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ORIGINAL RESEARCH

Estimating the Cost-Effectiveness of Tumor Treating Fields (TTFields) Therapy with an Immune Checkpoint Inhibitor or Docetaxel in Metastatic Non-Small Cell Lung Cancer

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Purpose: Lung cancer remains a leading cause of cancer-related mortality. Tumor Treating Fields (TTFields) therapy extended survival in patients with metastatic non-small cell lung cancer (NSCLC) on or after platinum-based therapy. This study evaluates the cost-effectiveness of TTFields therapy concomitant with immune checkpoint inhibitors (ICIs) or docetaxel.

Methods: A model-based health economic evaluation estimated lifetime costs, clinical benefits, and humanistic outcomes of TTFields therapy plus ICI or docetaxel versus ICI or docetaxel alone in metastatic NSCLC. The model used clinical data from the LUNAR study, US healthcare cost data, and quality-adjusted life year (QALY) measures.

Results: The addition of TTFields therapy to an ICI or docetaxel resulted in a mean life-year gain of 0.92 and a QALY gain of 0.66, with an incremental cost-effective ratio (ICER) of $89,808 per QALY gained. TTFields therapy plus an ICI had 1.67 additional life years and 1.21 additional QALYs compared to an ICI alone, with an ICER of $58,764 per QALY gained. For TTFields therapy plus docetaxel, the life-year gain was 0.23 and the QALY gain was 0.17, with an ICER of $306,029 per QALY gained. Sensitivity analyses confirmed the robustness of these findings.

Conclusion: The addition of TTFields therapy to an ICI or docetaxel in metastatic NSCLC demonstrates comparable cost-effectiveness to other approved treatments. ICERs fall within the accepted range for US cost-effectiveness thresholds, supporting their use in clinical practice. TTFields therapy extended mean lifetime survival, offering a clinically meaningful and economically justifiable option for patients progressing after platinum-based chemotherapy.

Plain language summary: Recent clinical data from the LUNAR study has shown that Tumor Treating Fields (TTFields) therapy concomitant with immune checkpoint inhibitors (ICIs) or docetaxel improves survival in patients with metastatic non-small cell lung cancer (NSCLC) on or after platinum-based therapy. TTFields therapy recently received FDA approval for use in this setting. The aim of this study was to assess whether the addition of TTFields therapy was cost-effective compared to using ICIs or docetaxel alone. A model assessing treatment benefit, costs over the patient's lifetime, and general health and well-being or life satisfaction was generated using clinical data from the LUNAR study and quality-adjusted life year (QALY) measures. QALY is a metric incorporating length of life and quality of life. The study shows that TTFields therapy concomitant with ICIs or docetaxel is cost-effective in comparison with other treatments currently approved for metastatic NSCLC treatment supporting a potential approval for TTFields therapy in this setting.

Keywords: lung cancer, chemotherapy, immunotherapy, cost-effectiveness, Tumor Treating Fields

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Introduction

Approximately 235,000 new lung cancer cases and 125,000 deaths from lung cancer are expected to occur in the United States (US) during 2024.[1] Non-small cell lung cancer (NSCLC) accounts for the vast majority of these cases. About half of NSCLC patients have metastatic disease (stage IV),[1–4] which has a 5-year survival rate of only 9%.[1] Beyond the profound clinical burden, metastatic NSCLC has an immense financial burden. A US study (2010–2019) found the mean cost for treating advanced NSCLC was $158,908, or $250,942 annually. Outpatient costs for immune checkpoint inhibitor (ICI) treatment were associated with over 60% of these costs.[5] The determination of first line treatment for metastatic NSCLC depends on clinical guidelines that consider performance status, histology, and molecular pathology. Most patients are recommended either targeted therapy (if an oncogenic driver is present) or an ICI (with or without platinum chemotherapy based on programmed death-ligand 1 [PD-L1] status).[6–9] Second-line treatment depends on the first-line therapy and includes ICIs, docetaxel, and docetaxel plus ramucirumab. Tumor Treating Fields (TTFields) are alternating electric fields that disrupt cancer cell division, potentially leading to immunogenic cell death (ICD). ICD enhances antitumor immunity, potentially improving the anticancer effects of ICIs. Preclinical studies show that adding TTFields to ICIs (anti-programmed death protein 1 [PD-1] or anti-PD-L1) results in greater tumor reduction, more immune cells, and increased T-cell activity.[10,11] These findings suggest that TTFields therapy can improve existing treatments for metastatic disease. TTFields therapy is delivered locoregionally and noninvasively to the tumor site by a portable medical device that uses two pairs of arrays placed on the skin surrounding the primary tumor.[12,13] TTFields therapy (Optune Gio®) is approved for newly diagnosed glioblastoma (concomitant with maintenance chemotherapy) and recurrent glioblastoma (as a monotherapy), in the US, Canada, China, Israel, Japan, and Australia. In Europe, the device is Conformité Européenne (CE)-marked by the European Union (EU) for grade 4 glioma.[14–19] It is also CE-marked and approved in the US (Optune Lua™) for the treatment of pleural mesothelioma to be used concurrently with pemetrexed and platinum-based chemotherapy.[12,20,21] Additionally, TTFields therapy recently received FDA approval for metastatic NSCLC, to be used concurrently with PD-1/PD-L1 inhibitors or docetaxel in adult patients who have progressed on or after a platinum-based regimen.[22]

LUNAR (NCT02973789) was a Phase 3, randomized, controlled study evaluating TTFields therapy plus an ICI or docetaxel, compared to an ICI or docetaxel alone, for patients with metastatic NSCLC who had progressed on or after platinum-based therapy.[23] The LUNAR study demonstrated that the addition of TTFields therapy had a significant benefit on overall survival (OS; median OS was 13.2 months versus 9.9 months [hazard ratio (HR): 0.74, 95% confidence interval (CI): 0.56–0.98; P = 0.035]). The safety profile of TTFields therapy was predominantly limited to easily managed grade 1–2 dermatological adverse events (AEs).

