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RESEARCH ARTICLE

The New Frontier of Low-Cost Neoadjuvant Therapy

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ABSTRACT

Background: We previously reported that the 2-year costs of the immune check inhibitors (ICI) were equitable with outcomes. Extended use multiplied costs. Nivolumab neoadjuvant plus chemotherapy improved event-free survival in early resectable lung cancer at low cost. Neoadjuvant is a novel advance in earlier cancer treatment. The targeted therapy Osimertinib is currently utilized as neoadjuvant, adjuvant and in advanced/metastatic lung cancer with cost increasing yearly with further use. We aimed to quantify the cost and savings of ICI and targeted therapy in earlier vs advanced cancer stages in multiple solid tumors.

Methods: Annual 2019-2020 costs of Osimertinib were calculated ad monthly optimal dose x 12. Costs of ICI were calculated as dose x mg/m2 or per 80 kg x price x number of cycles per year.

Results: The 2-year Osimertinib cost in metastatic disease was $496,744, adjuvant 1-year $248,372 and neoadjuvant $31,046. Estimated neoadjuvant cost savings over 1-year were $217,326.

Pembrolizumab $134,796 annual cost was the median of 5- evaluated ICI. It is used as adjuvant at half the 2-year cost. Extended therapy by 6-12 months, beyond the 2-year approval, added an extra $67,398-$134,796.

Durvalumab following chemo-radiation, (Pacific) was approved in unresectable stage III NSCLC x 1-year at $148,007, saving a 2nd year-cost. Adjuvant Atezolizumab 1-year cost in 1st-line was $124,761. Approval was based on improving the disease-free survival using 4 cycles + chemo in resected stage II-IIIA lung (Impower010), Cost was $35,644 cost with $89,117 savings.

In the neoadjuvant space, Nivolumab + chemotherapy improved event-free survival in resectable lung cancer (Forde, 2022) at $31,425, saving $137,423. In early-stage triple negative breast cancer (GeparoNuevo-NCTO2685059), 8-cycle Durvalumab prolonged survival at $45,464. Cemiplimab x 4-cycle in stage II to IV, cutaneous squamous-cell carcinoma resulted in complete pathological response (Gross, 2022) at $35,652 vs 1-year $125,108. In early colorectal cancer (NICHE-2), 2-cycle Nivolumab plus 1- low-dose Ipilimumab followed by surgery resulted in major pathological response at $24,927.

Conclusions: Neoadjuvant Osimertinib and ICI cost a small fraction resulting in significant savings in early-stage lung cancer treatment. Cost advantages in other solid tumors warrant further confirmation.

Keywords: Costs, non-small lung cell cancer, Immune check point inhibitors, Adjuvant, Neoadjuvant

Abbreviations

(**a/m- NSCLC**)	advanced/metastatic non-small lung cancer
(**Atezo**)	Atezolizumab
(**Cemi**)	Cemiplimab
(**Durv**)	Durvalumab
(**DFS**)	Disease-free survival
(**EFS**)	Event-free survival
(**ICI**)	Immune check point inhibitors
(**Ipi**)	Ipilimumab
(**Nivo**)	Nivolumab
(**Pembro**)	Pembrolizumab

Introduction

The immune check point inhibitors (ICI) resulted in 2-year overall survival (OS) of patients with advanced advanced/metastatic non-small lung cancer (a/m- NSCLC)[1]. Costs were equitable with outcomes and dependent on a minimal 50% program death receptor-1 (PD-1) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic alterations. Costs multiplied with extended use. Recent ICI neoadjuvant trials demonstrated improvement in disease-free-survival (DFS), event-free survival (EFS) and/or pathological response in early lung cancer. Osimertinib, antagonist of EGFR, exon 19 deletions or exon 21 (L858R) substitutions, is approved as neoadjuvant, adjuvant and in a/m-NSCLC treatment [2,3]. The current clinical practice is to continue Osimertinib as long as effective and safe. Its 3-year cost was relatively high necessitating placement of $500,000 cap placement [4]. We surveyed various neoadjuvant trials aiming to quantify the cost savings of ICI-and targeted therapy in earlier vs advanced stages of multiple solid tumors.

