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Restricted mean survival time in advanced non-small cell lung cancer treated with immune checkpoint inhibitors

L. DI SPAZIO[1], L. CANCANELLI[2], M. RIVANO[3], M. CHIUMENTE[4], D. MENGATO[5], A. MESSORI[6]

[1]Hospital Pharmacy Department, S. Chiara Hospital, Trento, Italy
[2]Hospital Pharmacy Department, Azienda Ulss 2 Marca Trevigiana, Treviso, Italy
[3]Clinical Oncology Pharmacy Department, A. Businco Hospital, Cagliari, Italy
[4]Scientific Direction, Italian Society for Clinical Pharmacy and Therapeutics, Milan, Italy
[5]Hospital Pharmacy Department, Bolzano General Hospital, Bolzano, Italy
[6]HTA Unit, Regional Health Service, Firenze, Italy

Abstract. – OBJECTIVE: The purpose of this study was to review the effectiveness of immune checkpoint inhibitors (ICIs) in the first-line treatment of advanced non-small cell lung carcinoma with wild-type epidermal grow factor receptor (EGFR) or anaplastic lymphoma kinase.

MATERIALS AND METHODS: After a standard literature search, we identified all randomized studies published on this issue. Our first inclusion criterion was the use of pembrolizumab, nivolumab, atezolizumab or durvalumab in the treatment arm versus chemotherapy in the control arm. The second criterion was the availability of information on overall survival at 2 years. The restricted mean survival time (RMST) was used to analyze the survival curves and rank the treatments.

RESULTS: From the eligible studies, we selected 5 randomized trials that met our inclusion criteria. These trials studied a total of 11 cohorts of patients in whom the treatment arm received ICI as monotherapy (n=3) or in combination with either chemotherapy (n=2) or other monoclonal antibodies (n=1). All the control groups (n=5) received chemotherapy. Pembrolizumab (alone or in combination) showed improvement in overall survival compared with controls, but with borderline statistical significance. Nivolumab, atezolizumab and durvalumab failed to demonstrate any survival advantage. Overall, the RMSTs provided more conservative results than those previously reported using the hazard ratio. In comparing the values of RMST across treatments, pembrolizumab combined with chemotherapy ranked first.

CONCLUSIONS: Our results summarized the efficacy of these treatments and showed that only pembrolizumab can have a role as the first-line treatment of NSCLC. These findings are at variance with those previously reported using the hazard ratio as the outcome measure.

Key Words:
Advanced non-small cell lung carcinoma (NSCLC), Immune checkpoint inhibitors, Restricted mean survival time (RMST), Survival analysis.

Introduction

Advanced non-small cell lung carcinoma (NSCLC) is a disease associated with poor prognosis. Globally, it is the leading cause of cancer-related death[1]. First-line platinum-based combination chemotherapy is considered the standard of care for untreated advanced NSCLC. However, chemotherapy is associated with modest efficacy but substantial toxicity[2,3].

For advanced NSCLC with wild-type epidermal grow factor receptor (EGFR) or anaplastic lymphoma kinase (ALK), immune checkpoint inhibitors (ICIs), that target the programmed cell death 1 ligand 1 [PDL-1] and programmed cell death 1 [PD-1] pathways, have recently proved to be more effective and safe than chemotherapy[4-17].

Liu et al[18] performed a network meta-analysis (NMA) to comparatively assess the efficacy and safety of first-line ICIs for advanced NSCLC with wild-type EGFR or ALK. NMA is a standard methodological tool for indirectly comparing different treatments; the hazard ratio (HR) is the outcome measure commonly employed in these analyses.

In the past years, a growing literature[19,20] has emerged emphasizing important limitations of the HR. While the HR is based on proportional hazards, this assumption is violated in many sur-

Corresponding Author: Andrea Messori, PharmD; e-mail: andrea.messori.it@gmail.com

vival data sets, particularly in oncology. Using the restricted mean survival time (RMST) is the methodological solution proposed to solve this problem[19,20]. The RMST can now be considered a new standard for handling survival data[21-29].