TTFields therapy offers clinical benefits, including improved OS and no additional systemic toxicity, but also significant financial implications, making cost-effectiveness evaluations essential. This analysis uses a decision-analytic model to estimate the lifetime cost-effectiveness of TTFields therapy plus an ICI or docetaxel in treating metastatic NSCLC by analyzing clinical outcomes, costs, and quality-adjusted life years (QALYs). Given the clinical benefits and favorable safety profiles associated with TTFields therapy, economic evaluations are vital for understanding the therapy's value in the context of metastatic NSCLC.

Methods

The Model

A three-state partitioned survival model developed in Microsoft® Excel® (version 2311, Microsoft Inc., USA) estimated the lifetime costs, clinical benefits, and humanistic outcomes associated with TTFields therapy plus an ICI or docetaxel compared to an ICI or docetaxel alone. The model considered three health states: (1) stable disease, (2) progressive disease, and (3) death. All patients started the model in the stable disease health state. Patients could transition to death from either the stable disease or the progressive disease state. Patients progressing from stable disease to progressive disease could not transition back to stable disease.

The area under the curve framework, which leveraged the progression-free survival (PFS) and OS data from the LUNAR study, measured the time in each health state. Time on treatment was not tied to the mutually exclusive health

states. In addition, overall response rates (ORRs) in LUNAR (20% with TTFields therapy plus an ICI or docetaxel versus 17% for ICI or docetaxel alone) were comparable to other studies.

The model included a 20-year time horizon and took the perspective of a US payer. A discount rate of 3% was applied to future costs and clinical outcomes.

Patient Population

The patient population included in the model mirrored that of the LUNAR study, which enrolled 276 patients with metastatic NSCLC who had previously progressed on or after platinum-based chemotherapy.[23] The median age at enrollment was 64 years, 64% were male, and 57% had non-squamous NSCLC. The majority (87%) of patients had received only one prior line of systemic therapy.

Comparators

The LUNAR study randomized patients 1:1 to receive TTFields therapy plus an ICI or docetaxel versus an ICI or docetaxel alone. ICIs included pembrolizumab, nivolumab, and atezolizumab.[23] Three comparisons of treatment strategies (one intention-to-treat [ITT] population and two subgroups) were modeled, consistent with the comparisons in the LUNAR study: (1) TTFields therapy plus an ICI or docetaxel versus an ICI or docetaxel alone ie, ITT population, (2) TTFields therapy plus an ICI versus an ICI alone (ICI subgroup population), and (3) TTFields therapy plus docetaxel versus docetaxel alone (docetaxel subgroup population).

Effectiveness Estimates

The LUNAR study evaluated OS as the primary endpoint, comparing (1) TTFields therapy plus an ICI or docetaxel versus (2) an ICI or docetaxel alone. Key secondary endpoints were OS in the subgroups receiving either ICI or docetaxel; other secondary endpoints included PFS, objective response rate, quality of life and safety with subgroups analyses for patients receiving either ICI or docetaxel.

In the ITT population, TTFields therapy plus an ICI or docetaxel significantly extended the median OS to 13.2 months compared to 9.9 months with an ICI or docetaxel alone, reducing the risk of death by 26% (HR: 0.74, 95% CI: 0.56–0.98; P = 0.035).[23] TTFields therapy plus an ICI or docetaxel had a median PFS of 4.8 months compared to 4.1 months for the ICI or docetaxel alone group (HR: 0.85, 95% CI: 0.67–1.11; P = 0.23). In the subgroup population, TTFields therapy plus an ICI also increased median OS to 18.5 months compared 10.8 months to an ICI alone (HR: 0.63, 95% CI: 0.41–0.96; P = 0.030). Median OS for TTFields therapy plus docetaxel was 11.1 months compared to 8.7 months with docetaxel alone (HR: 0.81, 95% CI: 0.55–1.19; P = 0.28).

Due to the median follow-up of 10.6 months for TTFields therapy plus an ICI or docetaxel and 9.5 months for ICI or docetaxel alone, we extrapolated OS and PFS for the remaining time horizon. Extrapolation used the distributions of patients receiving docetaxel (52%) or an ICI (48%) in the TTFields therapy arm and an ICI (51%) or docetaxel (49%) alone arms, included in Table 1.[23–28]

We used Kaplan–Meier data from the LUNAR study through 36 months for OS and 6 weeks for PFS, applying fitted parametric curves for the remaining time. Extrapolations employed exponential, Weibull, log-normal, log-logistic, generalized gamma, and gamma distributions, with the best-fit selected based on statistical criteria and expert opinion. For PFS, TTFields therapy plus docetaxel, docetaxel alone, and an ICI alone used gamma distributions, while TTFields therapy plus an ICI used exponential distributions. For OS, TTFields therapy plus docetaxel, docetaxel alone, TTFields therapy plus an ICI, and an ICI alone used log-normal, gamma, generalized gamma, and log-normal distributions, respectively.

The resulting OS curves for the treatment comparisons are shown in Figure 1.