Methods

Annual 2019-2020 costs of Osimertinib were calculated as monthly optimal dose x 12. The ICI were calculated as dose x mg/m2 or per 80 kg x price x 1-year. Intravenous administration and adverse events treatment costs were not considered.

Results

Pembrolizumab annual cost of $134,796 was the median of 5- evaluated ICI. It is used in 1st-line and as adjuvant at 50% of the 2-year costs [5-7]. Extended therapy by 6-12 month added an extra $67,398-$134,796.

Few cycles of Nivolumab (Nivo) + one-cycle Ipilimumab (Ipi) in 1st-line treatment, with or without platinum-doublet chemotherapy in stage IV/recurrent NSCLC, resulted in positive outcome[8] at $31,425 cost.

The 2-year Osimertinib cost in metastatic lung disease was $496,744, adjuvant 1-year $248,372 and neoadjuvant $31,046.

Assuming 1000 patients in the United States, treated by ICI x 2.5 years, cost would be $336,990,000. Adding 100 patients treated by Osimertinib x 3-years at $74,511,600, the total would mount to essentially unsustainable $411,501,600. In Europe, with a higher populations number, cost would be more than doubled.

Adjuvant Durvalumab (Durv) resulted in long term overall survival (OS) following chemo-radiation therapy in unresectable stage III NSCLC[9] at $148,848 cost. Approval of Atezolizumab (Atezo)[10] was based on improving the disease-free survival (DFS) using 4 cycles + chemo in resected stage II-IIIA non-small lung cancer (NSCLC) (Impower010). Cost was $35,644 and $89,117savings.

Table 1: Annual Drug Costs in Lung Cancer

Drugs	**Annual Cost**
Generic chemo	< $1000
Pembrolizumab, median of 5- ICI	$134,796
Median of 5-target therapy in lung	$228,000
Osimertinib	$248,372
Trade name: Abraxane cost is dependent on dose and use in lung, Breast treatment costs more.	Lung: $56.559

Cost listing were quoted from 2019-2020 and might change annually

Pembrolizumab is currently utilized as adjuvant therapy in resected IIb or IIc melanoma (KEYNOTE-716) [11] and for patients with renal cell carcinoma post nephrectomy [12].

In the neoadjuvant space, Forde et al reported Nivolumab (Nivo) plus chemotherapy improved event-free survival (EVS) in resectable lung cancer (CheckMate 816) [13] at $31,425, saving $137,423.

Rosner et al [14] recently reported that the recurrence-free rates were 60% and OS 80% using 2-cycles neoadjuvant Nivo in patients with stage 1 to IIIA NSCLC 4-weeks before surgery. The cost was $12,996.

Neoadjuvant Durv prolonged survival has been documented in early triple negative breast cancer [15]. at $45,464 cost. In cutaneous squamous cell carcinoma [16,17], Cemiplimab (Cemi) in stage II to IV resulted in complete pathological response at $35, 652 vs annual $125,108 cost. In early colorectal cancer (NICHE-2) [18] Nivo 2-cycle + 1-low dose Ipi followed by surgery resulted in major pathological response at $24,927. Results of neoadjuvant generic chemo [19] and brand drugs [20] were recently reported. Treatment costs in stage IV, adjuvant, and neoadjuvant are shown in Table 2 and diagram.

Table 2: Costs of Adjuvant therapy

Drug	Cost
Adjuvant Durv vs best supportive care in unresectable NSCLC9	$148,007
Atezo in 1st-line[10] was approved in 1st-line and as adjuvant in resectable lung with PDL-1 >1%.	$124,761
Adjuvant Pembro: 1-Renal-Cell carcinoma after nephrectomy[11] 2-Resected stage IIb or IIc melanoma[12]	$134,796

