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RESEARCH ARTICLE

The Impact of The Immune Check Point on Cost in Lung Cancer: Duration of use

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ABSTRACT

Background: Monotherapy and combinations of Pembrolizumab (Pembro), Atezolizumab (Atezo) and Cemiplimab (Cemi), prolonged overall survival (OS) in advanced/metastatic non-small cell lung cancer (a/m NSCLC). Pembro demonstrated 5-year OS gain. The duration of therapy of the immune check point inhibitors (ICI) has not been defined. One-year adjuvant Durvalumab (Durv) and Atezo significantly extended OS. Neoadjuvant few cycles resulted in positive outcomes. ICI costs are relatively expensive and multiply with further use with no containment on sight. The 2019 CAR-T cost was limited to $450,000. There are unmet needs for coherent drug cost policies. We aimed 1- Explore the factors which impact ICI costs in lung cancer 2- Navigate cost-saving strategy based on generics, therapy duration 3- Explore the possibility whether adjuvant and neoadjuvant treatment impact costs

Methods: Annual drug prices were quoted and calculated. Utilization thresholds were set for ICI monotherapy at $450,000 and combinations at $550,000.

Results: Estimated annual Pemetrexed (Peme) costs were $113,793, generic chemicals < $1,000 and Bevacizumab (Bev) $150,126. The mean of 6 ICI was $148,000. Pembro 2-year costs were $334,652, below the the proposed $450,000 thresolds. The 3-year costs of $501,978 and the 5-year $836,630 were above $450,000. Atezo + Bev+ Peme combination had the highest 2-year $722,977 costs, above $550,000. There was no significant difference in cost between Atezo + Peme $422,725, Pembro + Peme $448,445 and Cemi + Peme $425,385. These combinations were below the $550,000 threshold. Costs decreased using generics by 25%. Extending ICI use by 6-12 months increased combination costs by 25-50%. Adjuvant 1-year Durv costs were $148,013 and Atezo $154,446, half the 2-year. Using response rates, cost of 2-4 cycles of neoadjuvant Nivolumab (Nivo) were only $25,000 - $50,000.

Conclusion: Generics, limited ICI duration, utilization thresholds and neoadjuvant therapy significantly reduced drug costs. Neoadjuvant therapy had the highest impact on cost reduction.

Keywords: Immune check point inhibitors, ICI; Costs; OS; HR, non-small lung cancer; NSLC; Cemiplimab; Pembrolizumab; Pemetrexed; Atezolizumab; Nivolumab; Ipilimumab