Safety Estimates

The model considered device-related AEs that were grade ≥3 (Table 1). However, we only included grade 3 device-related events as there were no grade 4 device-related events or deaths in the LUNAR study.[23] These included dermatitis, pruritus, skin ulcer, pain, skin infection, bronchopleural fistula, erythema, and maculopapular rash.

Table 1 Model Inputs

Parameter	Base case	Lower	Upper	Source(s)
Distribution of ICI and docetaxel				
TTFields therapy + an ICI or docetaxel				
Docetaxel	52%	–	–	Leal et al 2023[23]
ICI	48%	–	–	Leal et al 2023[23]
ICI or docetaxel alone				
Docetaxel	51%			Leal et al 2023[23]
ICI	49%			Leal et al 2023[23]
Median duration of therapy, months				
TTFields therapy (with docetaxel)	2.92	2.34	3.50	Leal et al 2023[23]
TTFields therapy (with ICI)	3.36	2.69	4.03	Leal et al 2023[23]
Docetaxel (with TTFields therapy)	2.66	2.13	3.19	Leal et al 2023[23]
ICI (with TTFields therapy)	3.99	3.19	4.79	Leal and Langer 2023[24]
Docetaxel (alone)	2.30	1.84	2.76	Leal and Langer 2023[24]
ICI (alone)	2.79	2.23	3.35	Leal and Langer 2023[24]
Utilities				
Progression-free[a]	0.769	0.62	0.92	Chaudhary et al 2021[25]
Progressive disease	0.716	0.57	0.86	Chaudhary et al 2021[25]
Costs				
Treatment costs[b] per month				
TTFields therapy + docetaxel	$21,587	$17,270	$25,904	Medi-Span 2023[26]; CMS physician fee schedule
TTFields therapy + ICI	$34,041	$27,233	$40,849	Medi-Span 2023[26]; CMS physician fee schedule
Docetaxel alone	$587	$470	$704	Medi-Span 2023[26]; CMS physician fee schedule
ICI alone	$13,041	$10,433	$15,649	Medi-Span 2023[26]; CMS physician fee schedule
Adverse event costs				
Dermatitis	$19,285	$15,428	$23,142	Wong et al 2018[27]
Pruritus	$32,131	$25,705	$38,557	Wong et al 2018[27]
Skin ulcer	$32,131	$25,705	$38,557	Assumed the same as pruritus
Pain	$35,582	$28,466	$42,698	Wong et al 2018[27]
Skin infection	$19,285	$15,428	$23,142	Assumed the same as bronchopleural fistula
Bronchopleural fistula	$19,500	$15,600	$23,400	Wong et al 2018[27]
Erythema	$27,664	$22,131	$33,197	Wong et al 2018[27]
Rash maculopapular	$16,605	$13,284	$19,926	Wong et al 2018[27]

(*Continued*)

Table 1 (Continued).

Parameter	Base case	Lower	Upper	Source(s)
Supportive care costs				
Monthly cost	$194	$155	$233	Cai et al 2021[28]; expert opinion; CMS laboratory fee schedule; CMS physician fee schedule

Note: [a]A weighted average was used to calculate the utility value based on the prevalence of patients with squamous and non-squamous disease in the LUNAR studies. [b]Includes drug acquisition and administration costs.
Abbreviations: CMS, Centers for Medicare & Medicaid Services; ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

Costs and Healthcare Resource Utilization

The model included direct medical costs (treatment, drug administration, supportive care, and AEs). We multiplied the median time on treatment by unit wholesale acquisition cost (WAC) to calculate treatment costs in each subgroup. In addition to drug acquisition costs, we included administration costs while on therapy. We assumed a cost per month of TTFields therapy of $21,000.[29] The model used WAC as listed, without consideration for rebates and/or discounts.[26] The cost of TTFields therapy was also exclusive of potential rebates and/or discounts. The Centers for Medicare & Medicaid Services physician fee schedule, based on the first hour of chemotherapy infusion (CPT: 96413) estimated drug administration costs for docetaxel, pembrolizumab, nivolumab, and atezolizumab.[30] The distribution of patients within the specific ICIs included in the LUNAR study across each of the arms including ICIs, has not been published. Therefore, we assumed a distribution of 55% for nivolumab, 31% for atezolizumab, and 14% for pembrolizumab based on the actual distribution of the ICI alone subgroup in the LUNAR study.

Adverse event costs from the commercial perspective were from previously conducted analysis of Truven Health Analytics MarketScan database (January, 01, 2006 to September 30, 2015) examining the costs associated with AEs in patients with cancer.[27] In the study, a retrospective matched cohort design was used to assess incremental costs associated with 36 AEs during 1,617,368 matched cancer treatment episodes among 412,005 eligible patients. For Medicare-insured patients, AE costs were collected from the Healthcare Cost and Utilization Project using diagnosis-related group codes. The model considered supportive care costs across the stable disease and progressed disease health states. These included outpatient visits, complete blood counts, liver function tests, renal function tests, computed tomography scans, and magnetic resonance imaging scans informed by clinical opinions. All costs were inflated to the first half of 2023 US dollars based on the medical care consumer price index from the Bureau of Labor Statistics.[31]

Quality-of-Life and Utility Values

We used utilities sourced from a previously conducted cost-effectiveness model that used quality-of-life data from the CheckMate 017 and 057 trials.[25] In both trials the utility in the stable disease health state was estimated to be 0.765 for patients with squamous NSCLC and 0.772 for patients with non-squamous NSCLC. We applied the distribution of patients with squamous and non-squamous disease in the ITT population of the LUNAR study to calculate a utility value of 0.769 for patients with stable disease. A utility value of 0.716, calculated by Chaudhary et al,[25] was used for patients with disease progression. The model did not consider disutilities associated with AEs.

