TOX} was considered to be 0.5 regardless of AE type/severity

Botteman et al. ESMO 2017

Q-TWiST Analysis of Treatment-naïve Patients with Advanced Melanoma in CheckMate 067

Differences in Restricted Mean Durations Between Treatment Arms

Health State, months (95% CI)	NIVO+IPI vs IPI	NIVO vs IPI	NIVO+IPI vs NIVO[a]
ΔTOX	0.5 (0.3, 0.8)	0.2 (0, 0.5)	0.3 (0, 0.7)
ΔTWiST	10.7 (8.4, 13.2)	8.4 (6.1, 10.8)	2.3 (-0.6, 5.1)
ΔREL	-5.6 (-7.8, -3.6)	-4.2 (-6.5, -2)	-1.4 (-3.6, 0.7)
ΔQ-TWiST	8.2 (6.1, 10.2)	6.5 (4.4, 8.7)	1.7 (-0.6, 4.2)
Relative Q-TWiST gain, %	36.81	29.18	6.35
Range in ΔQ-TWiST in threshold analyses, months (relative gain, %)	5.1-11.3 (23 to 51)	4.3-8.7 (19 to 39)	0.9-2.6 (3 to 10)

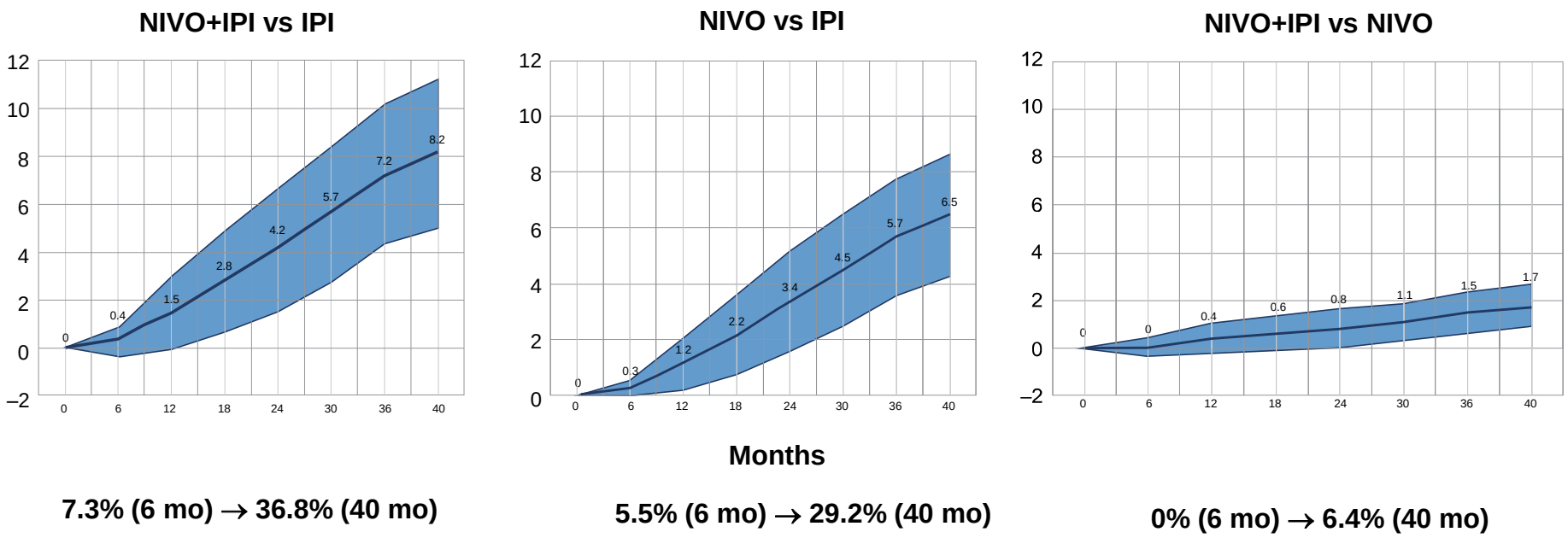
[a]Checkmate 067 trial was not adequately powered to detect a difference between NIVO+IPI and NIVO
Relative gains in Q-TWiST were calculated as the Q-TWiST difference divided by the mean OS of the comparator