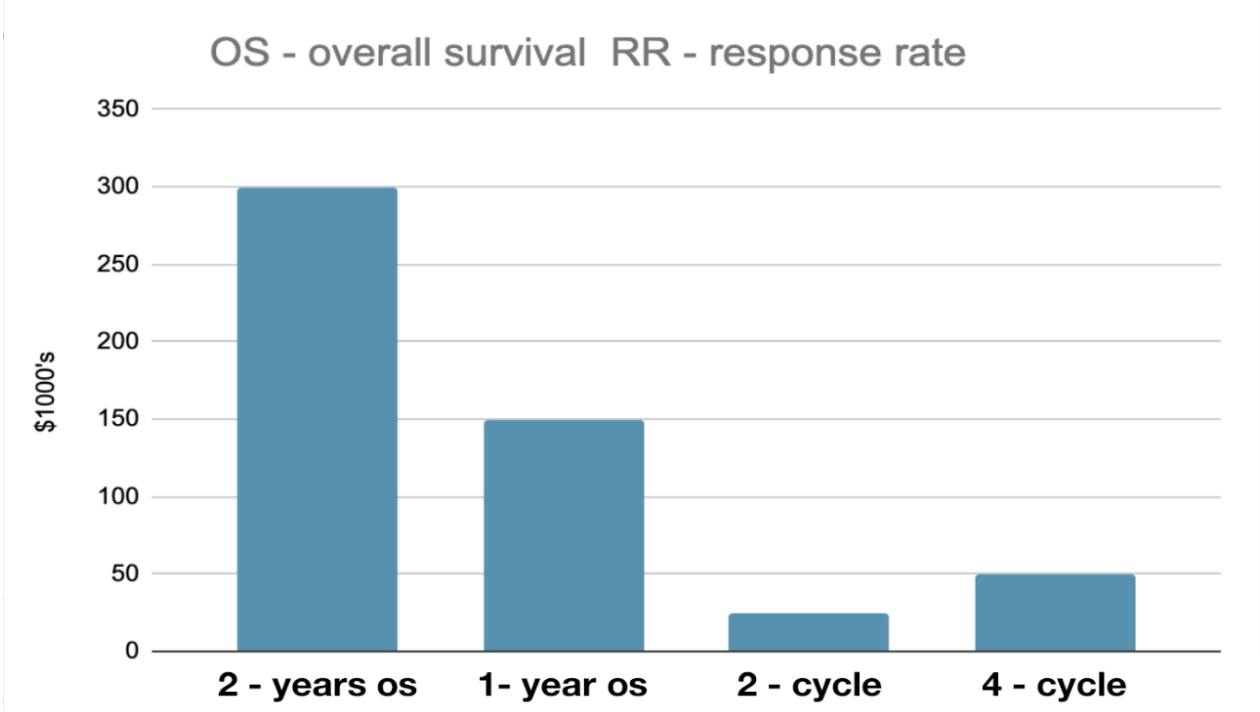
Abbreviations: Advanced/metastatic non-small cell lung cancer (a/m-NSCLC), Adverse events (AEs), Atezolizumab (Atezo), Bevacizumab (Bev), Biosimilar (Bio), Cemiplimab (Cemi), Cytotoxic T-lymphocyte -associated antigen 4 (CTLA), Durvalumab (Durv), Hazard Ratio (HR), Nivolumab (Nivo), Immune check point inhibitors (ICI), Ipilimumab (Ipi), Pembrolizumab (Pembro), Pemetrexed (Peme), Programmed death receptor-1 (PD-1). Programmed death receptor-ligand-1 (PD-L1).