In this context, a traditional narrative review combined with the estimation of multiple RMST values can replace the role of NMA and, at the same time, generate more reliable results than a NMA owing to the methodological advantages of the RMST over the HR. The RMST can be used for making comparisons and keeps the ability to rank the effectiveness of treatments under comparison[9,30,31].

In the present report, we used the RMST to comparatively analyze the ICIs that have thus far been studied in advanced NSCLC. The time horizon of our analysis was set at 2 years. The endpoint was overall survival (OS).

Our objective was to show that in the context of a narrative review, the RMST can be an efficient though simple tool to make indirect comparisons and to obtain survival results methodologically better than those deriving from HR.

Materials and Methods

Study Design

Our study was aimed at evaluating the outcomes at 2 years (or more) in patients with advanced NSCLC receiving first-line treatment with ICIs (alone or in combination with chemotherapy). Only randomized studies were eligible. We searched PubMed using the keywords "pembrolizumab OR nivolumab OR atezolizumab OR durvalumab" in combination with a PubMed filter on "randomized controlled trials". From these studies, we selected the subgroup that met the criterion of reporting OS at 2 years or more. Our analysis was based on RMST as the outcome parameter determined from the graphs of survival curves. Our purpose was to present a narrative overview of the available evidence supported by the estimation of RMST.

Analysis of the Evidence

A standard literature search (date of the search: 7 September 2020) was employed to identify pertinent papers. Then, we estimated the RMST from all survival curves, performed the comparisons on effectiveness between cohorts and determined the rankings across treatments.

Estimation of RMSTs and Statistical Analysis

We retrieved the published graphs of OS curves, and for each curve, we analyzed the survival percentage-vs-time data points with a digitizer (WebPlotDigitizer https://automeris.io/WebPlotDigitizer). Each survival curve was truncated ("restricted") up to the last time point in the follow-up (the so-called "milestone" or t*). Thereafter, to calculate RMST with its 95% confidence interval (CI), we employed the "survRM2" statistical package in the R platform[33] which is the method most widely used for this purpose. This package requires that the graphs of the Kaplan-Meier curve are converted into an individual patient data population (accounting for the size of the population and the number of events). We performed this conversion using a method of curve reconstruction originally described in 2000[34].

To determine whether the difference between the two RMSTs was statistically significant, we simply compared the confidence intervals for those groups. If those intervals overlap, the difference between groups is not statistically significant. If there is no overlap, the difference is significant[35,36]. While this visual method of assessing the overlap is easy to perform, it is known to be slightly too conservative. However, a conservative approach can be adequate in the context of multiple simultaneous comparisons. In assessing specific pairwise comparisons, the p-value was calculated for the difference between the two RMSTs and their 95%CIs, as previously described[37]. No adjustment was made for the presence of multiple simultaneous pairwise comparisons. The threshold for statistical significance was set at p=0.05 (two-tailed).

Ranking of the Treatments According to RMST values

As final result, the patients' cohorts were ranked according to their RMST values at 27 months in descending order.

Results

Our PubMed search extracted a total of 70 eligible papers. After excluding the papers that did not report OS at 2 years, we eliminated duplicate entries and identified 5 randomized studies that met our inclusion criteria (Figure 1).