- The relative gain observed for NIVO+IPI vs IPI was 36.8% and NIVO vs IPI was 29.2%
  - These met the criteria for clinically (≥10%) and clearly clinically (≥15%) important improvement
- Q-TWiST gains were numerically higher for NIVO+IPI than for NIVO

Botteman et al. ESMO 2017

Q-TWiST Analysis of Treatment-naïve Patients with Advanced Melanoma in CheckMate 067

Q-TWiST Gain Function over Follow-Up Time



7.3% (6 mo) → 36.8% (40 mo)

5.5% (6 mo) → 29.2% (40 mo)

0% (6 mo) → 6.4% (40 mo)

- The relative Q-TWiST gains consistently increased with greater follow-up from 3 to 40 months for all 3 comparisons

Botteman et al. ESMO 2017

Quantifying Treatment-free Interval (TFI) (CheckMate 069 & CheckMate 067)

- **TFI** assessed using pooled patient-level data from 069 (NIVO+IPI [n = 95], IPI [n = 47]) & 067 (NIVO+IPI [n = 314], NIVO [n = 316], IPI [n = 315])
  - Minimum follow-up of 2 years; hence, parametric survival analyses conducted to extrapolate outcomes over patient lifetime
- **TFI** defined as time between first-line treatment discontinuation and subsequent treatment initiation

First line treatment duration and Treatment-free interval

Treatment Duration (years)	NIVO + IPI	NIVO	IPI
Mean (95% CI)	1.0 (0.9 – 1.1)	1.3 (1.2 – 1.4)	0.6 (0.6 – 0.7)
Median	0.4	0.6	0.36
Range (Min – Max)	<0.1 – 12.6	<0.1 – 12.6	<0.1 – 6.9
Treatment-free Interval (years)	**NIVO + IPI**	**NIVO**	**IPI**
Mean (95% CI)	5.3 (4.8 – 5.8)	3.4 (3.0 – 3.8)	2.3 (2.0 – 2.6)
Median	0.6	0.1	0.1
Range (Min – Max)	<0.1 – 20.2	<0.1 – 20.2	<0.1 – 20.2

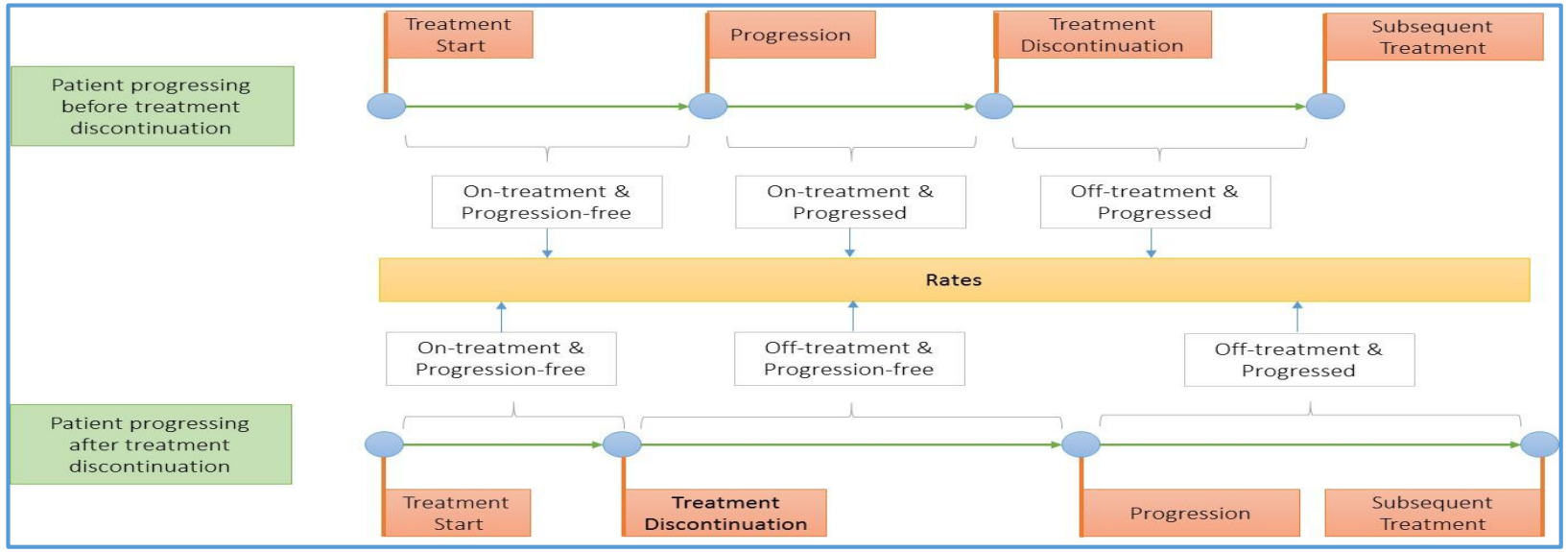
- The mean **TFI** with NIVO+IPI (5.3 years) was 1.9 years longer than NIVO and 3.0 years longer than IPI