The LUNAR study evaluated quality of life through the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire and demonstrated that the addition of TTFields therapy to ICI or docetaxel did not adversely affect quality of life compared to ICI or docetaxel alone.[23] Additionally, no decline in global health status for TTFields therapy plus an ICI or docetaxel or ICI or docetaxel alone over 54 weeks of follow-up was observed.

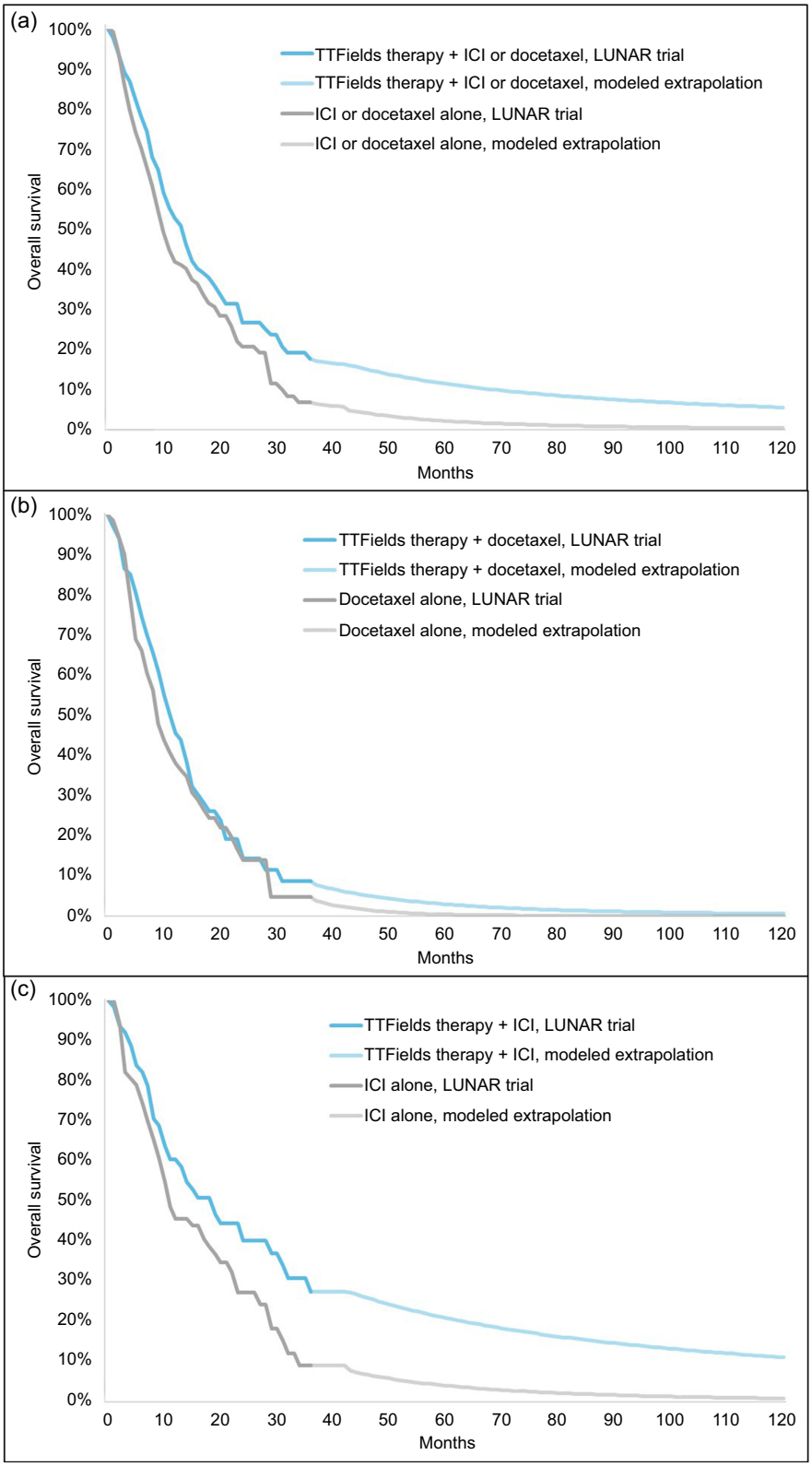

Figure 1 Modeled overall survival curves.
Notes: (**a**) TTFields therapy + an ICI or docetaxel versus an ICI or docetaxel alone, (**b**) TTFields therapy + an ICI versus an ICI alone, and (**c**) TTFields therapy + docetaxel versus docetaxel alone.
Abbreviations: ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

Base Case Results

The model calculated direct medical costs, life-years, and QALYs for TTFields therapy plus an ICI or docetaxel, and for ICI or docetaxel alone. The ICI or docetaxel arm was further divided into subgroups for comparison with or without TTFields therapy. The incremental cost-effective ratio (ICER) was calculated as the cost per additional QALY for the intervention compared to the baseline comparator of an ICI or docetaxel alone.

Sensitivity Analyses

Sensitivity analyses included one-way and probabilistic methods. One-way sensitivity analysis varied each parameter ±20% individually, with results visualized in a tornado diagram. Probabilistic sensitivity analysis varied all parameters simultaneously based on their probability distributions, with 5,000 Monte Carlo simulations plotted on a cost-effectiveness acceptability curve to represent the uncertainty around the intervention's cost-effectiveness.

Results

Base Case results

The discounted lifetime mean costs and clinical outcomes for a representative patient according to the treatment strategy are detailed in Table 2.