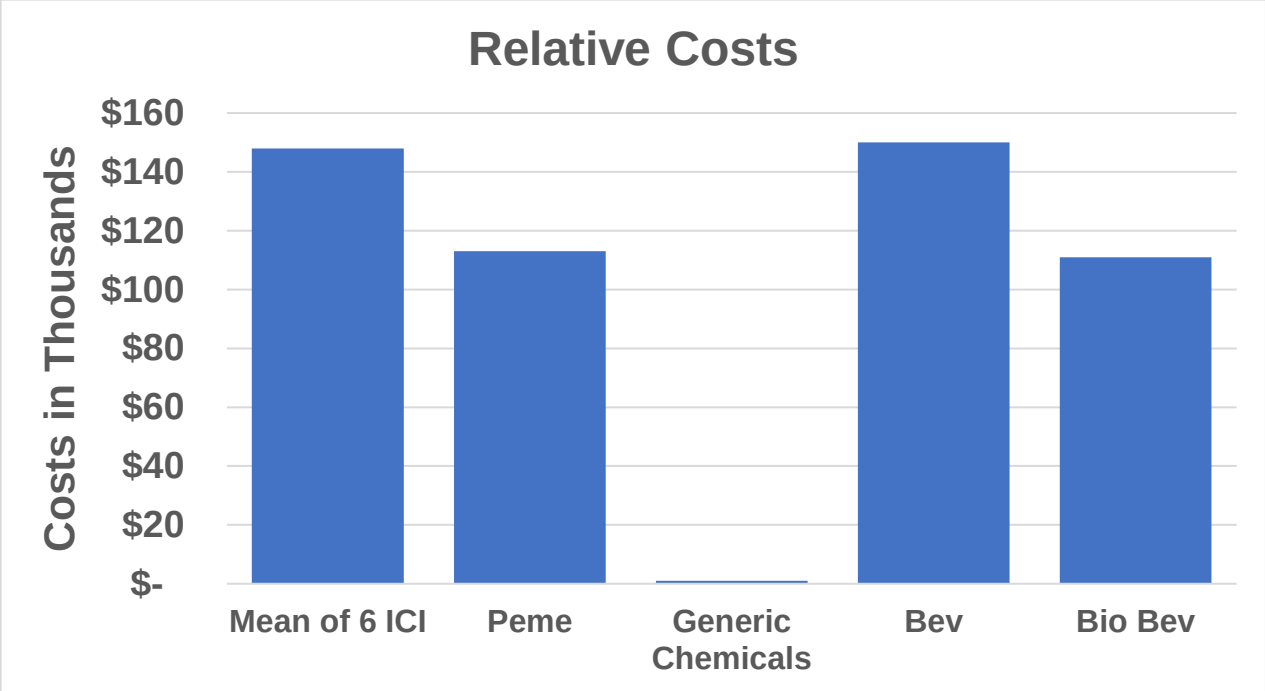
Introduction

The 1st immune check point inhibitors (ICI) Pembrolizumab (Pembro) was first introduced in 2016. It significantly prolonged the overall survival (OS) in 1st line advanced/metastatic non-small cell lung cancer (a/m NSCLC) with high programmed death receptor-1 (PD-L1), lacking epidermal growth factors (EGFR) and anaplastic lymphoma kinase (ALK) genomic aberrations (1). Survival and 5-year OS were further confirmed (2-5). Duration of therapy after 2-years has not been defined. Atezolizumab (Atezo) (6) and Cemiplimab (Cemi) (7) later demonstrated OS. Chemo-drugs in combinations with Pembro (8), Atezo (9-11), and Cemi (12) showed effectiveness regardless of PD-L1. Nivolumab/Ipilimumab (Nivo/Ipi), with and without chemo, have also shown OS gain (13,14). One-year adjuvant Durvalumab (Durv) (15) and Atezo significantly prolonged OS (16). Value (18-21) and cost effectiveness (22-23) were extensively studied. However, drug costs have rarely been scrutinized except by the press, media, and few scattered reports (24). ICI costs are rather expensive, multiplying with further therapy. Two precedents were identified to cap drug costs. CAR-T cell therapy 2019 cost was contained at $450,000 (17). The affordable Insulin bill 6833 limiting insulin prices at $35 per month was approved by the U.S. House of Representatives. There are unmet needs for coherent policies to contain the rising of already unaffordable drug costs. We aimed 1- Explore the factors which impact ICI costs in various lung cancer stages 2-Navigate cost-saving strategies based on generics, ICI duration and applications of utilization thresholds 3- Explore using adjuvant and neoadjuvant therapy as cost- containing approaches.

Methods

Annual drug 2019-2021 prices were quoted. Cost of injected drugs was calculated as the dose x mg/m2 or per body weight x purchase price x planned number of cycles for the entire treatment. Oral medications were calculated as daily dose x 28-30 days x planned number of cycles. Utilization thresholds were set at $450,000 for ICI monotherapy and $550,000 for combinations.





Results

A-Monotherapy: The estimated annual costs of the 3 approved ICI in 1st-line a/m NSCLC in PD-L1 >50% were Pembro $167,326, Atezo $154,446 and Cemi $154,896. The mean cost of 6 ICI was $148,431. Pemetrexed (Peme) was $113,793 and generic chemical drugs < $1,000. Bev cost was $150,126 and Bio-similar Bev $111,566, 0.74 the cost of Bev (Graph 1).

Table Graph 1: **Approximate Relative Drug Costs**

Mean of 6 ICI	$148,000
Peme	S113,000
Generic Chemicals	<$1,000
Bev	$150,000
Bio Bev	$111,000

The reported OS gain of Pembro in > 50% PD-L1, was 201-day at HR of 0.54-0.60. The 2-year costs were $334,652, not significantly different from the 35 cycles. Use of a third-year increased costs to $501,978, $51,078 above the $450,000 proposed threshold. The $51,978 savings multiplied with further use. With the documentation of 5-year OS, cost of continuous Pembro use would be $836,630 (Table (1). Treatment of only 1000 patients in the US would mount to $836,630,000.