Tarhini et al. SMR 2017

Resource Use and Cost Implications Associated with TFI (CheckMate 069 and CheckMate 067)

- Annual rates of healthcare resource use associated with **TFI** were assessed
  - Concomitant medications, laboratory tests, procedures, consultations, hospitalizations and surgeries
  - Estimated according to treatment status (on or off) and progression status for each arm

Schematic of Resource Use Estimation by Phases

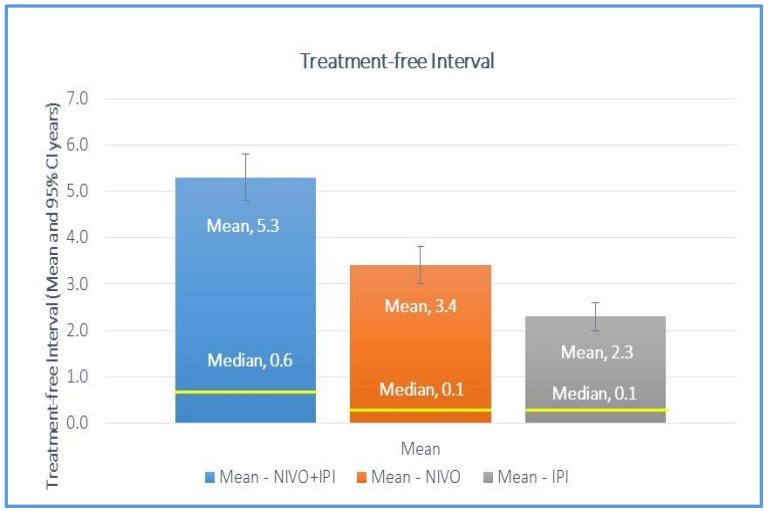


- Annual costs were estimated by applying the rates of healthcare resource use to the costs
  - Unit costs were obtained from RedBook, Medicare payment limits and Healthcare Utilization Project

Atkins et al. SMR 2017

Resource Use and Cost Implications Associated with TFI (CheckMate 069 & CheckMate 067)

Treatment-free interval[a]



Mean Annual Cost Healthcare Resource Use

	Mean Annual Cost (95% CI)			
	On-Treatment/ Progression-free	On-Treatment/ Progressed	Off-Treatment/ Progression-free	Off-Treatment/ Progressed
IPI	$10,002 ($6,709 - $17,922)	$12,704 ($7,503 - $27,944)	$8,679 ($4,070 – $22,782)	$19,375 ($11,239 - $38,288)
NIVO	$5,695 ($4,253 - $9,596)	$13,919 ($8,870 - $25,073	$2,198 ($695 – $10,296)	$19,021 ($6,177 – $69,230)
NIVO+IPI	$9,407 ($6,798 - $14,313)	$14,653 ($8,394 - $30,168)	$3,055 ($1,541 – $7,917)	$15,541 ($9,757 – $27,778)