Discounted mean life-years were 0.92 higher with TTFields therapy plus an ICI or docetaxel (2.17) compared to an ICI or docetaxel alone (1.25), and QALYs were 0.66 higher for TTFields therapy plus an ICI or docetaxel (1.58 versus 0.92). Lifetime total costs were $59,663 higher for TTFields therapy plus an ICI or docetaxel ($77,410) compared to an ICI or docetaxel alone ($17,747), which resulted in an ICER of $89,808 per QALY gained. Costs were primarily driven by the cost of treatment in both the TTFields therapy plus an ICI or docetaxel arm (88.4%) and an ICI or docetaxel alone arm (75.6%).

When compared to an ICI alone, TTFields therapy plus an ICI had 1.67 additional life years (3.14 versus 1.48) and 1.21 additional QALYs (2.29 versus 1.09). Costs were also higher by $70,901 for the TTFields therapy plus an ICI arm, with $102,404 in mean lifetime total costs compared to $31,504 for the ICI alone arm. The ICER for TTFields therapy plus an ICI compared to an ICI alone was $58,764 per QALY gained.

TTFields therapy plus docetaxel had 0.23 more life years (1.26 versus 1.03) and 0.17 more QALYs (0.92 versus 0.76) compared to docetaxel alone. Mean lifetime total costs were $54,485 for TTFields therapy plus docetaxel compared to $3,979 for docetaxel alone. The $50,505 increase in mean lifetime total costs and 0.17 additional QALYs resulted in an ICER of $306,029 per QALY gained for TTFields therapy plus docetaxel compared to docetaxel alone.

Table 2 Deterministic Discounted Results

Regimen	Costs					Life-years	QALYs	ICER
	Treatment	Administration	Adverse events	Supportive care	Total			
TTFields + an ICI or docetaxel	$68,431	$428	$3,511	$5,039	$77,410	2.17	1.58	–
ICI or docetaxel alone	$13,425	$323	$1,100	$2,900	$17,747	1.25	0.92	–
Incremental	$55,006	$105	$2,412	$2,140	$59,663	0.92	0.66	$89,808
TTFields + an ICI	$91,655	$614	$2,824	$7,311	$102,404	3.14	2.29	–
ICI alone	$26,778	$427	$866	$3,433	$31,504	1.48	1.09	–
Incremental	$64,877	$187	$1,958	$3,878	$70,901	1.67	1.21	$58,764
TTFields therapy + docetaxel	$47,235	$281	$4,041	$2,928	$54,485	1.26	0.92	–
Docetaxel alone	$767	$223	$600	$2,389	$3,979	1.03	0.76	–
Incremental	$46,467	$58	$3,433	$538	$50,505	0.23	0.17	$306,029

Abbreviations: ICER, incremental cost-effective ratio; ICI, immune checkpoint inhibitor; QALY, quality-adjusted life year; TTFields, Tumor Treating Fields.

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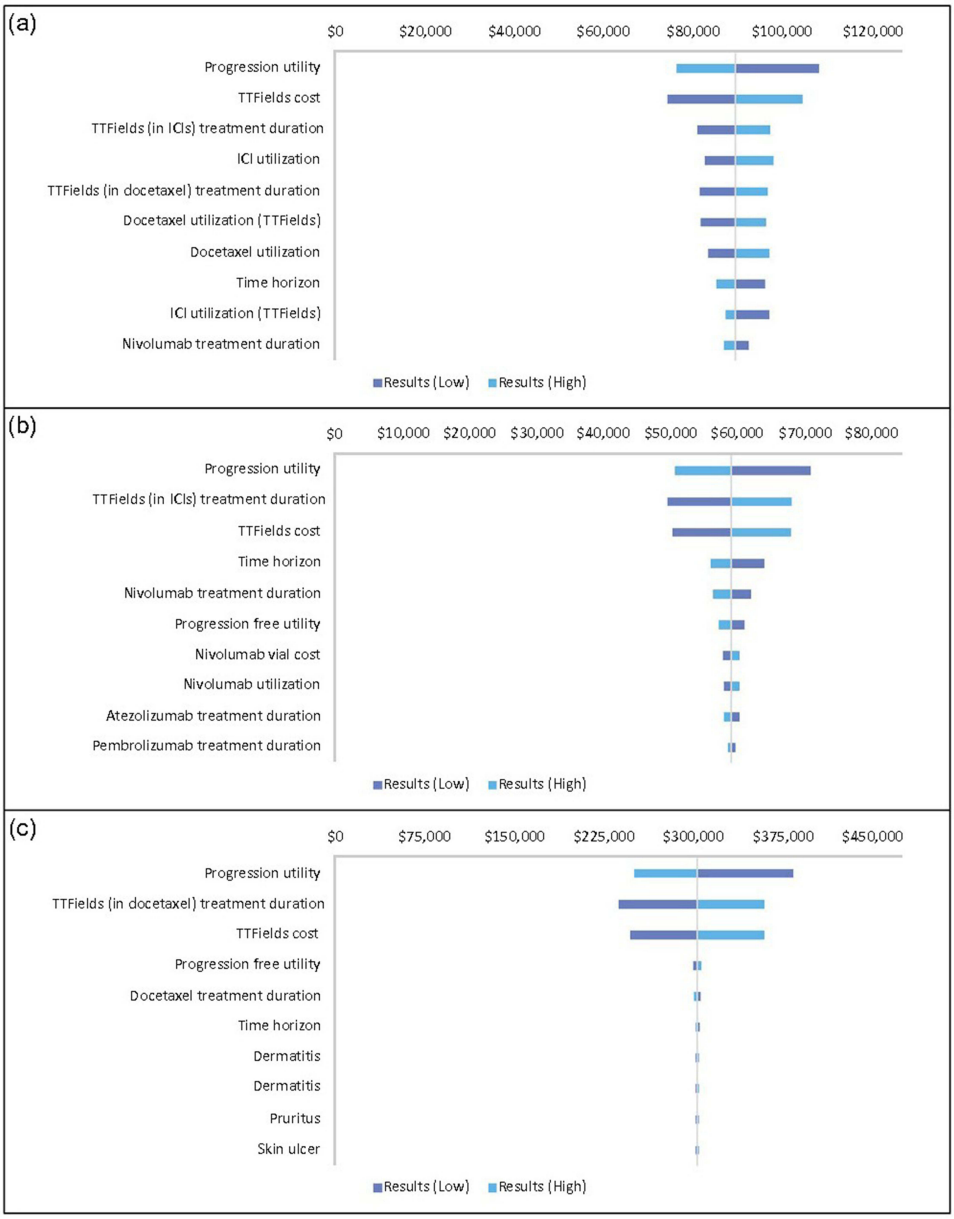

