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RESEARCH ARTICLE

Target Therapy vs the Immune Check Point Inhibitors in Lung Cancer: Costs and Caps Platform

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ABSTRACT

The immune check point inhibitors (ICI) and target therapy (TT) Osimertinib (Osi) prolonged survival in advanced/metastatic non-small cell lung cancer (a/m-NSCLC). Costs of ICI were previously investigated (ESMED, July 2022) while TT being overlooked. In 2022, insulin monthly cost was capped at $35 for Medicare patients. We aimed to 1- Attach a $ amount to results of the major relevant TT and ICI clinical studies and weigh their relative costs 2- Reason that utilization threshold caps are necessary to contain cost of extended therapy

Methods: In this prospective observational study, annual costs of the approved and widely used TT were calculated as the monthly optimal dose x 12. Costs of the 5-approved ICI in 1-st-line a/m NSCLC were calculated as mg/m2 or per 80 kg x price x number of cycles.

Results: Median annual 5-TT cost was $228,000 vs 5-ICI of $134,786 at 1.69 ratio. At 10%, estimated coverage of pharmacy and nursing costs, ratio dropped to 1.52. The 1-3-year Osi costs were $248,372-$745,116, Crizotinib $226,308 -$678,924 and Larotrectinib $399,372-$1,198,116. Pembrolizumab were $134,796-$404,388, Atezolizumab $124,761-$374,283 and Cemiplimab $125,108-$375,324.

Applying $500,000 caps, the ICI 3-year costs were all below threshold. TT medium 3-year cost was $684,000, exceeding cap by $184,000, Osi by $245,116 and Crizotinib by $178,924. Larotrectinib 2-3-year costs were higher by $298,744 - $698,116. We reasoned that if 1,000 US patients treated with TT at the annual median, cost mounts to $684,000,000. In Europe, 2,000 patients' cost would be $1,368,000,000.

Conclusions: The median TT/ICI was more costly at 1.52 ratio. Drug costs were determined by the number of re-purchases, the 1st-buy, if followed, was considered a down payment. Cap implementations are necessary to contain costs of extended therapy.

Keywords: Costs, non-small lung cell cancer, Immune check point inhibitors, Osimertinib, Targeted Therapy

Abbreviations: advanced/metastatic non-small lung cancer (a/m-NSCLC), Anaplastic lymphoma kinase (ALK), Atezolizumab (Atezo), Cemiplimab (Cemi), c-ros oncogene 1 (ROSE1), Crizotinib, Durvalumab (Durv), Epidermal growth factor receptor (EGFR), Immune check point inhibitors, (ICI), Larotrectinib (Laro), Neurotrophic Tropomyosin receptor kinases (NTRK), Nivolumab (Nivo), Osimertinib (Osi), Targeted therapy (TT), Pembrolizumab (Pembro).

Introduction

We previously investigated costs of Pembrolizumab (Pembro) (2-5), Atezolizumab (Atezo) (6) and Cemiplimab (Cemi) (7) in non-small cell lung cancer (a/m-NSCLC) with programmed death receptor-1 (PD-1) >50 with no epidermal growth factor receptor (EGFR), or anaplastic lymphoma kinase genomic alterations (ESMED, 2022) (1). The approved 1st-line ICI demonstrated 2-year overall survival (OS). The targeted therapy, Osimertinib (Osi) improved survival as adjuvant and in NSCLC (8,9). In contrast to ICI, TT costs have been overlooked. In 2018, the parent pharmaceutical company voluntarily limited CAR T-cell cost to $450,000. In 2022, insulin monthly cost for Medicare patients was capped at $35. The growing financial burden of oral targeted anticancer medicines on Medicare beneficiaries was recently addressed (10). There is unmet need for coherent drug cost oversight. We aimed in this observational study to 1- Attach a $ amount to results of the major relevant TT and ICI clinical studies and weigh their relative costs 2- Reason that utilization threshold caps are necessary to contain cost of extended therapy.

Methods: This prospective observational study was opened on August 2022 as a follow-up of ESMED July 2022 (1) and modified December 2022. The results were presented in the current manuscript. The annual costs of the approved and widely used TT were calculated as monthly optimal dose x 12. Costs of the 5-approved ICI in 1-st-line a/m NSCLC were calculated as mg/m2 or per 80 kg x price x number of cycles.

Results

The estimated costs of testing and identification of molecular markers aberrations ranged from $1,000-$1,500. At present, PDL1 testing are performed rapidly by in-house immunohistochemistry at a modest cost. The 5- ICI annual cost ranged from Atezo $124,761 to Nivolumab (Nivo) $168,848 (Table 1). The median cost was $134,796, increasing q 6-months by $67,398. Median TT was $228,000, the lowest being Alectinib $198,840 and the highest Larotrectinib (Laro) $399,372. The TT/ICI cost ratio was 1.69. At an estimated 10% coverage of pharmacy and nursing costs, ratio dropped to 1.52. ICI and TT costs are shown in Table 1.

Utilization thresholds caps were initially tested at $450,000-$600,000 range. The $500,000 cap was decided on as optimal to fairly compensate drug costs.