- The mean annual **Off treatment/ Pogressed** Phase costs are lowest for NIVO+IPI compared to NIVO and IPI
- In **Off-treatment/ Progression-free** Phase, NIVO+IPI and NIVO are associated with lower annual cost compared to IPI
- NIVO + IPI has the **longest TFI** and **higher proportion of progression-free** patients; therefore, the lower annual costs associated with off-treatment phase and progression-free phase are accrued for a longer time

Tarhini et al. SMR 2017
Atkins et al. SITC 2017

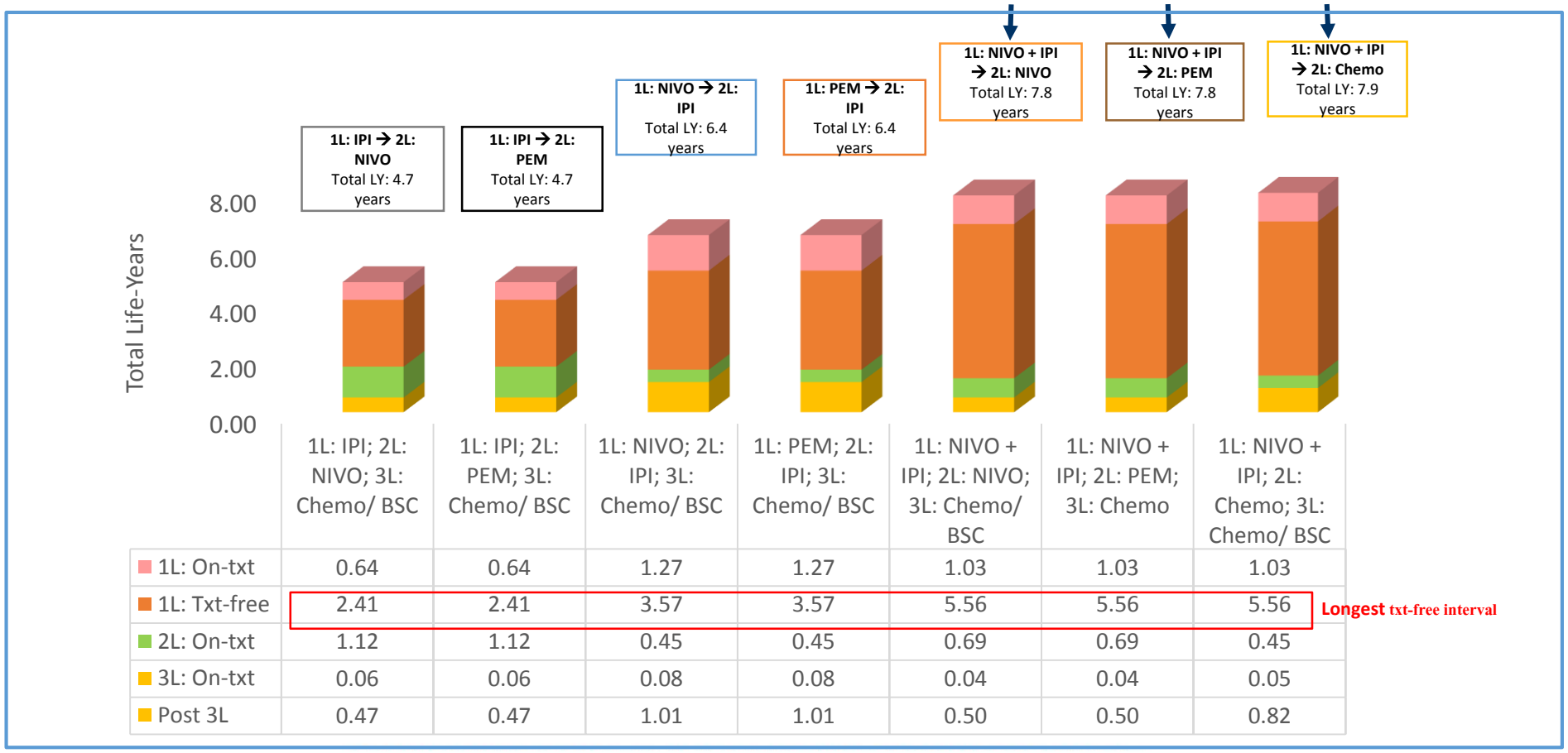
Economic Sequencing Model - Overview & Methods

