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# **Use of Late-life Expectancy for Assessing the Long-Term Benefit of Immune Checkpoint Inhibitors**

Short Running title: Long-term benefit of immune checkpoint inhibitors

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2 Figures

1 Supplementary Figure & 1 Supplementary Table

## **ABSTRACT**

To grade the long-term benefit of anticancer agents, the American Society of Clinical Oncology Value Framework (ASCO-VF) awards tail-of-the-curve bonus points by using milestone survival at twice the median control survival. Here we propose an alternative, late-life expectancy that we defined as the area under the Kaplan-Meier curve from median control survival to the end of follow-up. We analyzed all indications of immune checkpoint inhibitors with survival data and found that nine indications out of 13 (69%) qualified for ASCO-VF tail of the curve bonus points either in progression-free or overall survival. Our proposed score recognized a long-term benefit not captured by the ASCO-VF, for example, for CHECKMATE-66 where twice the median overall survival was not reached. We found that nivolumab was associated with an increase of 65% (95% CI: 39–90) in OS late-life expectancy, which highlights its important long-term benefit. In conclusion, the ASCO-VF could be improved with the use of late-life expectancy.

**Key Words:** Relative Value Scales; Prescription Drugs; Melanoma; Non-small Cell Lung Cancer; Survival Analysis; Immunotherapy

Immune checkpoint inhibitors (ICIs) have raised hopes for durable survival.<sup>1,2</sup> For assessing the value of anti-cancer drugs, the American Society of Clinical Oncology Value Framework (ASCO-VF) recognizes the long-term benefit by awarding tail-of-the-curve bonus points using milestone survival at twice the control median survival.<sup>3</sup> This approach may have some drawbacks. First, milestones only reflect one point of the survival curve.<sup>4</sup> Second, the milestone is not always reached with a short follow-up. Finally, dichotomization represents a loss of information<sup>5</sup> and some drugs could fall short of the cut-off. Alternative treatment effect measures that could better estimate the magnitude of a drug's clinical benefit include the ratio of life expectancy (or restricted mean survival times).<sup>6,7</sup> To quantify the long-term benefit of ICIs, Horiguchi et al. recently suggested using the area under the Kaplan-Meier curve between two milestones.<sup>8</sup> Here, building on their idea, we propose a measure to quantify the long-term benefit of anticancer agents, the late-life expectancy, which we defined as the area under the Kaplan-Meier curve from median survival time in the control arm to the end of the follow-up.

We included all FDA-approved ICI indications for treatment of solid tumors from March 2011 to June 11, 2018. We used data from published reports of pivotal trials submitted to the FDA and first classified results from each trial for tail-of-the-curve bonus points. In ASCO-VF<sup>3</sup>, tail-of-the-curve bonus points are awarded with an improvement of at least 50% in survival provided the survival in the control group was at least 20%. Bonus points are 20 points for overall survival (OS) and 16 for progression-free survival (PFS). For indications, in an overview of recently FDA-approved cancer drugs, the ASCO-VF total score ranged from 3.4 to 66.5 points.<sup>10</sup>

We then assessed long-term survival by computing, for each treatment arm, the late-life expectancy (LLE) as defined above. We reconstructed individual patient data (IPD) from the

digitalized curves<sup>11</sup> and then computed LLE with the R `surv2sampleComp` package.<sup>12</sup> Because the median survival and the end of follow-up are not constants, we used non-parametric bootstrap with 999 replicates and computed the confidence interval (CI) with the bias-corrected and accelerated bootstrap techniques. Finally, we computed the ratio of LLE between experimental and control arms. Figure 1 exemplifies these calculations for the Checkmate 057 trial.<sup>13</sup>

Finally, we proposed a scoring frame based on the ratios of LLEs. This formula was created such that it gives 20 points for OS (16 points for PFS) for a ratio of LLEs  $> 1.5$  (to mimic the 50% relative difference in milestone survival that the ASCO-VF uses) and 0 points for a ratio  $\leq 1$  and a bonus proportional to the ratio between 1 and 1.5 (with 20% lower scores for PFS as in the ASCO-VF).