A-ICI: The 2-year ICI costs were previously described as fair and justified. At the annual medium, the 3-year costs of $404,388 were under $500,000 and as such were fully covered (Table 2).

B-TT: Crizo, the 1st generation TT, targets the anaplastic lymphoma kinase (ALK) (11) at an estimated mutation incidence of 3%-10%. The 1-3-year optimal 250 mg cost was $226,308 - $678,924. The $500,000 cap would save $178,924 from the 3-year cost (Table 2).

The 3rd generation Osi, an epidermal growth factor (EGFR) antagonist (8,9), initially designed to treat T790 mutations, is presently prescribed for EGFR aberrations regardless of presence or absence of T790m at an estimated 0.23 hazard ratio (HR). The 1–3-year cost of 80 mg daily was $248,136-$744,408. With 3-year survival confirmed, a 4th-year cost was $992,544. The $500,000 cap would save $492, 544.

Larotrectinib, approved in US and Europe, targets the activated tropomyosin receptor kinase (TRK) 1/2/3 fusion at estimated 1.0% incidence. Laro 1-2-3-year cost of the 100 mg bid dosage was $399,372 - $798,744 - $1,198,116. Applying $500,000 cap would save $298,744 from the 2- and $698,116 from the 3-year cost.

Entrectinib (11) targets the c-ros positive oncogene (ROS1) at 1.0-2.0% rearrangement incidence in a/m-NSCLC. Yearly cost of 600 mg once daily dosage was $210,528.

Based on 2021 US census of 332,278,200 and looking ahead, if 1,000 US TT-treated patients, at $228,000 median cost, the 3-year price tag would be $684,000,000. In 2020 Europe census of 747,636,045 (12), treatment cost of 2,000 patients mounts to $1,368,000,000.

Table 1: The 1–3-year costs of ICI vs TT

Cost	Pembro	Atezo	Cemi	Crizo	Osi	Laro
1-year	$134,796	$124,761	$125,108	$226,308	$248,372	$399,372
2-year	$269,592	$249,522	$250,216	$452,616	$496,744	$798,744
2.5-year	$336,990	$311,903	$312,770	$565,770	$620,930	$998,430
3-year	$404,388	$374,283	$375,324	$678,924	$745,116	$1,198,116

Table 2: Cap Implementation at $500,000 Limit

Drug/Class all approved	Cost	Result
ICI	3-year $404,388	< $95,612
Nivo♣	3-year $506,544	> $6,544♣
TT♣♣ median	1-year $228,000	
	3-year $684,000	>$184,000
Osi	3-year $744,408	>$244,408
	4-year $992,544	>$492,544
Laro,	2-year $798,744	>$298,744
	3-year $1,198,116	>$698,116
Entrec	3-year $631,584	>$131,584

Nivo♣3-year cost was $506,544, the only ICI above the $500.000 Applying caps would save $6,544.
All the class members of TT♣♣ end up in "tinib" and are sometimes referred to as "nibs".

Discussion

Lung cancer is the most common cancer globally, claiming an estimated 1.8 million lives in 2018. It is the leading cause of cancer-related deaths in Europe, responsible for approximately 388,000 deaths in 2018 (12). In US, lung cancer is the second most common, responsible for an annual 130,180 death. During 2020 Covid epidemic, the Centers for Medicare & Medicaid Services (CMS) reported that the health care spending in the US topped $4 trillion with prescription drugs were probably and partly responsible for such high expenditure (13). Our primary focus was on costs since value and cost effectiveness (14-16) have been customarily scrutinized by drug companies and academia prior to approval and marketing. In the business world, the benefit/cost ratio is widely used, a testimonial of the intimate relationship between benefit and cost.

ICI: The discovery of PD-1 was a milestone in the application of monotherapy ICI in 2015. At least 50% PDL-1 is required for effectiveness with the higher the PDL-1, the higher the response. The OS of all approved ICI was documented at 2-year. Some patients/oncologists prefer, for peace of mind, to continue treatment. Longer survival beyond 2-years, though, has not yet been documented and duration of therapy remains undefined. Of interest, cost of Pembro, the 1st ICI introduced, was like the medium 5 ICI of $134,798. Other ICI followed with costs not significantly different from Pembro.

TT: Identification of molecular aberrations paved the way towards TT use. At present, there are 9 molecular markers, the number is still counting. In the current investigation, costs of 5 drivers were analyzed. HER2 was not addressed since it was previously investigated. Ret fusion was also extensively studied by Subbiah et al (17). Its prevalence in NSCLC is 1-2% but relatively high in papillary thyroid and salivary gland cancer.

The EGFR incidence in lung cancer is associated with adenocarcinoma histology and varies with smoking. It is 15% in the US, 10-15% and Europe, and 40% in Asia. In California, Orange County US, EGFR incidence is 20% compared with 15% in Los Angeles (LA), 50-60 miles apart. The LA area has a higher number and percentage of smokers.