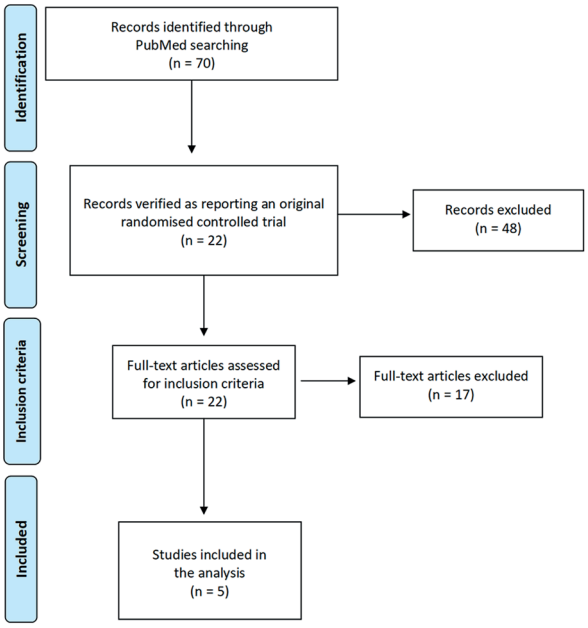

Figure 1. PRISMA flow diagram of our literature search.

The following 11 cohorts were included in these 5 trials (abbreviations: T, treatment group; C, control group):

- Cohorts 1T and 1C from the KEYNOTE-021 trial (2019)[10] with follow-up of 35 months: pembrolizumab (200 mg) plus pemetrexed (500 mg/m^2) and carboplatin (AUC of 5 mg/mL/min) every 3 weeks or pemetrexed (500 mg/m^2) and carboplatin (AUC of 5 mg/mL/min) every 3 weeks.
- Cohorts 2T and 2C from the CheckMate-026 trial (2017)[11] with follow-up of 27 months: nivolumab (3 mg/kg every 2 weeks) vs investigator's choice of platinum doublet chemotherapy. Choice of chemotherapy regimens was dependent on NSCLC histology:
  – squamous: gemcitabine (1250 mg/m^2) with cisplatin (75 mg/m^2); or gemcitabine (1000 mg/m^2) with carboplatin (AUC of 5 mg/mL/min); or paclitaxel (200 mg/m^2) with carboplatin (AUC of 6 mg/mL/min).
  – non-squamous: pemetrexed (500 mg/m^2) with either cisplatin (75 mg/m^2) or carboplatin (AUC of 6 mg/mL/min).
- Cohorts 3T and 3C from the KEYNOTE-042 trial (2019)[38] with follow-up of 38 months: pembrolizumab (200 mg every 3 weeks) *vs* investigator's choice of chemotherapy (carboplatin AUC of 5–6 mg/mL/min plus paclitaxel 200 mg/m^2 or pemetrexed 500 mg/m^2 every 3 weeks).
- Cohorts 4T and 4C from the IMpower-130 trial (2019)[39] with follow-up of 31 months: atezolizumab (1.200 mg every 3 weeks) plus carboplatin every 3 weeks (AUC of 6 mg/mL/min) plus nab-paclitaxel 100 mg/m2 every week *vs* carboplatin every 3 weeks (AUC of 6 mg/mL/min) plus nab-paclitaxel 100 mg/m2 every week.
- Cohorts 5T1, 5T2, and 5C from the MYSTIC trial (2020)[40] (with follow-up of 33 months) treated respectively with durvalumab (20 mg/kg every 4 weeks) *vs* durvalumab plus tremelimumab (durvalumab 20 mg/kg every 4 weeks plus 1mg/kg of tremelimumab every 4 weeks for up to 4 doses) vs platinum based chemotherapy. Choice of chemotherapy regimens was dependent on NSCLC histology:
  – squamous: gemcitabine (1250 mg/m^2) with cisplatin (75 mg/m^2); or gemcitabine (1000 mg/m^2) with carboplatin (AUC of 5 mg/mL/min); or paclitaxel (200 mg/m^2) with carboplatin (AUC of 6 mg/mL/min).
  – non-squamous: pemetrexed (500 mg/m^2) with either cisplatin (75 mg/m^2) or carboplatin (AUC of 6 mg/mL/min).

To evaluate these cohorts, 11 separate procedures of curve fitting were performed, followed by estimation of RMST with 95% CI. All our analyses employed a milestone at 27 months, which was the longest follow-up reached by all included cohorts.