Figure 2 One-way sensitivity analysis.
Notes: (**a**) TTFields therapy + an ICI or docetaxel versus an ICI or docetaxel alone, (**b**) TTFields therapy + an ICI versus an ICI alone, and (**c**) TTFields therapy + docetaxel versus docetaxel alone. Results low and high bounds fluctuate by ±20% in the deterministic sensitivity analysis.
Abbreviations: ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

Sensitivity Analysis

The model was most sensitive to the utility value of disease progression across all the comparisons as revealed by the one-way sensitivity analysis (Figure 2). The cost of TTFields therapy and treatment duration of TTFields therapy were also influential across all the treatment comparisons.

In the probabilistic sensitivity analysis, all simulations were cost-effective at a willingness to pay threshold of $150,000 per QALY for the comparisons of TTFields therapy plus an ICI or docetaxel versus an ICI or docetaxel alone and TTFields therapy plus an ICI versus an ICI alone (Figure 3). TTFields therapy plus docetaxel was cost-effective in 36.5% of scenarios at a willingness to pay threshold of $250,000 and 76.2% of scenarios at a willingness to pay threshold of $300,000 per QALY.

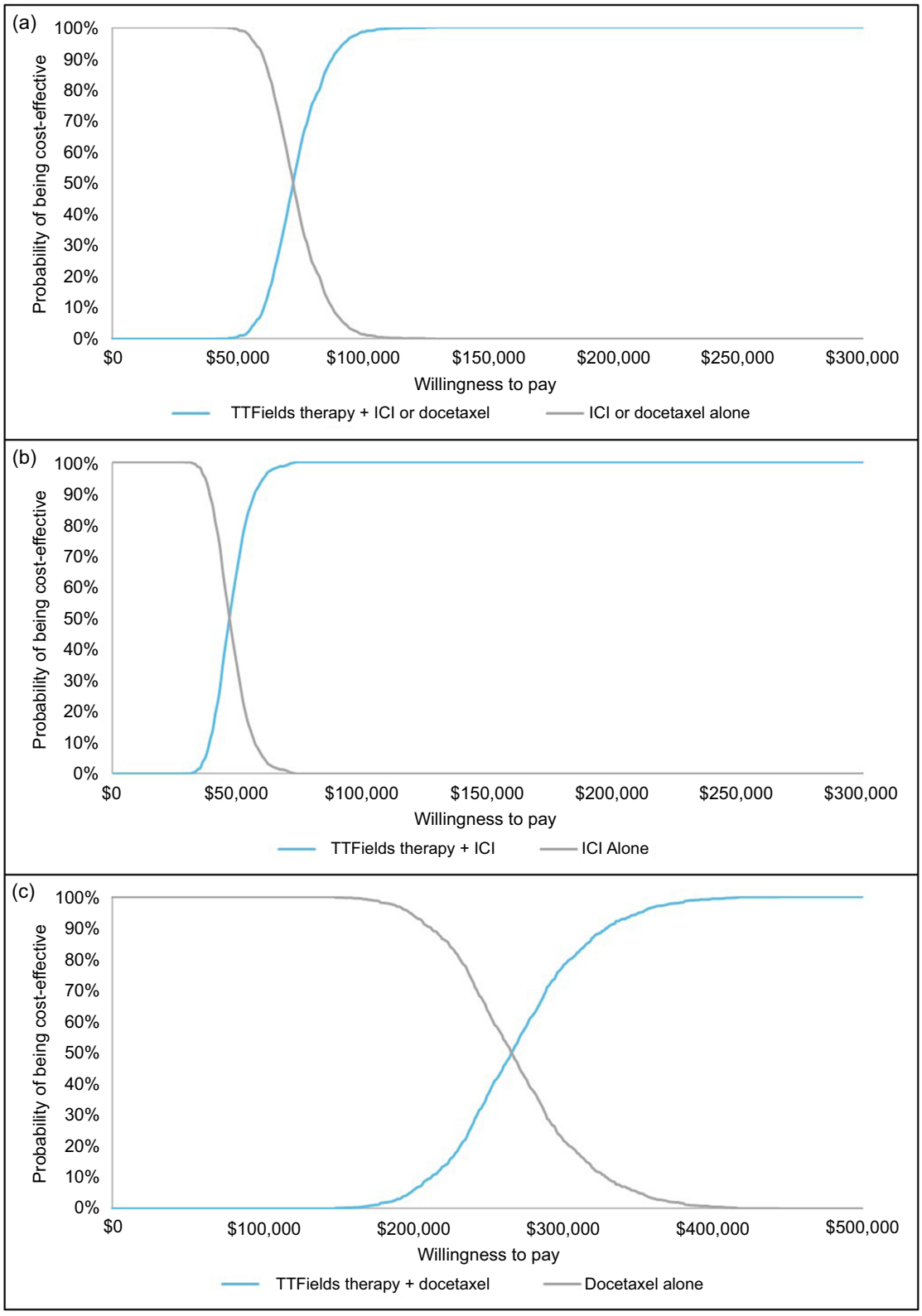

Figure 3 Cost-effectiveness acceptability curves.
Notes: (**a**) TTFields therapy + an ICI or docetaxel versus an ICI or docetaxel alone, (**b**) TTFields therapy + an ICI versus an ICI alone, and (**c**) TTFields therapy + docetaxel versus docetaxel alone docetaxel alone.
Abbreviations: ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

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Discussion

The LUNAR study demonstrated that the addition of TTFields therapy to an ICI or docetaxel significantly extended OS compared to an ICI or docetaxel alone in patients with metastatic NSCLC after progression on or after platinum-based therapy.[23,] Given the recent FDA approval of TTFields therapy concurrent with PD-1/PD-L1 inhibitors or docetaxel for this indication, we evaluated the cost-effectiveness of TTFields therapy plus an ICI or docetaxel, compared to an ICI or docetaxel alone, from the perspective of a US healthcare payer. The results of our analysis demonstrate a discounted gain of 0.91 life-years and 0.66 QALYs for TTFields therapy plus an ICI or docetaxel compared to an ICI or docetaxel alone. We also separately considered ICI and docetaxel treatments and found that adding TTFields therapy resulted in 1.21 additional QALYs with an ICI, and 0.29 additional QALYs with docetaxel.

Although direct comparisons across studies can be misleading given differences in design and baseline patient characteristics, the performance of the control arm in the LUNAR study suggests it is appropriate to compare the OS benefit achieved with TTFields therapy to prior pivotal studies in the same post-platinum setting. This includes the landmark 1-year survival rates for the control arm of LUNAR (46% with an ICI, 38% with docetaxel[23]) that were similar to other pivotal studies of ICI monotherapy 35–55% with ICI monotherapy and 35–41% for docetaxel.