From 2011 to June 11, 2018 the FDA approved six ICIs (ipilimumab, pembrolizumab, nivolumab, avelumab, atezolizumab, and durvalumab) in 27 indications (Supplementary Table 1). Half of the indications (14/27, 52%) were based on trials not reporting OS or PFS. Because the ASCO-VF requires OS or PFS data, we analyzed data for 13 trials (plus the updated analysis for Checkmate-057). Four out of 13 indications (31%) reached the threshold for long-term benefit by the ASCO-VF in PFS (Supplementary Figure 1) and six indications out of 12 (50%) in OS (Figure 2). Overall, nine indications out of 13 (69%) qualified for ASCO-VF tail of the curve bonus points either in PFS or OS. This finding is different from that of a previous study in which only 3 out of 10 indications were awarded bonus points.<sup>14</sup> The difference could be explained by the fact that we use Kaplan-Meier curves to estimate milestone survival in contrast of the previous study that used the proportion of patients still at risk at a given time.<sup>15</sup>

LLEs ratios and derived scores are depicted in Figure 2 for OS and in Supplementary Figure 1 for PFS. LLEs ratios ranged from 1.18 (Checkmate-025) to 1.89 (MDX010-20) for OS and from 1.28 (Checkmate-214) to 3.35 (MDX010-20) for PFS. For two indications, median control OS was not reached. Maturity of survival data is indeed a crucial point. A sufficient follow-up is necessary to observe medians and because high censoring will result in unstable estimates. Indeed, analyses of the same trial at different updates could yield very different estimates of the drug benefit. However, there is also a need to grade the long-term benefit as early as possible (e.g. for reimbursement decision). In our proposal, we not only give a score but also the ratio of LLE itself with its confidence interval so that one can directly assess the certitude around the estimate. It would be of great interest if the medical community could define, for each indication, the time point beyond which the treatment benefit is likely to remain stable. When we observe median control survival but not twice the median, calculation with our proposal is still possible. In Checkmate 66, no bonus points were awarded in OS because twice the median survival was not reached,<sup>16</sup> but our analysis found a ratio of LLEs of 1.65 (95% CI: 1.39 to 1.90) and a score of 20 points, which highlight the important long-term benefit of nivolumab. However, 16 bonus points were awarded in PFS in the ASCO-VF and thus the difference is only of 4 points at the indication level.

We showed that the use of LLEs ratios may provide a fine-grained assessment of long-term benefit. However, we only proposed a scoring to be further discussed and improved by the oncology community. For instance, to reward more precise studies, statistical significance could be easily incorporated in our approach, by assigning a null score for indications without a significant result or by using the lower bounds of the 95% CI instead of the point estimate to reward more precise studies. Further improvements could also considerate incorporate absolute

magnitude of long term benefit in addition to relative effect. Our approach requires reconstructed (or original) IPD and re-analysis of these data, which might be a limitation of our approach.

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## **Notes**

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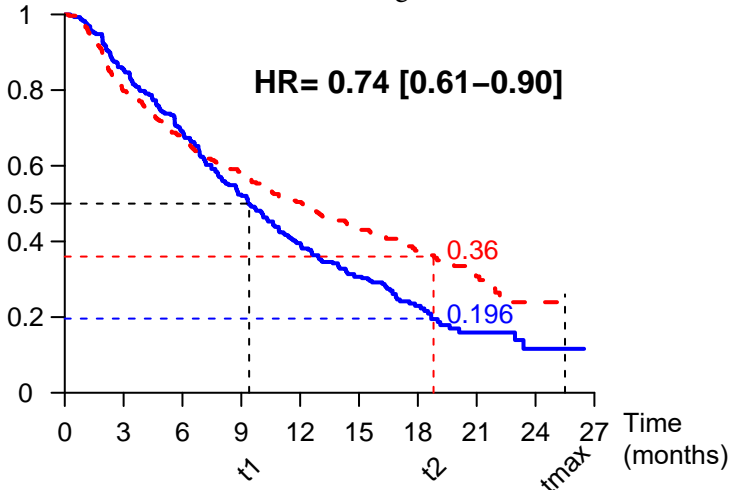
## **Figure Legends**

Figure 1. Illustration of Late-life Expectancy Computation Based on Data from the CHECKMATE-057 trial. HR, hazard ratio; OS, overall survival; RMST, restricted mean survival times

Figure 2. Association Between Ratios of Late-life Expectancy and Tail-of-the-curve Bonus Points Within The ASCO-VF for Overall Survival. Note: There are only 12 indications (13 analyses with the CHECKMATE-057 update) represented because there was no overall survival data for PACIFIC study (Durvalumab in maintenance therapy of NSCLC).

Abbreviations: NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma.