Larotrectinib (Laro) had the highest drug cost analyzed cost and probably the most expensive drug ever marketed. The incidence of NTRK 1/2/3 aberrations is <1.0%. Coupled with the small number of potential candidate patients render Laro high cost understandable. Discovers of such rare aberrations are rather pioneers, than profiteers

Cost bundling and/or caps on utilization thresholds, so far, received limited enthusiasm in the US. Previous investigations (18-20) have set the stage for acceptable caps. Two precedents ignited interest in caps applications: namely CAR T-cell by the pharmaceutical company and the insulin-affordable act. The most difficult hurdle in cap use has been the inability to satisfy both consumers and drug companies.

Based on a modest estimate of 1000 US patients, the 3-year TT costs were $684,000,000 and 2000 European were $1,368,000,000. Such costs in US and Europe are unsustainable in the long run, making cap applications necessary.

The number of potent TT has increased over the last few years. Many patients with ROS1+ experienced intracranial response during Entrectinib treatment (11). Alectinib was more potent versus Crizo in untreated ALK-positive non-small-cell lung (21). Lorlatinib improved the DFS significantly longer

than Crizo in ALK+ metastatic NSCLC (22). Data on Lorlatrectini, other than approval, are scarce.

Parent pharmaceutical companies could declare cost losses as tax-deductible charity, thus securing benefits for the industry, the overall economy, government, and patients.

The detailed methodology and accounting could render the cost platform suited for applications in other cancers and drugs. Nonetheless, it is important to draw the inter-play between drug cost, outcome, and number of candidate patients. In our investigation, ICI results demonstrated OS and TT survival. Lecanemab, an antibody-amyloid antibody, approved early 2023 by the FDA, did not improve either, but slowed progression of early Alzheimer disease and mild cognitive impairment. The twice-monthly infusion yearly cost was $26,000, as compared with $134,848 ICI.

In summary, the current TT cost coverage and reimbursement are neither workable nor sustainable in the long run. The high cost of extended therapy is a wake-up call to act. Caps seems necessary to restore and preserve the national and global economy.

References

1-Guirgis HM. The Impact of The Immune Check Point on Cost in Lung Cancer: Duration of use. ESMED, July 200,https://doi.org/10.18103/mra.v10i7.2859

2-Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small cell lung cancer. N Engl J Med. 2015; 372:2018–28.

3-Garon EB, et al. Pembrolizumab monotherapy 5-year data from KEYNOTE-001 in patients with advanced non–small cell lung cancer (NSCLC), ASCO annual meeting, Chicago, May 2019 (Abstract LBA9015)

4- Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small lung cancer. N Engl J med. 2016: 375:823-833.

5- Reck M, Rodriguez-Abreu D. Updated analysis of KEYNOTE-024: Pembrolizumab vs. platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. JCO 37, 7, 537-546, 2019.

6-Herbst RS, Gluseppe G, de Marinis F, et al, Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. NEJM. 2020, 383,1328-1339.

7-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

8- Chihara Y, Takeda T, Goto Y, et al. Osimertinib as first-line treatment for EGFR mutation-positive advanced NSCLC in elderly patients. The oncologist. 27, no 11, November 2022

9- Wu Yi-L, Tsuboi M, He J, et al. Osimertinib as adjuvant therapy in patients with resected EGFRm stage IB-IIIA NSCLC: updated results from ADAURA. Presented at: ESMO Congress 2022; September 9-13, 2022; Paris, France.

10- 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

11- OU Si, Zhu VW. CNS metastasis in ROS1 +NSCLC: an urgent call to action, to understand, and to overcome lung cancer. 130, 201-207; 2019

12- World Health Organization- International Agency for Research on Cancer. World Fact Sheet. Available at https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf. Accessed May 2020.

13-Hartman M, et al. Health Aff. (Millwood). 2021; doi:10.1377/hlthaff.2021.01763. The Centers for Medicare & Medicaid Services (CMS). National Health Care Spending In 2020: Growth Driven By Federal Spending In Response To The COVID-19 Pandemic.

14-Schnipper LE, Davidson NE, Wollins DS, et al. Updating the American Society of Clinical Oncology Value Framework: Revisions and reflections in response to comments Received. J Clin Oncol. May 31,2016. 18-

15-Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol. 2017;28(10):2340- 2366. doi:10.1093/annonc/mdx310PubMedGoogle

16-Siegel JE, Weinstein MC, Russell LB, et al. Panel on cost-effectiveness in health and medicine. Recommendations for reporting cost effectiveness analyses. JAMA. 1996;276(16):1339–1341

17-Subbiah V et al. Prevalence of RET fusion in cancer. J Clin Onc 2020,38: 1209-1221

18- Guirgis, HM. Drug Costs vs. Probability of Survival in Lung Cancer, Impact of Dosage,

Duration, and Immune Check Point Inhibitors Combinations. JCP 5, 32-36, 2019. Doi:10.25270/jcp.2019.06.00083

19-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

20-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

21-Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Eng/ J Med. 2017; 377:829-838.

22-Solomon BJ, Besse B, Bauer TM, et al: Lorlatinib in patients with ALK-positive non-small-cell lung cancer: Results from a global phase 2 study. Lancet Oncol 19: 1654-1667, 2018