Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
Meta-analysis of difference in mean changes

We performed two separate meta-analyses, considering as effect size of interest the difference between the intervention group I and control group C of the mean change of PROs score from baseline to 12 weeks, and the difference from baseline to 24 weeks. We extracted, for each study, the mean change at week $w$ in the intervention group $d_{I(w)}$ and in the control group $d_{C(w)}$, along with the standard deviations of the individual changes $SD(d_{I(w)})$ and $SD(d_{C(w)})$. The standard error of the mean change in the intervention group was calculated as $SE(d_{I(w)}) = SD(d_{I(w)})/\sqrt{n_{I(w)}}$, with $n_{I(w)}$ the number of respondents in the intervention arm at the week $w$ of interest; $SE(d_{C(w)})$ was similarly derived. When in the intervention group or in the control group $n_{w}$ was not reported, we imputed it multiplying the number of patients $n_{0}$ evaluated at baseline (usually reported in the paper) by the average proportion of respondents at time $w$ calculated from all the other studies reporting $n_{w}$.

For each study, we estimated the effect size as $\delta_{w}=(d_{I(w)}-d_{C(w)})$, and its standard error as $SE(\delta_{w}) = \sqrt{SE(d_{I(w)})^2 + SE(d_{C(w)})^2}$. For studies reporting only the mean $\mu_{w}$ and the standard deviation $SD_{w}$ of the PRO scores for each arm separately, we calculated the mean change at week $w$ as $d_{w} = \mu_{w} - \mu_{0}$. The standard deviation of the individual changes was calculated taking into account the correlation between the paired measures, as $SD(d_{w}) = \sqrt{SD_{0}^2 + SD_{w}^2 - 2\rho SD_{0} SD_{w}}$. The correlation coefficient $\rho$ was imputed as the average coefficient derived from the studies reporting the $SD$ of the scores both at baseline and at week $w$, and the SD of the mean difference between week $w$ and baseline. When the arm-specific mean changes or the absolute values were reported only in line plots showing the time-point estimates and their 95% confidence intervals (CIs), we digitized the plots and extracted the relevant information, using the software WebPlotDigitizer. (20) For studies in which mean PROs information were presented only for weeks from baseline different than the week of interest (i.e. 12th or the 24th),
and in which the values relative to a previous and a subsequent week, with respect to the week of interest, were both presented, \(d_{I(w)}\) and \(d_{C(w)}\), and the corresponding \(SE(d_{I(w)})\) and \(SE(d_{C(w)})\) were imputed. The imputed value was calculated as the weighted mean of the two values relative to the previous and the subsequent weeks, with weights inversely proportional to the distance from the week of interest being estimated and the two available ones.

To estimate the pooled difference in mean changes at 12 and 24 weeks, we used a random-effects model, weighting each study estimate by the inverse of its variance. A pooled difference in mean change greater than 0 indicated a greater benefit in PROs score for the immunotherapy-containing arm. We also calculated the I\(^2\) statistics, which express the percentage of the total observed variability due to heterogeneity between studies’ results, and the Q statistic to test the null hypothesis of homogeneity between studies.

To adjust the overall pooled difference in mean changes at 12 and 24 weeks for potential baseline imbalances in PRO scores between treatment and control groups, we used a two-stage meta-analytical approach based on pseudo individual patient data (IPD), as described by Papadimitropoulou et al. (21) This approach proceeded as follows: for each included study, we first constructed the pseudo IPD using the means and the standard deviations of PRO scores reported at baseline and at the follow-up week of interest. Then, in the first meta-analytical stage, we fitted, for each of the \(N\) included studies, a linear model with the follow-up score as dependent variable and the treatment and the baseline score as independent variables. This yields \(N\) treatment effects \(\delta_i\) with standard error \(SE_i\), adjusted for baseline imbalance. At the second stage, a random-effects meta-analysis was run on the estimated study specific \(\delta_i\) to estimate the pooled adjusted treatment effect.
Meta-analysis of the time to deterioration hazard ratio.

The hazard ratios (HRs) for TTD in the treatment arm compared with those in the control arm, along with their 95% CIs, were extracted from each single study. For studies reporting only the Kaplan-Meier (KM) curves for TTD we use the algorithm proposed by Guyot et al. (3) to reconstruct the individual patient time data from published curves. The software WebPlotDigitizer (1) was used to digitize the KM curves. A Cox proportional hazard model was fitted to the reconstructed data to estimate the HR for TTD and the corresponding 95% confidence interval.

HRs and 95% CIs were translated into log-hazard ratios (logHRs), and the corresponding variances were calculated. Overall and subgroup-specific pooled hazard ratios of TTD were calculated using random-effects models. The weight associated to each study was given by the inverse of the study logHR variance. A pooled HR lower than 1 indicates a longer TTD for the immunotherapy-containing arm. I² and Q statistics were also calculated.