Figure 1



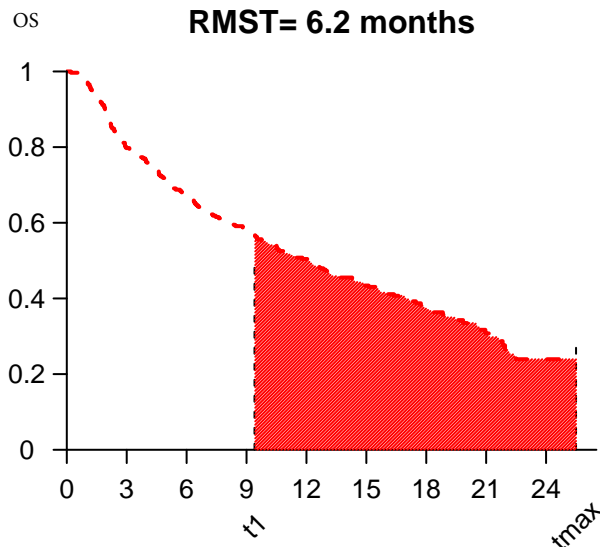
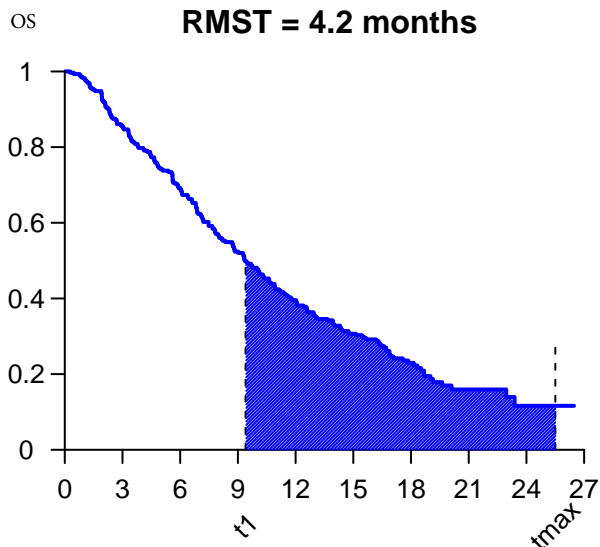
— Docetaxel  
- - - Nivolumab

