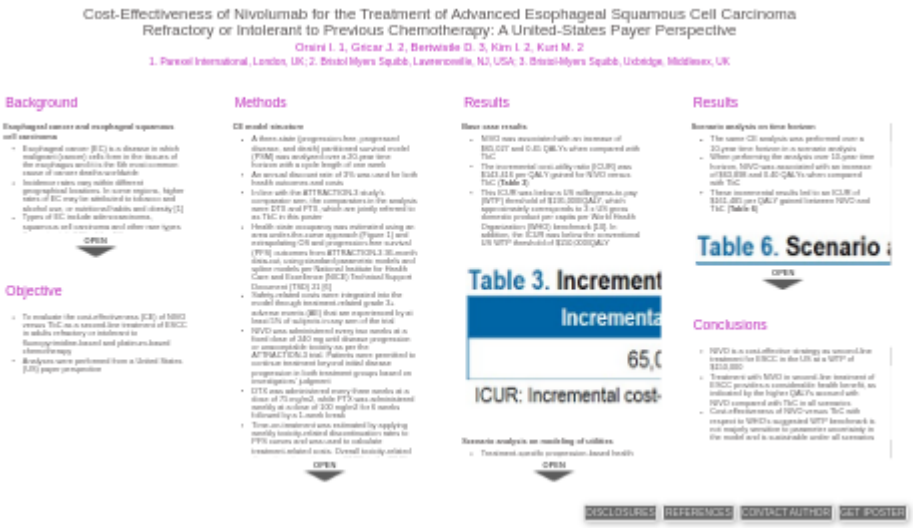
Cost-Effectiveness of Nivolumab for the Treatment of Advanced Esophageal Squamous Cell Carcinoma Refractory or Intolerant to Previous Chemotherapy: A United-States Payer Perspective



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BACKGROUND

Esophageal cancer and esophageal squamous cell carcinoma

- Esophageal cancer (EC) is a disease in which malignant (cancer) cells form in the tissues of the esophagus and it is the 6th most common cause of cancer deaths worldwide
- Incidence rates vary within different geographical locations. In some regions, higher rates of EC may be attributed to tobacco and alcohol use, or nutritional habits and obesity [1]
- Types of EC include adenocarcinoma, squamous cell carcinoma and other rare types
- Approximately 84% of the EC cases are histologically defined as esophageal squamous cell carcinoma (ESCC) [2]
- Fluoropyrimidine and platinum doublet chemotherapy are considered acceptable first-line therapy options for patients with unresectable advanced, recurrent, or metastatic ESCC [3]
- Although second-line treatments with docetaxel (DTX) and paclitaxel (PTX) are used for patients with advanced ESCC that have progressed after first-line chemotherapy, they are associated with poor long-term survival [4]
- Until recently, there was an unmet need for treatment options for recurrent, locally advanced, or metastatic ESCC patients who are previously treated with chemotherapy. Prior to nivolumab (NIVO), based on the results of KEYNOTE-181 trial, pembrolizumab was the only other immunotherapy agent approved by Food and Drug Administration (FDA) in this population as a second-line treatment. However, its label was restricted only to tumors expressing PD-L1 (Combined Positive Score [CPS] > 10%), as determined by an FDA-approved test

Clinical background of NIVO

- ATTRACTION-3 was a randomized, open-label phase 3 study investigating the efficacy and safety of NIVO versus taxane-based chemotherapy (TbC) in patients with unresectable ESCC who were refractory or intolerant to fluoropyrimidine-based and platinum-based chemotherapy [5]
- The primary outcome of this study was overall survival (OS), defined as the time from randomization until death from any cause
- After promising results from the ATTRACTION-3 study, NIVO received FDA and the European Medicine’s Agency’s approvals in 2020 as a treatment for adults with unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy, irrespective of PD-L1 expression

OBJECTIVE

- To evaluate the cost-effectiveness (CE) of NIVO versus TbC as a second-line treatment of ESCC in adults refractory or intolerant to fluoropyrimidine-based and platinum-based chemotherapy
- Analyses were performed from a United States (US) payer perspective