Finally, a sensitivity analysis was performed excluding RCTs only available as congress abstracts. Pooled HR-TTD and pooled difference in mean change at 12 and 24 weeks were provided.
eFigure 1. PRISMA flow chart

Identification of studies via databases and registers

Records identified from*: Pubmed, Embase, Cochrane, ESMO, ASCO
(n =2259)

Records removed before screening:
(n =1086 )

Records screened
(n =1173 )

Records excluded
(n = 1112)

Reports sought for retrieval
(n =61)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 61)

Reports excluded:
Cost effectiveness analysis: (n =9)
Adjuvant trial (n =3)
ICIs as control arm (n =8)
Incomplete data(n =3 )
Trials not reporting PROs by
QLQ-C30 GHS or EQ 5D-VAS
scales (n=4)

Reports of included studies
(n = 34)
### eTable 1. Assessment of risk of bias in RCTs included in the analysis.

| Study                  | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome of data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|------------------------|---------------------------------------------|----------------------------------------|----------------------------------------------------------|----------------------------------------------|-------------------------------------------|-------------------------------------|------------|
| Andre T, 2020 (4)      | Low                                         | Low                                    | High                                                    | Low                                          | Low                                       | Low                                 | Low        |
| Van Cutsem E, 2019 (5) | Low                                         | Low                                    | Low                                                     | Low                                          | Low                                       | Low                                 | Low        |
| Harrington KJ, 2020 (6)| Low                                         | Low                                    | High                                                    | Low                                          | Low                                       | Low                                 | Low        |
| Long GV, 2016 (7)      | Low                                         | Low                                    | Low                                                     | Unclear                                      | Low                                       | Low                                 | Low        |
| Reck M, 2018 (017) (8) | Low                                         | Low                                    | High                                                    | Unclear                                      | Low                                       | Low                                 | Low        |
| Reck M, 2018 (057) (9) | Low                                         | Low                                    | High                                                    | Unclear                                      | Low                                       | Low                                 | Low        |
| Barlesi F, 2018 (10)   | Low                                         | Low                                    | High                                                    | Unclear                                      | Low                                       | Low                                 | Low        |
| Bordoni R, 2018 (11)   | Low                                         | Low                                    | High                                                    | Unclear                                      | Low                                       | Low                                 | Low        |
| Hui R, 2019 (12)       | Low                                         | Low                                    | Low                                                     | Low                                          | Low                                       | Low                                 | Low        |
| Brahmer JR, 2017 (13)  | Low                                         | Low                                    | High                                                    | Low                                          | Low                                       | Low                                 | Low        |
| Vaughn DJ, 2018 (14)   | Low                                         | Low                                    | High                                                    | Low                                          | Low                                       | Low                                 | Low        |
| Powles T, 2017 (15)    | Low                                         | Low                                    | High                                                    | High                                         | Low                                       | Low                                 | Low        |
| Van Cutsem E, 2019; (062) (16) | Low                     | Low                                    | Low                                                     | Low                                          | Low                                       | Low                                 | Low        |
| Harrington KJ, 2017; Ferris R, 2016 (17,18) | Low                     | Low                                    | High                                                    | Unclear                                      | Low                                       | Low                                 | Low        |
| Ryoo BY, 2020 (19)     | Low                                         | Low                                    | Low                                                     | Low                                          | Low                                       | Low                                 | Low        |
| Study Reference                                      | Risk of Bias | Performance | Adherence | Overall Quality | Compliance |
|----------------------------------------------------|--------------|-------------|-----------|----------------|------------|
| Larkin J, 2018 (20)                                 | Low          | Low         | High      | Low            | Low        |
| Schadendorf D; 2016 (21)                            | Low          | Low         | High      | Unclear        | Low        |
| Sezer A, 2020; Sezer A, 2021 (22,23)               | Low          | Low         | High      | Unclear        | Low        |
| Cella D, 2016 (24)                                  | Low          | Low         | High      | Unclear        | Low        |
| Finn RS, 2019 (25)                                  | Low          | Low         | High      | Low            | Low        |
| Lewis K, 2020 (26)                                  | Low          | Low         | Low       | Low            | Low        |
| Bedke J, 2020 (27)                                  | Low          | Low         | High      | Low            | Low        |
| Adams S, 2020 (28)                                  | Low          | Low         | Low       | Unclear        | Low        |
| Mazieres J, 2019 (29)                               | Low          | Low         | Low       | Low            | Low        |
| Garassino MC, 2020 (30)                             | Low          | Low         | Low       | Low            | Low        |
| Kim HR, 2020 (31)                                   | Low          | Low         | Low       | Low            | Low        |
| Bamias A, 2020 (32)                                 | Low          | Low         | Low       | Low            | Low        |
| Goldman JW, 2020 (33)                               | Low          | Low         | High      | Unclear        | Low        |
| Reck M, 2020 (34)                                   | Low          | Low         | High      | Low            | Low        |
| Mansfield AS, 2020 (35)                             | Low          | Low         | Low       | Unclear        | Low        |
| Reck M, 2019 (36)                                   | Low          | Low         | High      | Low            | Low        |
| Cella D, 2019 (37)                                  | Low          | Low         | High      | Unclear        | Low        |
| Sherpereel A, 2020 (38)                             | Low          | Low         | High      | Low            | Low        |
| Reck M, 2020 (39)                                   | Low          | Low         | High      | Low            | Low        |
**eTable 2. Assessment of quality of PROs reporting in RCTs included in the analysis.**