Our results are shown in Table I. Rankings are presented in Table I and Figure 2. A total of 55 post-hoc pairwise comparisons between treatment arms were made (Figure 3). Seventeen comparisons were statistically significant. Among these, only six involved ICI arms with 4 cases of superiority (1T *vs.* 3T; 1T *vs.* 2T; 1T *vs.* 5T1; 1T *vs.* 5T2) and 2 of inferiority (1C *vs.* 5T1; 1C *vs.* 5T2). In the comparison between the treatment that ranked best (pembrolizumab plus chemotherapy from Cohort 1T of KEYNOTE-021 trial) and the one that ranked worst (chemotherapy from Cohort 5C of MYSTIC trial), the difference was 7.31 months. The numerous cases where the treatment arm was significantly more effective than the controls of the same trial were an expected finding.

Of interest, the good performance of the control group of the KEYNOTE-021 trial (that, according to the RMST values, did not significantly differ from the treatment arm of the same trial) and the poor outcomes of all 3 arms of the MYSTIC trial.

Table I. Characteristics of the 11 cohorts and values of RMST estimated from the time-to-event curves with t*= 27 mos.

Dataset	Cohort	t*	Length of follow-up (mos)	No. of patients	RMST (mos) with 95% confidence interval	Rank	Gain mos
Cohorts 1T and 1C from the KEYNOTE-021 trial (2019)[9]: pembrolizumab + chemotherapy *vs*. chemotherapy	1T 1C	27	35	60 63	21.77 (95% CI: 19.68 to 23.86) 8.92 (95% CI: 16.69 to 21.15)	1 2	2.85
Cohorts 2T and 2C from the CheckMate-026 trial (2017)[10]: nivolumab *vs*. chemotherapy	2T 2C	27	27	211 212	15.26 (95% CI: 13.85 to 16.66) 16.03 (95% CI: 14.66 to 17.40)	6 5	0.77 in favor of 2C
Cohorts 3T and 3C from the KEYNOTE-042 trial (2019)[38]: pembrolizumab vs chemotherapy	3T 3C	27	38	637 637	16.72 (95% CI: 15.90 to 17.54) 14.68 (95% CI: 13.93 to 15.44)	4 10	2.04
Cohorts 4T and 4C from the IMpower130 trial (2019)[39]: atezolizumab + chemotherapy *vs*. chemotherapy	4T 4C	27	31	451 228	17.01 (95% CI: 16.04 to 17.98) 15.12 (95% CI: 13.77 to 16.47)	3 7	1.89
Cohorts 5T1, 5T2, and 5C from the MYSTIC trial (2020)[40]: durvalumab *vs*. durvalumab + tremelimumab *vs*. chemotherapy	5T1 5T2 5C	27	33	163 163 162	15.05 (95% CI: 13.45 to 16.64) 14.78 (95% CI: 13.18 to 16.38) 14.46 (95% CI: 13.11 to 15.82)	8 9	0.27 (5T1 *vs* 5T2); 0.32 (5T2 *vs* 5C) and 0.59 (5T1 *vs* 5C)

Abbreviations: RMST, restricted mean survival time; mos, months; t*, milestone.

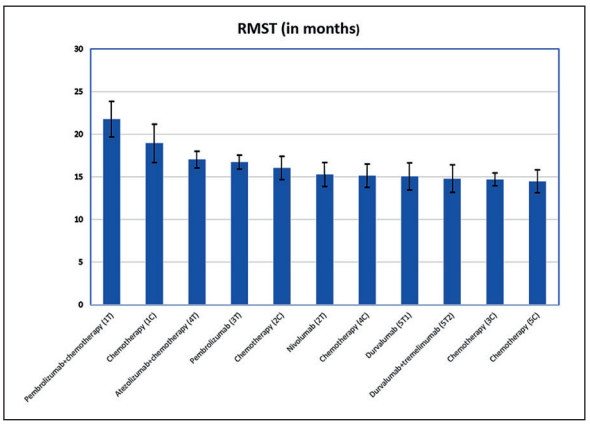

Figure 2. Values of RMST (t*=27 mos) ranked in descending order. The endpoint is overall survival. For each bar, the vertical line with tickmarks shows the 95% confidence interval.