Diagram

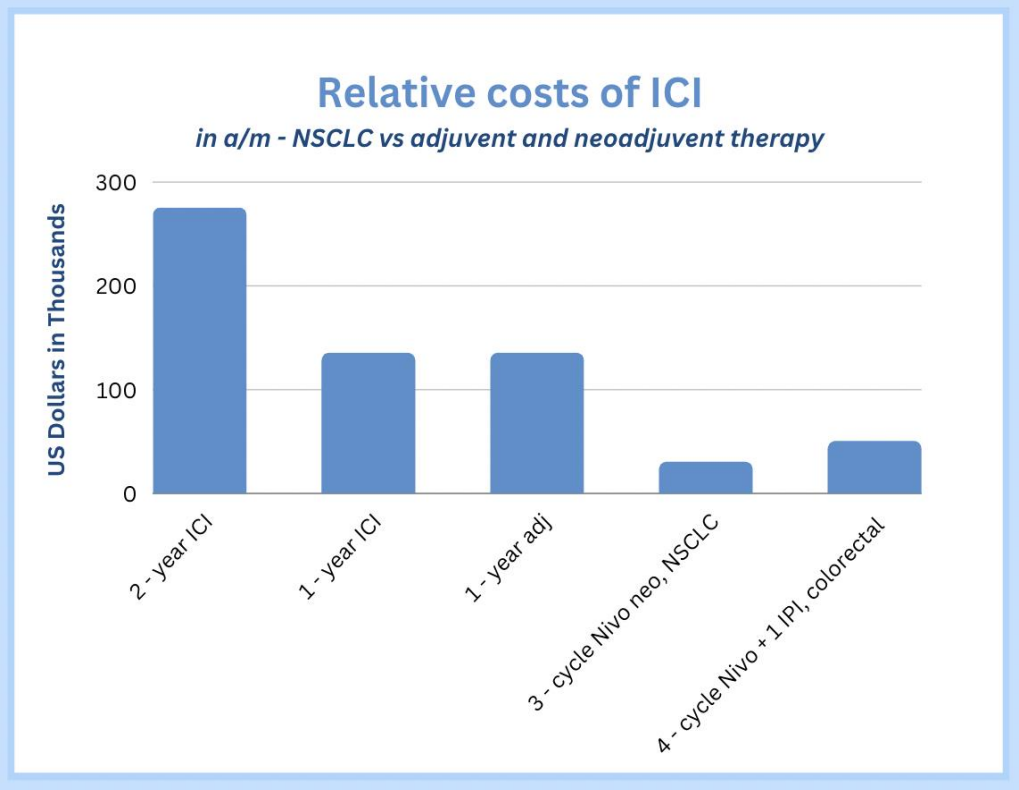

Table 3: Costs of Neoadjuvant therapy

Neoadjuvant Nivo (CheckMate 816) + platinum-based chemo x 3-cycle in resectable lung cancer [13,14].	$31,425
Durv 8-cycle in early-stage triple negative breast cancer (GeparoNuevo-NCTO2685059)[15].	$45,544
Cemi x 4-cycle in stage II to IV, cutaneous squamous-cell carcinoma[16,17].	$35,652
In early colorectal cancer, Nivo-2 cycles + 1-low dose Ipi (NICHE-2)[18]	$24,927
Generic chemo[19]	$1.000
Nab-paclitaxel followed by dose dense Epirubicin/cyclophosphamide in neoadjuvant chemotherapy for refractory metastatic triple negative breast cancer: A phase II study Abraxane, paclitaxel nanoparticle-albumen-bound[20]	$83,330

Discussion

The rising costs of oral anti-cancer cancer have raised serious economic concern [21]. The relatively high costs of IMpower150 using Atezo and Bevacizumab with chemotherapy in 1st-line metastatic non-squamous a/m-NSCLC (22) have drastically curtailed use. It is vital, therefore, to keep prices affordable to promote patients' compliance and ultimately increase sales. Cost, cost effectiveness and value [23-25] are intricately connected and ought not be decoupled. Value, cost effectiveness and safety rate first while cost matters second. Cost is a touchy subject, rarely addressed in medical journals.

There is an ongoing war between the host and cancer. Drug resistance is bound to develop. Newer drugs are continuously being developed. Due to sophisticated synthesis and rarity of eligible patients, costs tend to be high. Such drugs are sometimes sold at marginal gain, but with a demonstrable academic achievement.

Osimertinib was originally planned to treat T790M mutations. It is presently used to prevent the potential development of such mutations. Without Osimertinib, survival was limited to few months. In general, targeted therapy drugs were 1.52 as costly as ICI [4]. The ICI OS is unlikely to be extend beyond 2-year- therapy. Nonetheless, some patients, with their oncologists' approval, opt to prolong treatment of a/m NSCLC by Osimertinib or ICI beyond 2-years for peace of mind and/or fear of recurrence.