Atezo 2-year costs were $308,892 at reported 141 OS days and 0.79 HR (6). Cemi cost was $309,782 at reported 240 days OS and O.68 HR (7). A %50 PD-L1 is required for ICI effectiveness and the higher the PD-L1 was, the higher the response. There was no significant cost difference between the 3 ICI, all were below $450,000. Keeping in mind that each study had its own specified population and set conditions, it would be ill-advised to compare one with another (Table 1).

Surgery is the current treatment of early lung cancer, still standing the test of time. Unfortunately, use of adjuvant chemotherapy following surgery resulted in only 5% 5-year OS. The 1-year adjuvant Durv in unresectable stage III NSCLC (15) after chemo-radiation demonstrated 363 -day OS at 0.53 HR. Initial and later reports of Atezo following chemotherapy in resected IB-IIIA (16) demonstrated significant outcome benefit. Durv cost was $148,013 and Atezo $154,446, essentially half the 2-year costs.

B-Combinations of ICI have the advantage over monotherapy of effectiveness regardless of PD-L1 levels. The $450,000 threshold was raised to $550,000 to cover the $100,000 cost of patent chemo-drugs. Peme annual price was $113,793, 0.68 that of Pembro.

Table 1: ICI Monotherapy Costs at 3-year or $450,000 Thresholds

Drugs	Costs	At $450,000 Threshold
Pembro, 200 mg q3 weeks, PD-L1 > 50%, sq. and non-sq. vs chemo, KEYNOTE 1& 024, Updated analysis Hazard ratio (HR) 0.60 (2-5)	2-year $334,652 3-year $501,978 4-year $669,304 5-year $836,630	below by $115,348 over by $51,978 over by $219,304 over by $386,630
Atezo, 1200 mg q3 weeks, high PDL1, sq & non-sq, vs chemo, HR 0.59, EMPOWER 110 Trial (6)	2-year $308,892	below by $141,108
Cemi, 350mg q3 weeks, PD-L1 >50%, vs, chemo, HR 0.68 EMPOWER-Lung Trial (7)	2-year $309,782	below by $140,218

Peme-platin combination had the lowest cost. The OS was modest at 87-day OS and HR 0.78 (25). There was no significant cost difference between Pembro + Peme (8) at $448,445, Atezo + Peme (11) $422,725 and Cemi + Peme (12) $423,585, all below the $550,000. All the 2-year combination costs of Pembro-Peme (8), Atezo+Bev+Peme, Atezo+Bio-Bev+Peme, Atezo+chemo (9-11), Cemi-chemo (12) were shown in Table 2. Costs of Nivo/Ipi and Nivo/Ipi + 2-Peme cycles (13,14) hovered around $550,000. The Nivo/Ipi combination is unique being chemo-free and effective across multiple cancers.

Atezo+Bev+Peme demonstrated the highest combination cost of $722,977. Bev Bio-similar decreased costs to $645,857 by 11%. Using generics, costs of all combinations dropped by Peme cost of $113,793. Extending use beyond 2-years by 6-12 months increased costs by 25-50%. After 6 more months, Pembro-Peme 2-year $334,652 cost rose up to $418,315 and the 3-year to $669,304.

In Table 3, the 2-Year costs of ICI combinations were weighed relative to Pembro Peme. Atezo+Bev+Peme had the highest 1.61 weight. Combinations of Pembro-, Atezo- and Cemi- with generics were lower at 0.69 - 0.75.