$t_1$ : median survival time in the control arm

$t_2$ : twice  $t_1$

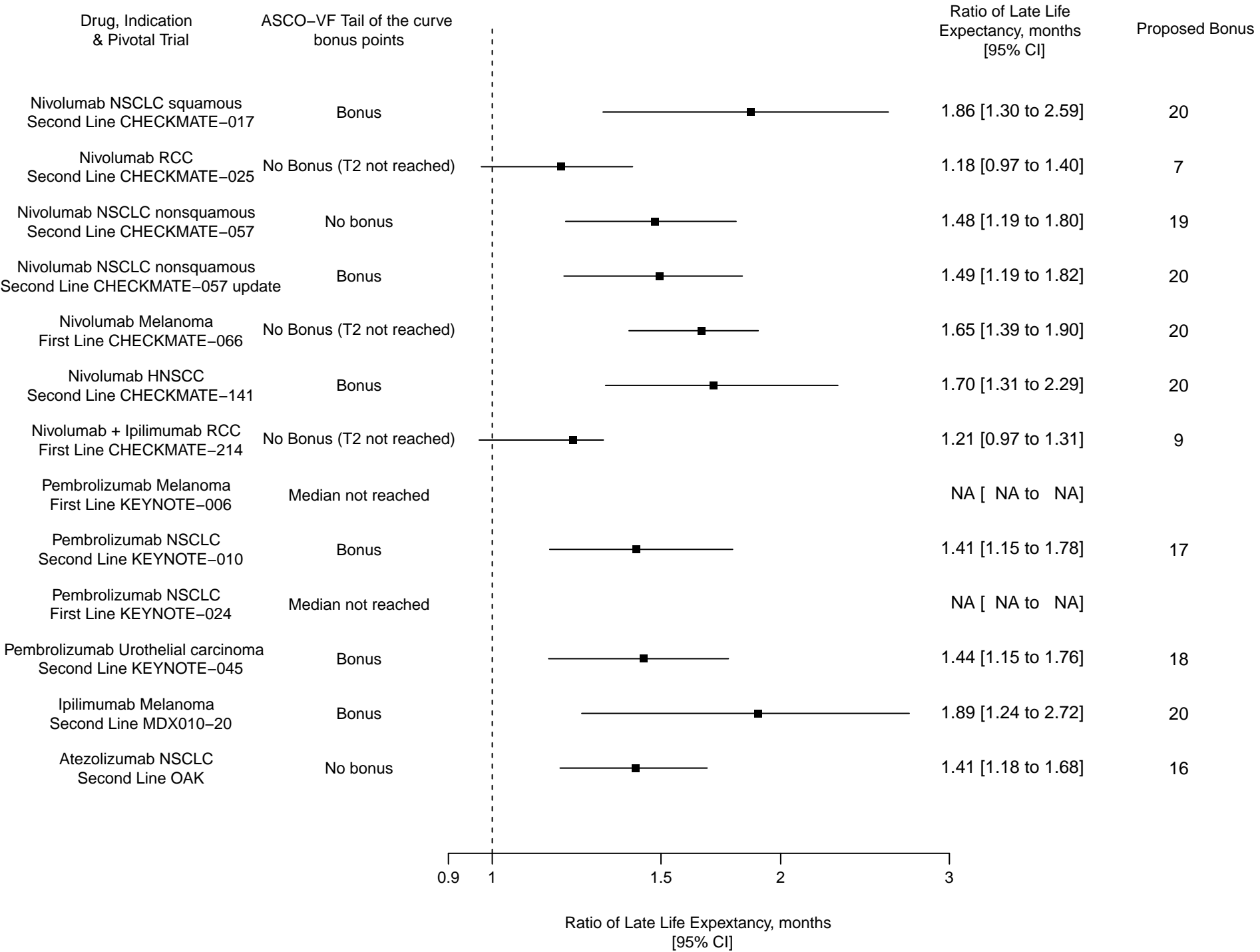
$t_{max}$ : end of follow-up

The relative difference in OS is 80%.  
However, this indication does not qualify for tail of the curve bonus points because survival at  $t_2$  is lower than 20%.



The ratio of RMST is 6.2 divided by 4.2, i.e. 1.48

Figure 2



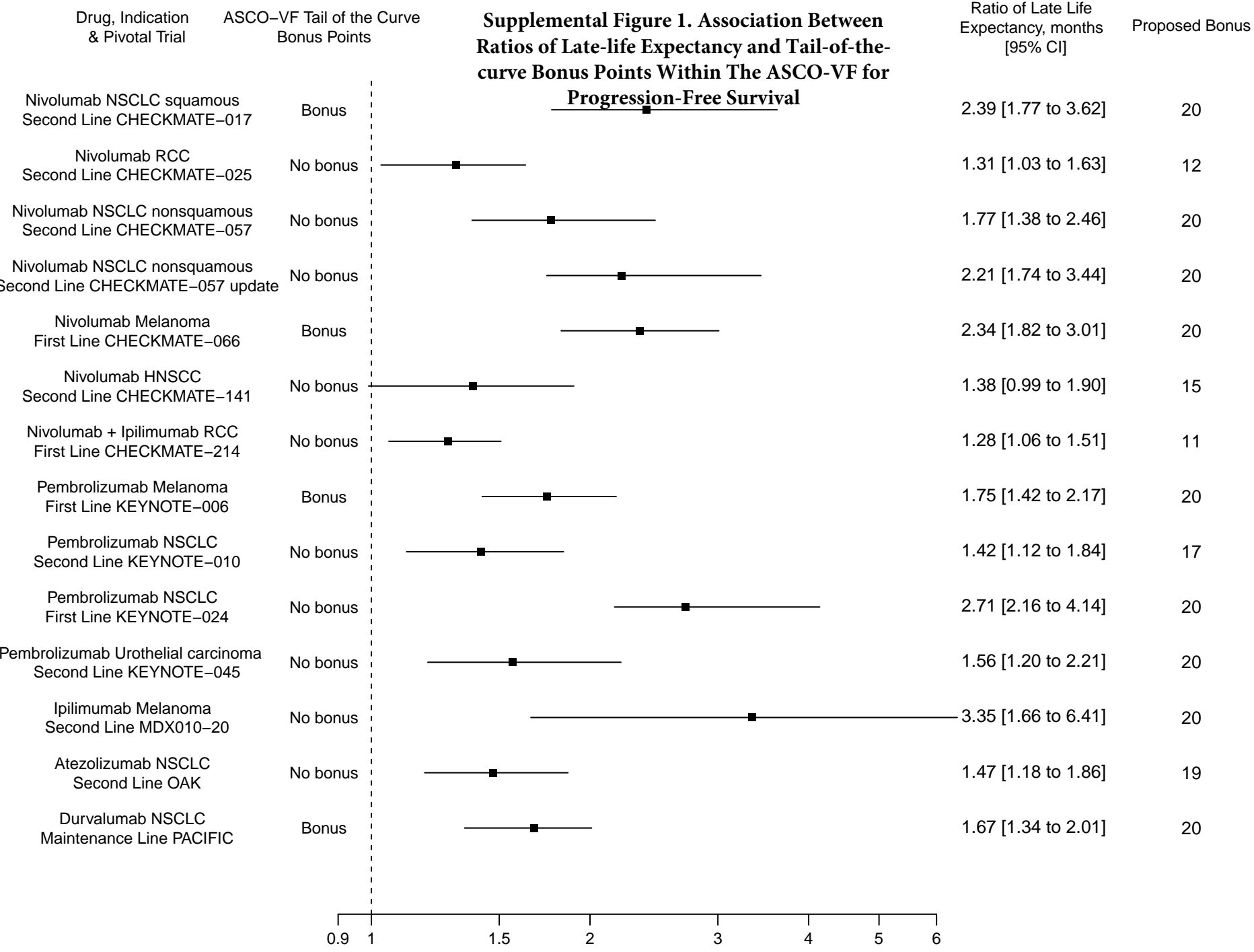
**Online-only Table 1. Indications for Immune Checkpoint Inhibitors Approved by the US Food and Drug Administration (FDA) from March 2011 to May 2018.**