It seems that order of administration of therapy significantly alters the outcome. Adjuvant is traditionally administered after surgery whereas radiation and/or chemo prior. Neoadjuvant outcomes seem superior prior to surgery or any other intervention.

Admittedly, neoadjuvant low cost is an expected finding. However, the present work demonstrated that treating 100 United States patients, a small subset of lung cancer; by Osimertinib x 3-years and 1000 by ICI x 2.5 years, would carry a price tag of $411,501,600, an unexpected economic burden. Treatment of other cancers, heart, infectious and other diseases would compound the economic risk, leading to economic collapse of the health system. To put ICI $134,796 cost in comparison, Alzheimer treatment by the newly developed monoclonal antibody costs $26,000 annually. Of note, the expected number of eligible Alzheimer patients is much higher than lung cancer.

Prior to ICI the era, chemotherapy was widely used as adjuvant and neoadjuvant at higher risk of adverse events. This prompted the development of safer paclitaxel nanoparticle albumin-bound at higher cost (Table 1). Chemo is currently presented as payload and shielded by the development of antibody drug conjugates.

Neoadjuvant therapy is still at its early phase of discovery and utilization, with a lot of room for more research and expansion. Nivo + chemotherapy was probably the 1st example of approved neoadjuvant trials in resectable lung cancer [11]. More research is still needed to clarify the role of chemo and PD-L1.

Cost and cap platform [4] and bundling models [26,27] are effective tools to control drug costs. However, they have received minimal endorsements.

Neoadjuvant therapy has been developed by physicians, requiring no governmental approval or pharmaceutical industry participation Their low cost is an added asset since patients at early-stage cancers are usually at their best physical health status and performance. Neoadjuvant use is genrally accepted in lung cancer. In other solid tumors, cost advantages require validation by appropriate modeling for costs with imaging. Nonetheless, the yield of imaging is low in earlier stages. The currently investigated endpoints circulating DNA or minimal residual tumor (MRD) are to be preferred. Such studies ought not delay or constrain use of the early-stage neoadjuvant low-cost advantages.

Adding adjuvant after ICI neoadjuvant therapy [28,29] would significantly increase costs. Creative cost-creative avenues could use adjuvant ICI at shorter intervals of 4-6 cycles rather than 1-full-year. Medical schools need to include in their curriculum a course on drug cost mathematics.