| Study                                      | The PRO should be identified in the abstract as a primary or secondary outcome | The PRO hypothesis should be stated and relevant domains identified, if applicable | Evidence of PRO Instrument validity and reliability should be provided or cited if available | Statistical approaches for dealing with missing data are explicitly stated. | PRO-specific limitations and implications for generalizability and clinical practice should be discussed |
|--------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Andre T, 2020 (4)                          | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Van Cutsem E, 2019 (5)                     | 1                                                                               | 1                                                                               | 1                                                                                          | 0                                                                              | 0                                                                               |
| Harrington KJ, 2020 (6)                    | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Long GV, 2016 (7)                          | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Reck M, 2018 (017) (8)                     | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Reck M, 2018 (057) (9)                     | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Barlesi F, 2018 (10)                       | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Bordoni R, 2018 (11)                       | 1                                                                               | 1                                                                               | 1                                                                                          | 0                                                                              | 1                                                                               |
| Hui R, 2019 (12)                           | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Brahmer JR, 2017 (13)                      | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Vaughn DJ, 2018 (14)                       | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Powles T, 2017 (15)                        | 0                                                                               | 1                                                                               | 1                                                                                          | 0                                                                              | 0                                                                               |
| Van Cutsem E, 2019 (16)                    | 1                                                                               | 1                                                                               | 1                                                                                          | 0                                                                              | 0                                                                               |
| Harrington KJ, Ferris R, 2016 (17,18)      | 1                                                                               | 1                                                                               | 1                                                                                          | 1                                                                              | 1                                                                               |
| Ryoo BY, 2020 (19)                         | 1                                                                               | 1                                                                               | 1                                                                                          | 0                                                                              | 1                                                                               |
| Larkin J, 2018 (20)                        | 0                                                                               | 1                                                                               | 1                                                                                          | 0                                                                              | 0                                                                               |
| Reference                              | Year(s)       | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 |
|---------------------------------------|---------------|------|------|------|------|------|------|
| Schadendorf D, 2016 (21)             |               | 1    |      | 1    |      |      |      |
| Sezer A, 2020; Sezer A, 2021 (22,23) |               | 1    | 1    |      | 1    |      | 0    |
| Cella D, 2016 (24)                   |               | 1    |      |      |      |      |      |
| Finn RS, 2019 (25)                   |               | 0    |      |      | 1    |      | 0    |
| Lewis K, 2020 (26)                   |               | 1    |      |      |      |      | 0    |
| Bedke J, 2020 (27)                   |               | 1    |      |      |      |      | 0    |
| Adams S, 2020 (28)                   |               | 1    | 1    |      | 1    |      | 0    |
| Mazieres J, 2019 (29)                |               | 1    |      | 1    |      |      |      |
| Garassino MC, 2020 (30)              |               | 1    |      |      | 1    |      | 1    |
| Kim HR, 2020 (31)                    |               | 1    |      |      |      |      | 0    |
| Bamias A, 2020 (32)                  |               | 1    |      |      |      |      | 0    |
| Goldman JW, 2020 (33)                |               | 1    |      |      |      |      |      |
| Reck M, 2020 (34)                    |               | 1    |      | 1    |      |      | 0    |
| Mansfield AS, 2020 (35)              |               | 1    |      |      |      |      | 0    |
| Reck M, 2019 (36)                    |               | 1    |      |      |      |      | 0    |
| Cella D, 2019 (37)                   |               | 1    |      |      |      |      |      |
| Sherpereel A, 2020 (38)              |               | 1    |      |      |      |      | 0    |
| Reck M, 2020 (39)                    |               | 1    |      |      |      |      | 0    |
**eTable 3.** Sensitivity analysis of TTD and GHS mean change excluding RCTs only available as congress abstracts.

|                      | TTD analysis | GHS mean change analysis |   |   |   |
|----------------------|--------------|--------------------------|---|---|---|
|                      | N comparisons | Pooled HR (95% CI) | N comparisons | Pooled difference in mean change (95% CI) | N comparisons | Pooled difference in mean change (95% CI) |
| ICI monotherapy      | 9            | 0.78 (0.68, 0.90)      | 15           | 4.2 (2.2, 6.1)     | 13           | 5.8 (3.6, 8.0)   |
| ICI + chemotherapy   | 2            | 0.90 (0.76, 1.07)      | 6            | 1.2 (-0.6, 3.1)    | 6            | 3.0 (-1.2, 7.1)  |
| Other ICIs-containing combinations | 3 | 0.71 (0.61, 0.81) | 3 | 4.7 (-1.5, 10.9) | 3 | 2.7 (-1.0, 6.3) |
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