METHODS

CE model structure

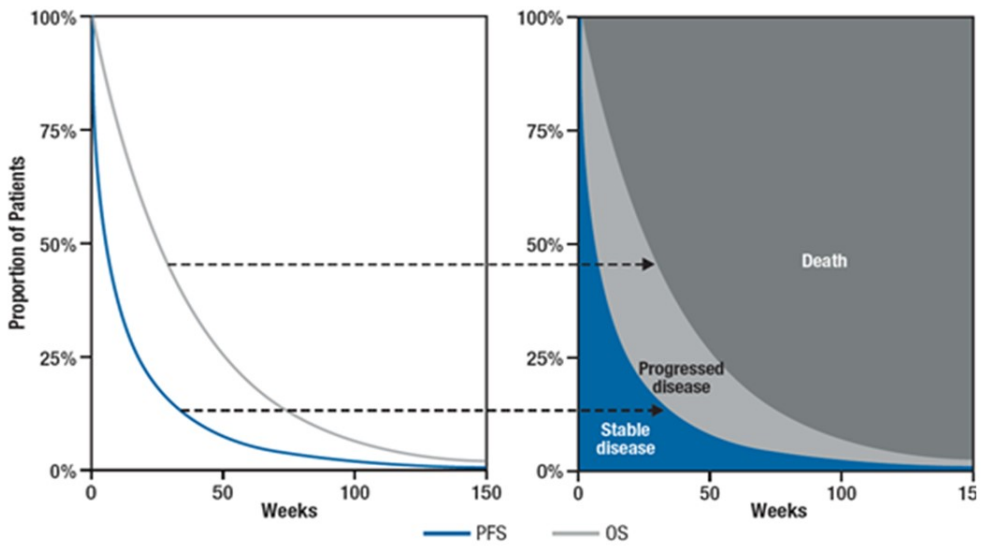
- A three-state (progression-free, progressed disease, and death) partitioned survival model (PSM) was analyzed over a 20-year time horizon with a cycle length of one week
- An annual discount rate of 3% was used for both health outcomes and costs
- In line with the ATTRACTION-3 study's comparator arm, the comparators in the analysis were DTX and PTX, which are jointly referred to as TbC in this poster
- Health state occupancy was estimated using an area under-the-curve approach (Figure 1) and extrapolating OS and progression-free survival (PFS) outcomes from ATTRACTION-3 36-month data-cut, using standard parametric models and spline models per National Institute for Health Care and Excellence (NICE) Technical Support Document (TSD) 21 [6]
- Safety-related costs were integrated into the model through treatment-related grade 3+ adverse events (AE) that are experienced by at least 5% of subjects in any arm of the trial
- NIVO was administered every two weeks at a fixed dose of 240 mg until disease progression or unacceptable toxicity as per the ATTRACTION-3 trial. Patients were permitted to continue treatment beyond initial disease progression in both treatment groups based on investigators' judgment
- DTX was administered every three weeks at a dose of 75 mg/m2, while PTX was administered weekly at a dose of 100 mg/m2 for 6 weeks followed by a 1-week break
- Time-on-treatment was estimated by applying weekly toxicity-related discontinuation rates to PFS curves and was used to calculate treatment-related costs. Overall toxicity-related discontinuation rates were 13.9% in the NIVO arm and 15.9% in the TbC arm
- Drug acquisition, administration, subsequent therapy, AE, routine disease management, and terminal care costs were sourced from official US databases and literature data [7,8]. 2020 costs were used in the analysis
- Drug acquisition costs were based on wholesale acquisition costs [7] (no price discounts or rebates were considered in the model)
- The distribution of subsequent systemic anticancer therapies was based on data from ATTRACTION-3
- Total quality-adjusted life-years (QALY) were estimated via treatment-specific time-to-death (TTD)-based utilities, which were derived by applying US tariffs to the trial's EQ-5D data (**Table 1**)

Table 1. Estimated utility values by TTD – US weights

Arm	TTD			
	<30 days	31-90 days	91-180 days	>180 days
NIVO	0.389	0.658	0.795	0.890
TbC	0.371	0.656	0.749	0.856

NIVO: Nivolumab; TbC: Taxane-based chemotherapy; TTD: Time-to-death; US: United States

Figure 1. Illustrative example of PFS and OS curves being used to inform health state occupancy in a PSM

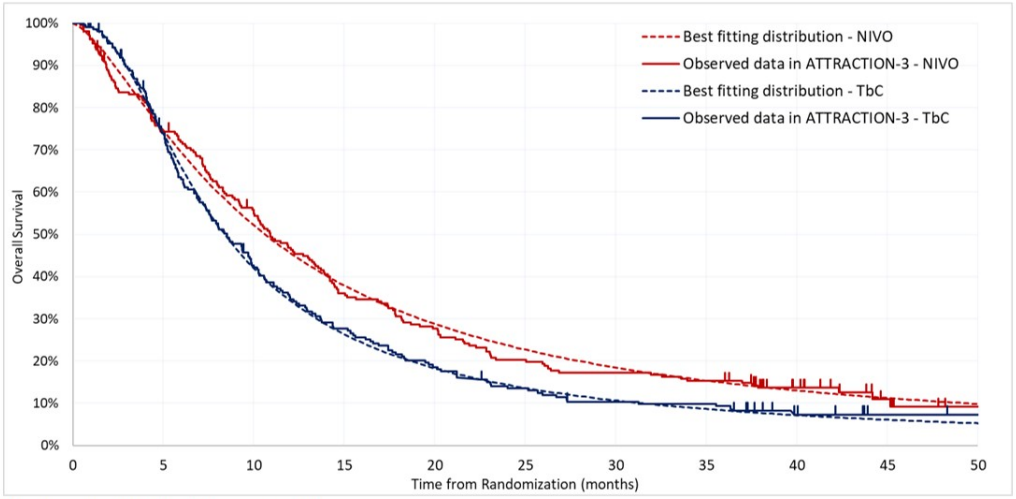


OS: Overall survival; PFS: Progression-free survival; PSM: Partitioned survival model