References

1. Guirgis, HM. The Impact of The Immune Check Point on Cost in Lung Cancer: Duration of use. ESMED, July 31, 2022. Medical Research Archives, [online] 10(7). https://doi.org/10.18103/mra. v10i7.2859. ISSN: 2375-1924.
2. Herbest RS, Wu Yi-long, John T, Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non–Small-Cell Lung Cancer: Updated Results from the Phase III Randomized ADAURA Trial, J Clin Oncol, 2023 Jan 31; JCO2202186. doi: 10.1200/JCO.22.02186.
3. Lv C, Fang W, Wu N, et al. Osimertinib as Neoadjuvant Therapy for EGFR-Mutant Resectable Stage II–IIIB Lung Adenocarcinoma. Lung Cancer; 2023 Feb 17; 178,151-156.
4. Guirgis, Helmy M. Target Therapy vs the Immune Check Point Inhibitors in Lung Cancer: Costs and Caps Platform. ESMED February 2023.
5. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small cell lung cancer. N Engl J Med. 372:2018–28, 2015
6. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 375:823–1833, 2016.
7. Herbst RS, Baas P, Kim D-W, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-postive, advanced non-small-cell lung cancer (KEYNOTE -010): A randomised controlled trial. Lancet 387: 1540-1550, 2016.
8. Reck M, Ciuleanu TE, Cobo Dols M, et al. Nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA. J Clin Oncol. 2020;38 (suppl; abs 9501). doi:10. 1200/JCO.2020.38.15.
9. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemo-radiotherapy in stage III NSCLC. N Engl J Med. 2018, 379:2342-2350 DOI:10.1056//NEJMoa1809697
10. Herbst RS, Gluseppe G, de Marinis F, et al, Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. N Engl J Med. 383,1328-1339. 2020.
11. Long GV, Luke JJ, Khattak MA, et al. Pembrolizumab versus placebo as adjuvant therapy in resected IIb or IIc melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double blind, randomized 3 trial. Lancet Oncol, 10,1379-1387, November 2023.
12. Choueiri TK, Piotr, Park SH et al. Pembrolizumab versus placebo as post nephrectomy adjuvant therapy for patients with renal cell carcinoma: Randomized, double-blind, phase III KEYNOTE-564 study. ASCO annual meeting 2019: LBAS, available online August 2022.
13. Forde PM, Spicer J, Lu S et al. Neoadjuvant Nivolumab plus chemotherapy in resectable lung cancer. N Engl J med. April 2022. 10.doi 10.1056/NEJMoa2202170
14. Rosner S. et al. Neoadjuvant 2-Nivo-cycles in patients with stage 1 to IIIA NSCLC 4-weeks before surgery. Clinical cancer research, 2023.
15. Loibi S, Schneeweiss A, Huober J, et al. Neoadjuvant Durvalumab Improves Survival in Early Triple-negative Breast Cancer Independent of Pathological Complete Response. Annal of Oncology, available online 9 August 2022.
16. Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet. 397(10274):592-604, 2021.
17. Gross ND, Miller DM, Khushalani NI et al., Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell carcinoma. N Engl J Med, 387:1557-1568, 2022. DOI: 10.1056/NEJMoa2209813.
18. Chalabi M, et al. Neoadjuvant Nivolumab and Ipilimumab in early-stage resectable colon cancer (NICHE-2). The European Society of Medical Oncology Congress 2022.
19. Hao Z, Parasramka S, Chem Q, et al. Neoadjuvant chemotherapy for resectable metastatic colon cancer in non-academic and academic programs. The Oncologist 28, 48-58, 2023.
20. Liu Y, Fan L, Wang Zhong-Hua, Shao Zhi-Ming, et al. Nab-paclitaxel followed by dose dense Epirubicin/cyclophosphamide in neoadjuvant chemotherapy for triple negative breast cancer: A phase II study. The Oncologist 28, 80-e76, 2023.
21. Li M, Liao K, Pan I-Wen et al. Growing Financial burden from high cost targeted oral anticancer medicines among Medicare beneficiaries with cancer. JCO oncology practice ,18,11,759, 2022.
22. Kowanetz M, Socinski MA, Zou W, et al. IMpower150: Efficacy of atezolizumab (atezo) plus bevacizumab (bev) and chemotherapy (chemo) in 1L metastatic nonsquamous NSCLC

(mNSCLC) across key subgroups. ASCO, Program and abstracts 2018 annual meeting: April 14-18, 2018; Chicago, Illinois. Abstract CT076

23. Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology statement: A framework to assess the value of cancer treatment options. J Clin Oncol. June 22, 2015.
24. Cherny NI, Sullivan R, Dafni U, et al. A standardized, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies. The European Society for Medical Oncology: magnitude of clinical benefit scale (ESM-MCBS): Oxford University Press; 2015.
25. Siegel JE, Weinstein MC, Russell LB, et al. Panel on cost-effectiveness in health and medicine. Recommendations for reporting cost effectiveness analyses. JAMA. 276(16):1339–1341,1996.
26. Guirgis, HM. Costs of extended immune check point inhibitors treatment in advanced/ metastatic lung cancer: Bundling of cost proposal. ASCO May-June 2020 annual meeting, Chicago, abstract 291815.
27. Kline RK. Bundled Payment Models in Oncology: Learning to Think in New Ways DOI: 10.1200/OP.20.00735 JCO Oncology Practice, Published online February 04, 2021, PMID: 33539197.
28. Wakelee HA, Altorki NK, Zhoe C et al. Impower010: Primary results of a III global study of atezolizumab in addition to chemo versus best supportive care in resected IB-IIIA non-small cell lung cancer (NSCLC)(ASCO), Abstract 8500: J Clin Onc.2021:39 (15) (suppl),17- 14, 2021, World Conference om lung cancer (WCLC 2021).
29. Wakelee HA, Liberman M, Kato T, et al: KEYNOTE-671: Randomized, double-blind, phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early-stage NSCLC. 2023 ASCO Annual Meeting. Abstract LBA100. Presented June 3, 2023.