Table 2: Combination Costs

Peme 500mg/m2 iv q 3 weeks+ Platin, non-squamous, HR 0.78, PARAMOUNT (25)	1-year $113,793 2-year $227,586
2-year Pembro with one-year Pemetrexed (Peme) + platin, irrespective of PDL-1, non-squamous, HR 0.49 (8)	2-year $448,445 3-year $615,771
Atezo + Bevacizumab (Bev) + Peme vs. Bev + chemo, non-sq, intent to treat, IMPOWER 150, including EGFR and ALK alterations (HR 0.78) (9-10),	Atezo 2 year $308,932 Bev 2 year $300,252 Peme 1 year $113,793 **Total $722,977**
Atezo + Bev biosimilar (Bio-Bev) + Peme	**Total $645,857**
Cemi q3w x108 weeks + chemo x 4 cycles, sq and non-sq, non-candidates for definitive chemoradiation, regardless of PD-L1 expression, negative for ALK, EGFR and ROS1 mutations, HR 0.71, (EMPOWER-Lung 3) (12)	2-year $309,782
Chemo-free Nivo 240 mg q 2 weeks + Ipi 1 mg/Kg q 6 weeks vs. chemo x 4 cycles, stage IV or recurrent, maintenance up to 2 years, (HR 0.64) (CheckMate 227) (13)	2-year Nivo $337,896 2-year Ipi $206,800 **Total $544,696**
Nivo 240mg q 2 weeks + Ipi 1 mg/Kg q 6 weeks + Peme x 2 cycles vs. chemo x 4 cycles, stage IV or recurrent, maintenance up to 2 years, all histology, regardless of PD-L1, HR (0.66) (CheckMate 9-LA (14)	Peme x 2 cycles $13,130 **Total $557,826**

Table 3: The 2-year costs of ICI Combinations Relative to Pembro-Peme

Drugs	**Cost Relative to Pembro-Peme**
Pembro+Peme (8) Pembro+generics	1.0 0.75
Atezo+Bev+Peme (9,10)	1.61
Atezo+ Blo-similar Bev+Peme	1.44
Atezo+Peme (11)	0.94
Atezo+generics	0.73
Cemi+Peme (12)	0.95
Cemi+generics	0.69
Chemo-free- Nivo/Ipi (13)	1.21
Nivo/Ipi+ 2-Peme cycles (14)	1.24

In graph 2, ICI costs were depicted in various stage of lung cancer. Costs were the highest in a/m NSCLC, twice the adjuvant therapy. Neoadjuvant therapy using 2-4 cycles resulted in positive responses in early lung cancer stages (26-28) at the minimal costs of $25,000 - $50,000.

Discussion

High drug costs disproportionately target the financially- disadvantaged and poor patients. They constrain sales worldwide, cutting down company profits. Cost is a sensitive, complicated, and unpopular subject to tackle. Considering the years of ICI use, costs are expensive. If costs are unaffordable value is regrettably worthless. Admittedly, synthesis is technically complicated, time consuming and costly. With no guarantee of success, it is fair and imperative that the pharmaceutical companies retrieve their investments in such highly competitive business. Recognizing the delicate balance between worth and fairness, careful deliberation and years of investigation were given to the proposed thresholds. Success of the American pharmaceutical industry is vital to the health of the national economy. Two precedents of using caps were cited: 1- The CAR-T cell therapy 2019 cost was contained at $450,000 (17). 2-The affordable Insulin bill 6833 capping the monthly price of insulin to $35 became an act, being recently approved by the U.S. House of Representatives.

In the present work, posted drug prices constituted the sole basis of drug comparison. ICI value and cost effectiveness have been extensively studied by the parent drug companies. There was no need for further unnecessary investigations. Furthermore, the OS and HR of the monotherapy and combination therapies have been well documented in all the cited reports (1-16). The observations that 20% of Pembro-treated patients in 1st-line a/m NSCLC with PDL1 > 50% survived 5 years would justify the 2-year costs of $334,652. Pembro, the first ICI synthesized, has, so far, the distinctive advantage of long-term OS benefit. Its 3-year costs were $501,978, above the proposed $450,000. Costs multiplied with further use. Treatment of 1,000 patients, a small subset of a/m NSCLC, would be a heavy burden for any economy to bear. Atezo 2-year costs (6) were $308,892 and Cemi, (7) $309,782. There was no significant cost difference between the 3 ICI. They all fell below $450,000. Costs could play a differentiating factor between the 3 ICI, only if a significant 15- 20% reduction could be negotiated. At present, there is no head-to-head outcome and/or safety comparison between one ICI and another. It is doubtful that such study would be undertaken in the future.