- Cost-effectiveness of initiating treatment with NIVO+IPI or monotherapy (NIVO, PEM, IPI) in BRAF wild-type melanoma was assessed
- Model developed using **discretely integrated condition event (DICE)** methodology to simulate lifetime (30 years) costs and quality-adjusted life years
- Statistical analysis of pooled patient-level data from CheckMate067 & 069 was conducted to derive risk equations for treatment discontinuation, TFI, disease progression and death
  - Drug, administration and AE management costs were accrued while patients were on therapy
  - Routine disease management costs were estimated over a patient's lifetime
  - Quality of life was accounted for based on disease phase and disutilities due to AEs based on time to resolution

Economic Sequencing Model – Total Life-years

- NIVO+IPI initiating sequences had longest average life-years of 7.9 years driven by the TFI period
- TFI was longest for 1st line NIVO + IPI (5.6 yrs) compared to Anti-PD1 (3.6 yrs) and Anti-CTLA4 (2.4 yrs)

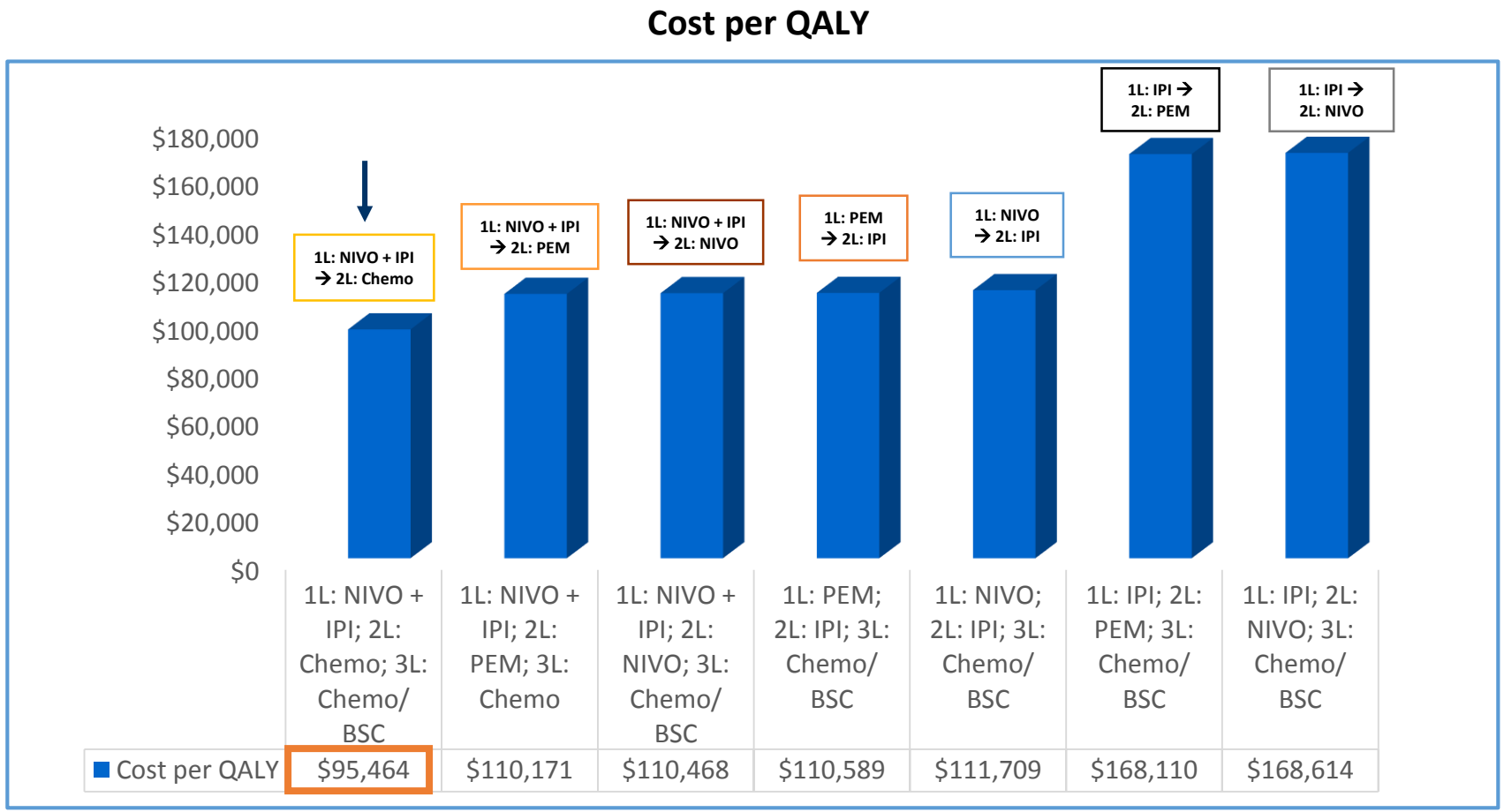
Total Life-years



	1L: IPI; 2L: NIVO; 3L: Chemo/ BSC	1L: IPI; 2L: PEM; 3L: Chemo/ BSC	1L: NIVO; 2L: IPI; 3L: Chemo/ BSC	1L: PEM; 2L: IPI; 3L: Chemo/ BSC	1L: NIVO + IPI; 2L: NIVO; 3L: Chemo/ BSC	1L: NIVO + IPI; 2L: PEM; 3L: Chemo	1L: NIVO + IPI; 2L: Chemo; 3L: Chemo/ BSC