Survival analysis of key clinical outcomes

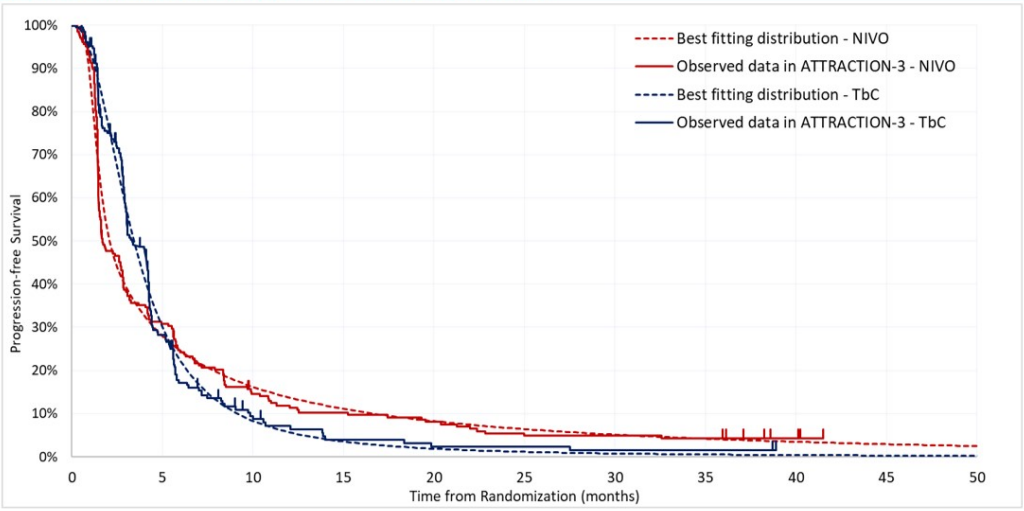
- The process of fitting parametric survival curves to OS, PFS, and duration of therapy (DoT) data was based on NICE TSD 14 [9]. Both standard parametric and spline models were tested
- Log-cumulative hazard plots were analyzed first to test the proportional hazards assumption between the arms. Since the assumption did not hold for any of the three aforementioned endpoints (also indicated by the Grambsch-Therneau test: OS $p=0.04$, PFS $p<0.001$, DoT $p=0.003$), independent survival models were fitted to OS, PFS, and DoT data in both arms
- In line with NICE TSD 14, the best-fitting base-case distributions for each endpoint in each arm were selected based on visual inspection, statistical goodness-of-fit (lowest Akaike information criterion [AIC]), and clinical plausibility
- Comparable efficacy was demonstrated between DTX- and PTX-treated patients via a propensity score matching analysis. Therefore, entire comparator arm data (TbC) were used as a single cohort for survival analyses
- NIVO OS was modeled using the log-logistic distribution, while TbC OS was modeled using the spline odds 1-knot distribution (**Figure 2**)
- NIVO PFS was modeled using the spline hazards 2 knots distribution, while TbC PFS was modeled using the log-logistic distribution (**Figure 3**)
- Landmark estimates from the base-case distributions of OS and PFS are provided in **Table 2**

Figure 2. Observed and modeled OS curves for each arm



Note: Vertical marks within the KM curves indicate censoring
KM: Kaplan-Meier; NIVO: Nivolumab; OS: Overall survival; TbC: Taxane-based chemotherapy

Figure 3. Observed and modeled PFS curves for each arm



Note: Vertical marks within the KM curves indicate censoring
KM: Kaplan-Meier; NIVO: Nivolumab; PFS: Progression-free survival; TbC: Taxane-based chemotherapy

Table 2. Landmark estimates for OS and PFS endpoints from the best-fitting distributions

Endpoint, Arm	3 months	6 months	1 year	5 years	10 years	20 years
OS, NIVO	86.0	69.5	45.8	7.7	3.0	1.1
OS, TbC	89.7	66.0	34.5	4.1	1.5	0.5
PFS, NIVO	39.3	24.6	13.8	1.8	0.5	0.1
PFS, TbC	57.6	22.4	5.7	0.2	0.0	0.0