The question remains whether therapy beyond 2-years is required. Would 6-months, rather than one full year, be sufficient? Further therapy is generally needed to for maintenance or consolidation. However, therapy duration having not yet been defined.

Peme, an inhibitor of the folate-dependent enzyme first reported in 2013 (25), is expected to lose its patency in the ensuing few years. Peme annual price was $113,793, with doubling if used for 2-years. The case of Peme trade name vs generic has been in court for the last few years. There would be a steep drop in Peme cost and a sharp rise in use on turning generic, The ICI class, with its longer duration of action, has essentially replaced Peme in 1st-line a/m NSCLC in

most of the affluent nations. The 2-year Peme use makes it less attractive.

With more information emerging, use of adjuvant therapy is at present widely accepted. The one-year cost of 50% of the 2-year seemed reasonable.

In ICI-combination therapy, the 2-year Atezo+Bev+Peme was the most expensive at $722,977, far above the $550,00. Its Bev Bio-similar regime was $645,857, only lower by 11%. It seemed that synthesis of ICI, whether originals or Bio-similar is complex and demanding. It would be self-inflicted wound to incur high costs considering the availability of cheaper combinations. Costs of Nivo/Ipi+2-Peme cycles were more expensive than Nivo/Ipi with $13,130, at approximate $550,000 costs. Pempro+Peme and Atezo+Peme and Cemi-Peme costs were significantly less expensive using generics. Unfortunately, the role of generics is presently being threatened by shortage and supply route disruptions.

The clearest cost-saving evidence was the use of neoadjuvant Nivo. At a cost fraction, few 2-4 cycles, with or without chemo (26,27) showed positive outcome. The results of the CheckMate 816 study (NCT02998528) demonstrated statistically significant improvement in event-free survival with OS forthcoming. The Federal Drug Administration (FDA) approved nivolumab plus chemotherapy vs chemotherapy alone among patients with early NSCLC (28). Circulating DNA biomarker is presently being explored to signal tumor clearance (29).

Cost divergence in drug prices between US and Germany was previously noted (30,31) with prices tending generally to be higher in the US where some drugs first originated. Cost reforms (32,33) have not been widely accepted and are urgently needed at present. Application of utilization thresholds would lower costs and help consumers. Drug companies would also benefit through wider global distributions and sales.

In summary, considering the well-documented OS and HR, the 2-year costs of the 3 ICI investigated namely Pembro, Atezo and Cemi seemed fair and reasonable in 1st-line a/m NSCLC with PDL1 > 50%. Costs fell below the proposed $450,000 monotherapy threshold. Beyond 2-years, costs multiplied with further use. The economic burden was and is too heavy to bear. The adoption of utilization threshold strategy deemed necessary. Combination therapy were set at $550,000 threshold to account for the added patent costs. Atezo+Bev+Peme demonstrated the highest combination cost, far above the $550,00. Bev Bio-similar decreased costs by only 11%. Pempro+Peme and Atezo+Peme and Cemi-Peme were lower and dropped further using generics. Extending combination use beyond 2-years by 6-12 months increased costs by 25-50%. Costs of adjuvant therapy by Durv or Atezo was half the 2-year ICI costs, justifying the current use. In the neo-adjuvant space, when patients are thought to have the best performance status and lowest cancer load, few cycles ICI resulted in event-free survival at minimal costs. With the newer approaches of adding a certain number of adjuvant ICI cycles after the 2-4 cycles of neoadjuvant, still cost would remain a bargain. Finally, while limited duration use, generics, and utilization thresholds significantly reduced costs, neoadjuvant therapy had the most cost cutting impact. Cost containment still needs to be a shared responsibility between dug companies, medical scientists and practicing physicians.

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