[32,33] The ORR was 18% with pembrolizumab in KEYNOTE-010,[32] 20% with nivolumab in pooled CheckMate-017/057 data,[34] 14% with atezolizumab in OAK,[33,] and 23% for ramucirumab plus docetaxel in REVEL[35] (ORRs with docetaxel [the comparator in each case] were 8–14%).[32–35] In LUNAR, the relative OS benefit was 33% (median OS with TTFields added to an ICI or docetaxel was 13.2 months, versus 9.9 months with an ICI or docetaxel alone[23]). This is comparable to ramucirumab with docetaxel (15% longer median OS versus docetaxel alone[35]) or ICIs (22% longer with pembrolizumab,[32] 37% with nivolumab,[34] and 44% with atezolizumab,[33] all versus docetaxel).

In our model, TTFields therapy plus an ICI or docetaxel was more costly than an ICI or docetaxel alone, adding an average of $58,505, of which the treatment cost of TTFields therapy was the majority. Costs were similarly higher for TTFields therapy plus an ICI ($70,901) and TTFields therapy plus docetaxel ($49,806) compared to an ICI or docetaxel alone, respectively. Across the ITT population and subgroups, administration costs, cost of AEs, and supportive care costs were also higher for the TTFields therapy arms.

This increase in cost is consistent with other treatments for NSCLC. At the time of introduction in the US, first-line use of the ICI pembrolizumab for NSCLC expressing PD-L1 was estimated to have an ICER of $130,155 per QALY compared to the existing standard of care (platinum-based chemotherapy).[36] Meanwhile, adding ramucirumab to docetaxel as second-line treatment had an ICER of $222,224 per QALY compared with docetaxel alone.[37] Overall, direct healthcare costs for patients with metastatic NSCLC have been reported as $10,055–$18,565 per patient per month in the US and €1,941 (UK)–€3,151 (France) in Europe.[38] This includes the costs of drugs and their administration, end-of -life costs (hospitalization), and costs relating to AEs from drug therapy; the latter being considerable, with serious AEs estimated to require an additional $4,700 per patient per month.[38] Estimated indirect costs are yet higher still, with those related to loss of productivity from lung cancer estimated for four EU countries at a combined €981 million, and more than €100 billion annually when considering the entire EU.[39]

The resulting ICERs per QALY gained were $89,808 for TTFields therapy plus an ICI or docetaxel versus an ICI or docetaxel alone, $58,764 for TTFields therapy plus an ICI versus an ICI alone, and $306,029 for TTFields therapy plus docetaxel versus docetaxel alone. While the US does not have an explicit cost-effectiveness threshold, there are several suggestions that the range should be between $100,000 to $300,000,[40,41] Additionally, the World Health Organization, has in the past, suggested a threshold between one and three times gross domestic product (GDP) per capita.[42,43] This method would set a threshold of around $229,000 using 2022 GDP per capita in ICER therapy plus an ICI are firmly considered cost-effective treatment options given these established precedents.