<b>Drug</b>	<b>Indication</b>	<b>Line</b>	<b>FDA approval year</b>	<b>Primary endpoint</b>	<b>RCT for FDA approval</b>	<b>Name of pivotal RCT used to assess long-term benefit</b>
Ipilimumab	Melanoma	First	2015	ORR	No	NA
Pembrolizumab	Melanoma	Second	2014	ORR	No	NA
Pembrolizumab	NSCLC	Second	2015	ORR	No	NA
Pembrolizumab	HNSCC	Second	2016	ORR	No	NA
Pembrolizumab	NSCLC	First	2017	ORR	No	NA
Pembrolizumab	MSI-H	Second	2017	ORR	No	NA
Nivolumab	Melanoma	Second	2014	ORR	No	NA
Nivolumab	Urothelial carcinoma	Second	2017	ORR	No	NA
Nivolumab	Hepatocellular Carcinoma	Second	2017	ORR	No	NA
Nivolumab	MSI-H	Second	2017	ORR	No	NA
Atezolizumab	Urothelial carcinoma	Second	2016	ORR	No	NA
Avelumab	Merkel cell carcinoma	Second	2017	ORR	No	NA
Avelumab	Urothelial carcinoma	Second	2017	ORR	No	NA

Durvalumab	Urothelial carcinoma	Second	2017	ORR	No	NA
Ipilimumab	Melanoma	Second	2011	OS	Yes	MDX010-20
Pembrolizumab	Melanoma	First	2015	OS	Yes	KEYNOTE-006
Pembrolizumab	Urothelial carcinoma	Second	2017	OS	Yes	KEYNOTE-045
Nivolumab	Melanoma	First	2016	OS	Yes	CHECKMATE-066
Nivolumab	Renal cell carcinoma	Second	2015	OS	Yes	CHECKMATE-025
Nivolumab	Squamous-cell NSCLC	Second	2015	OS	Yes	CHECKMATE-017
Nivolumab	Non-squamous NSCLC	Second	2015	OS	Yes	CHECKMATE-057
Nivolumab	HNSCC	Second	2016	OS	Yes	CHECKMATE-141
Atezolizumab	NSCLC	Second	2016	OS	Yes	OAK
Pembrolizumab	NSCLC	First	2016	PFS	Yes	KEYNOTE-024
Durvalumab	NSCLC	Maintenance	2018	PFS/OS	Yes	PACIFIC
Pembrolizumab	NSCLC	Second	2015	PFS/OS	Yes	KEYNOTE-010
Nivolumab + ipilimumab	Renal cell carcinoma	First	2018	PFS/OS	Yes	CHECKMATE-214

RCT, randomized controlled trial; NSCLC, non-small-cell lung cancer; HNSCC, head and neck squamous cell carcinoma; MSI-H, high level microsatellite instability; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; NA, not available

**Supplemental Figure 1. Association Between Ratios of Late-life Expectancy and Tail-of-the-curve Bonus Points Within The ASCO-VF for Progression-Free Survival**



Ratio of Late Life Expectancy, months [95% CI]

Abbreviations: NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma, T2, twice the median control survival.