NIVO: Nivolumab; OS: Overall survival; PFS: Progression-free survival; TbC: Taxane-based chemotherapy

RESULTS

Base case results

- NIVO was associated with an increase of $65,027 and 0.45 QALYs when compared with TbC
- The incremental cost-utility ratio (ICUR) was $143,416 per QALY gained for NIVO versus TbC (**Table 3**)
- This ICUR was below a US willingness-to-pay (WTP) threshold of $195,000/QALY, which approximately corresponds to 3 x US gross domestic product per capita per World Health Organization (WHO) benchmark [10]. In addition, the ICUR was below the conventional US WTP threshold of $150,000/QALY

Table 3. Incremental costs, QALYs and ICURs (discounted results) for NIVO against TbC

Incremental costs ($)	Incremental QALYs	Incremental cost per QALY gained ($)
65,027	0.45	143,416

ICUR: Incremental cost-utility ratio; NIVO: Nivolumab; QALY: Quality-adjusted life year; TbC: Taxane-based chemotherapy

Scenario analysis on modeling of utilities

- Treatment-specific progression-based health state utilities, derived from the trial's EQ-5D data, were used instead of TTD-based health utility scores in a scenario analysis
- When adopting progression-based health state utilities, NIVO was associated with an increase of 0.43 QALYs
- These incremental results led to an ICUR of $152,555 per QALY gained between NIVO and TbC (**Table 4**)

Table 4. Scenario analysis on modeling of utilities, results for NIVO against TbC

Incremental costs ($)	Incremental QALYs	Incremental cost per QALY gained ($)
65,027	0.43	152,555

NIVO: Nivolumab; QALY: Quality-adjusted life year; TbC: Taxane-based chemotherapy

Scenario analysis on modeling of treatment-related costs

- To account for the possibility of post-progression treatment, drug acquisition costs were calculated using the curves that are extrapolated from the trial's DoT data for NIVO and TbC
- When adopting DoT curves to calculate treatment-related costs, NIVO was associated with an increase of $80,644 when compared with TbC
- These incremental results led to an ICUR of $177,859 per QALY gained between NIVO and TbC (**Table 5**)

Table 5. Scenario analysis on modeling of treatment-related costs, results for NIVO against TbC

Incremental costs ($)	Incremental QALYs	Incremental cost per QALY gained ($)
80,644	0.45	177,859

NIVO: Nivolumab; QALY: Quality-adjusted life year; TbC: Taxane-based chemotherapy

RESULTS

Scenario analysis on time horizon

- The same CE analysis was performed over a 10-year time horizon in a scenario analysis
- When performing the analysis over 10-year time horizon, NIVO was associated with an increase of $63,898 and 0.40 QALYs when compared with TbC
- These incremental results led to an ICUR of $161,485 per QALY gained between NIVO and TbC (**Table 6**)

Table 6. Scenario analysis on time horizon, results for NIVO against TbC

Incremental costs ($)	Incremental QALYs	Incremental cost per QALY gained ($)
63,898	0.40	161,485

NIVO: Nivolumab; QALY: Quality-adjusted life year; TbC: Taxane-based chemotherapy

Scenario analysis on fitted OS and PFS distributions

- Second-best fitting distributions according to AIC estimates were adopted for OS and PFS endpoints for both arms: Lognormal for NIVO OS, spline hazards 1 knot for TbC OS, spline odds 2 knots for NIVO PFS, and spline hazards 2 knots for TbC PFS
- Under the second-best fitting OS and PFS curves, NIVO was associated with an increase of $65,240 and 0.43 QALYs when compared with TbC
- These incremental results led to an ICUR of $150,903 per QALY gained between NIVO and TbC (**Table 7**)

Table 7. Scenario analysis on OS and PFS distributions, results for NIVO against TbC

Incremental costs ($)	Incremental QALYs	Incremental cost per QALY gained ($)
65,240	0.43	150,903

NIVO: Nivolumab; QALY: Quality-adjusted life year; TbC: Taxane-based chemotherapy

CONCLUSIONS

- NIVO is a cost-effective strategy as second-line treatment for ESCC in the US at a WTP of $150,000
- Treatment with NIVO in second-line treatment of ESCC provides a considerable health benefit, as indicated by the higher QALYs accrued with NIVO compared with TbC in all scenarios
- Cost-effectiveness of NIVO versus TbC with respect to WHO's suggested WTP benchmark is not majorly sensitive to parameter uncertainty in the model and is sustainable under all scenarios

DISCLOSURES

- Bristol-Myers Squibb (Princeton, NJ) and ONO Pharmaceutical Company Ltd. (Osaka, Japan)

- This study was supported by Bristol-Myers Squibb

- All authors contributed to and approved the presentation; writing and editorial assistance was provided by Parexel International, funded by Bristol-Myers Squibb

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