Discussion

In this paper, we report the results of an analysis focused on the first-line treatment of advanced NSCLC with ICIs. Our results suggest that, among ICIs, pembrolizumab (alone or in combination with chemotherapy) determines an improvement in OS compared with standard chemotherapy whereas nivolumab, atezolizumab and durvalumab generate no survival benefit.

In the indirect comparison across the 11 values of RMST, pembrolizumab (plus chemotherapy) ranked first and fourth (in monotherapy). Atezolizumab plus chemotherapy ranked third and showed an OS shorter by more than 4 months than pembrolizumab plus chemotherapy (17.01 *vs* 21.77; $p<0.05$). Quite importantly, a message of heterogeneity across these patient cohorts emerged from our findings; for example, standard chemotherapy ranked second, fifth, seventh, tenth, and eleventh. This heterogeneity suggests much caution in interpreting these results. We have already reported other examples in which the use of the RMST as opposed to the HR resulting from an NMA generated more conservative results[31,41].

In summary, the combination of pembrolizumab plus chemotherapy showed a clinically relevant advantage over the other 10 treatments. Curiously enough, the smallest incremental benefit of pembrolizumab plus chemotherapy (as reported in KEYNOTE-021 trial) was versus the control arm of the KEYNOTE-021 trial itself, whereas the incremental benefits vs the other 9 treatments (including ICIs) were greater.

Pem + CT KEYNOTE-021 (1T)										
NS	CT KEYNOTE-021 (1C)									
NS	NS	Ate + CT IMPOWER130 (4T)								
p<0.05	NS	NS	Pem KEYNOTE-042 (3T)							
p<0.05	NS	NS	NS	CT CHECKMATE026 (2C)						
p<0.05	NS	NS	NS	NS	Niv CHECKMATE-026 (2T)					
p<0.05	p<0.05	NS	NS	NS	NS	CT IMPOWER130 (4C)				
p<0.05	p<0.05	NS	NS	NS	NS	NS	Dur MYSTIC (5T1)			
p<0.05	p<0.05	NS	NS	NS	NS	NS	NS	Dur+Tre MYSTIC (5T2)		
p<0.05	p<0.05	p<0.05	p<0.05	NS	NS	NS	NS	NS	CT KEYNOTE-042 (3C)	
p<0.05	p<0.05	p<0.05	p<0.05	NS	NS	NS	NS	NS	NS	CT MYSTIC (5C)

Figure 3. Statistical significance of pairwise comparisons. Since treatments are ordered according to decreasing effectiveness, all significant results are in favor of the treatment more on the left. The criterion for statistical significance ($p<0.05$) is no overlap of the 95%CIs of the two treatments being compared. Significant (indirect) comparisons between treatment arms are highlighted in red. Abbreviations: NS, not significant, Pem, pembrolizumab; CT, chemotherapy; Niv, nivolumab Ate, atezolizumab; Dur, durvalumab; Tre, tremelimumab.

In comparison with the NMA published by Liu et al[18], our rankings based on the RMSTs show a substantial agreement with the rankings based on HRs, even though this comparison is not straightforward because the two methods are qualitatively different and use different scales. In both approaches, however, pembrolizumab plus chemotherapy ranked first.

On the other hand, the incremental benefit of pembrolizumab (alone or in combination) compared with chemotherapy alone remained at limits of statistical significance in our analysis. In more detail, pembrolizumab plus chemotherapy in the KEYNOTE-021 trial[9] showed a better OS than the controls with a statistically significant HR. In contrast, the RMST of pembrolizumab plus chemotherapy was numerically, but not statistically, better than that of the controls. It should also be pointed out that the KEYNOTE-021 trial enrolled only 123 patients. These results confirm that the RMST is more conservative than the HR.