1L: On-txt	0.64	0.64	1.27	1.27	1.03	1.03	1.03
1L: Txt-free	2.41	2.41	3.57	3.57	5.56	5.56	5.56
2L: On-txt	1.12	1.12	0.45	0.45	0.69	0.69	0.45
3L: On-txt	0.06	0.06	0.08	0.08	0.04	0.04	0.05
Post 3L	0.47	0.47	1.01	1.01	0.50	0.50	0.82

Longest txt-free interval

Economic Sequencing Model – Cost per QALY



- Cost per quality adjusted life year was lowest for the sequence of NIVO + IPI followed by chemotherapy ($95,464)

Conclusions

- Net gains of quality-adjusted survival should be considered in addition to the efficacy and AE profile
- NIVO+IPI and NIVO alone patients had a statistically significant gain in quality-adjusted time without symptoms or toxicity (Q-TWiST) vs IPI alone
- NIVO+IPI was associated with the longest TFI compared with NIVO or IPI
    - For those in the TFI, patients progressing and those progression free on NIVO+IPI had lower disease management costs compared to those treated with IPI
- Treatment sequences starting with NIVO+IPI are cost-effective driven by a long TFI and provide important quality-adjusted survival gains to patients with *BRAF* wild-type advanced melanoma

Acknowledgment

- Michael Atkins, MD
- David McDermott, MD
- Meredith Regan, MD
- BMS team (Sumati Rao, PhD; Komal Singh, PhD; Corey Ritchings, PharmD)
- Evidera (Agnes Benedict, PhD; Apoorva Ambavane, PhD) and Pharmerit (Marc Botteman)

Thank you