The ICERs our analysis calculated for adding TTFields therapy to an ICI or docetaxel for metastatic NSCLC progressing on or after platinum-based therapy are similar or lower to those reported for other agents approved in this setting, as expected given that LUNAR data suggest TTFields therapy confers a similar degree of additional clinical benefit. An analysis of nivolumab compared to docetaxel in squamous NSCLC following platinum-based chemotherapy found an improvement of 1.23 life-years and 0.99 QALYs, resulting in an ICER of $100,776 per QALY.[25] In patients

with non-squamous NSCLC, life-years were 0.99 and QALYs were 0.80 higher than docetaxel resulting in an ICER of $117,739 per QALY.[25] An analysis of pembrolizumab versus docetaxel for patients with NSCLC and high PD-L1 expression (tumor proportion score [TPS] ≥50%) found a difference of 1.18 life years and 0.95 QALYs resulting in an ICER of $168,619 per QALY gained,[44] although noting the PD-L1 ≥50% TPS cutoff effectively restricts this analysis to a subset of patients likely to have greater benefit from pembrolizumab (versus all for whom pembrolizumab is indicated).[32,45] An analysis based on the Canadian publicly funded healthcare system using data from the OAK study found an ICER of $142,074 per QALY gained for atezolizumab versus docetaxel.[46] Ramucirumab added to docetaxel is also approved in the US in the post-platinum NSCLC indication,[47] with a relatively high ICER of $222,224 per QALY gained versus docetaxel alone.[37]

Other studies on the cost-effectiveness evaluations of TTFields therapy with an ICI or docetaxel in metastatic NSCLC have found higher ICERs compared to our results.[48,49] These differences stem from assumptions on modeling practice and treatment duration. For example, Zhang et al model uses a 5-year horizon, which underestimates TTFields' long-term benefits.[50] The most likely reason for the difference in ICERs (versus our analysis, and between the two analyses) is the duration of TTFields therapy assumed by each, given that the length of time receiving a treatment has a major impact on overall treatment cost. Our analysis considered the median duration of TTFields therapy as reported in LUNAR (14.6 weeks when added to an ICI and 12.7 weeks when added to docetaxel).[23] Previously published cost-effectiveness studies utilized Markov models to extrapolate the results of the LUNAR study. The model by Tien et al used discontinuation probabilities—affecting the cost of intervention—of 0.35 and 0.19 for the TTFields therapy plus an ICI or docetaxel and an ICI or docetaxel alone arms, respectively.[48] The study by Liu et al does not mention the methodology or inputs used to calculate time on treatment.[49] Our 20-year model better captures its full clinical and economic impact, considering extended survival benefits beyond their short-term analysis. Given the cost differences between the arms in these studies, it is likely their analyses did not accurately reflect the actual time on therapy in the LUNAR study.

There are several limitations to our decision-analytic model. First, this model uses survival extrapolation to estimate long-term outcomes, which were not available given the median follow-ups in the LUNAR study of 10.6 months for TTFields therapy plus an ICI or docetaxel and 9.5 months for an ICI or docetaxel alone.[23] While the use of survival models is an established and widely accepted practice to forecast outcomes, these models are subject to uncertainty and require validation with long-term data. Our approach utilized a partitioned survival model, which is frequently used in health technology assessments of interventions in oncology and lung cancer.[51] Second, the model considers the list prices for medications and services, which may not reflect the negotiated rates for payers. Third, the distribution of patients between the individual ICIs in both the TTFields therapy and non-TTFields therapy arms was assumed based on the market shares of the three ICIs and may not reflect the actual distribution in the study. Fourth, although the LUNAR study captured quality-of-life data, these were not yet fully available at the time of our analysis, and thus we used utilities captured in the CheckMate 017 and 057 studies and weighted with a US-specific scoring algorithm.[25] Given the difference in long-term survival rates between the LUNAR and CheckMate 017 and 057 studies it is possible that these utilities may not be fully representative of the LUNAR study population. Lastly, we did not conduct separate sensitivity analyses for HRs, OS, and PFS, which could further elucidate the robustness of our model outcomes.

Conclusion

The addition of TTFields therapy to an ICI or docetaxel for patients with metastatic NSCLC progressing on or after platinum-based chemotherapy extended mean lifetime survival and is cost-effective compared to an ICI or docetaxel alone.

Our analysis benefits from transparent reporting of LUNAR study data and realistic treatment duration estimates, ensuring an accurate assessment of TTFields therapy's value. Further clarification on real-world applicability, detailed sensitivity analyses, and long-term outcomes could enhance the robustness of these findings and inform their broader implications for clinical practice and healthcare policy.

Abbreviations

AE, adverse event; CE, Conformité Européenne; CI, confidence interval; GDP, gross domestic product; HR, hazard ratio; ICER, incremental cost-effective ratio; ICI, immune checkpoint inhibitor; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1: PFS, progression-free survival; QALY, quality-adjusted life year; TPS, tumor proportion score; TTFields, Tumor Treating Fields; US, United States; WAC, wholesale acquisition cost.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

WF and EW are employees of Real Chemistry, contractors of Novocure Inc. CYCK and FNdR are employees of and hold stocks/shares in Novocure Inc. RK reports honoraria from Accuray Inc., Elekta AB, ViewRay Inc., Novocure Inc., Elsevier Inc., Brainlab, Kazia Therapeutics, Castle Biosciences, and Ion Beam Applications; research funding from Medtronic Inc., Blue Earth Diagnostics Ltd., Novocure Inc., GT Medical Technologies, AstraZeneca, Exelixis, ViewRay Inc., Brainlab, Cantex Pharmaceuticals, Kazia Therapeutics, Peerview Institute for Medical Education, Insightec LTD, Plus Therapeutics, and Ion Beam Applications. CK is an employee of and holds stocks/shares in Novocure GmbH. The authors report no other conflicts of interest in this work.

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