Compared with the NMA by Liu et al[18], the RMSTs estimated in our analysis have the advantage, over the HRs, of avoiding the biases due to different lengths of follow-up and, more importantly, generate an absolute outcome measure and not a relative one. Finally, no assumption of proportional hazards is required by the RMST.

A comparison between our results and those reported in standard meta-analyses focused on anti-PD-1/PD-L1 agents[42-44] is worthwhile. These 3 meta-analytic studies were based on the HR as the outcome measure. Chen and coworkers[42] compared antiPD-1/PD-L1 plus chemotherapy as the first line (atezolizumab, pembrolizumab or nivolumab or ipilimumab; 12 trials with no restriction on the length of follow-up) *vs* chemotherapy alone in advanced NSCLC and, as regards OS, found a HR for OS of 0.77 (95% CI, 0.64 to 0.91, p=0.003) in favor of the two-agent regimen, which implies a 23% relative improvement in the end-point. Likewise, Landre et al[43] analyzed the same comparison and, as regards OS, found a HR of 0.75 (95% confidence interval, 0.63 to 0.89; p=0.0008), i.e. 25% relative improvement. In contrast, our analysis based on absolute outcome measures (i.e. the RMST) found an improvement in OS of around 2 months only, which is much less impressive (relative improvement around 10%). In our view, these differences depend on the ability of HR to (inappropriately) pool trials irrespective of the lengths of their follow-up and on the likely violation of the proportional hazard assumption that in general characterizes most immunotherapies. As regards the meta-analysis by Zeng et al[44], that included 8 trials, the clinical material is not comparable to ours because they included mostly second-line treatments.

Our study had several limitations. First, our analyses were not stratified according to the PD-L1 expressions; this is because, in the included studies, the presence of survival curves based on different PD-L 1 expression cut-offs did not allow for a homogeneous stratification of this data across the trials. Second, only OS was considered, and not progression-free survival, mainly because in many cases, the Kaplan-Meier curves of progression-free survival were not available. Adverse events were not considered because our study was a survival analysis, and this information cannot be represented through Kaplan-Meier curves. Finally, pairwise comparisons were based on the criterion of overlapping CIs, mainly because this approach has the advantage of being simple and, more importantly, the role of multiple simultaneous comparisons in NMA is currently a matter of debate[45,46].

The present example showed that a well-designed narrative analysis integrated with the estimation of RMSTs can represent an alternative to NMA. RMST analysis also allowed us to obtain survival values more easily quantifiable and identifiable.

Conclusions

From a methodological point of view, we have proposed an original approach that combines a narrative overview of clinical results with the application of RMST followed by the estimation of rankings across the therapeutic options. Further studies in other therapeutic areas will be needed to confirm the good performance of this approach in reviewing complex therapeutic issues.

Regarding the use of ICIs as first-line treatments in advanced NSCLC, we confirmed their effectiveness in terms of OS, but the magnitude of their incremental benefit was smaller in our analysis than is commonly thought.

Some evidence of increased effectiveness is available in support of pembrolizumab (particularly in combination with chemotherapy) and, to a lesser extent, atezolizumab, whereas nivolumab and durvalumab seem to determine no incremental survival benefit.

Unlike the most recent reports (Liu et al[19]; Landre et al[43]), our results based on a very reliable absolute outcome measure showed that the prolongation of OS determined by ICI was clinically relevant (but less than 3 months) for pembrolizumab plus chemotherapy, whereas all the other regimens including an ICI (alone or in combination with chemotherapy) gave essentially no meaningful survival advantage compared with chemotherapy.

Conflict of Interest

MC is a full-time employee of SIFaCT, a not-for-profit national scientific society based in Milan. All other authors declare no competing interests.

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