Supplementary material

Addition of immune checkpoint inhibitors to chemotherapy vs chemotherapy alone as first-line treatment in extensive-stage small-cell lung carcinoma: a systematic review and meta-analysis

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Table S1. Search strategy for MEDLINE accessed through PubMed (1966 to 16 July 2020)

SEARCH	*QUERY*	*RESULTS*
#1	*Search: (("Carcinoma, Small Cell"[Mesh] AND "Lung"[Mesh]) OR "Small Cell Lung Carcinoma"[Mesh]) OR (Small-Cell Lung Cancer OR SCLC OR "Lung neoplasm")*	93,759
#2	*Search: Chemo-naïve OR untreated OR "un-treated" OR "not treated" OR "first line" OR "1st line" OR "1st-line" Sort by: Most Recent*	265,438
#3	*Search: #1 AND #2*	6,868
#4	*Search: "atezolizumab" [Supplementary Concept] OR (anti-PDL1 OR immunoglobulin G1, anti-(human CD antigen CD274) (human monoclonal MDPL3280a heavy chain), disulfide with human monoclonal MDPL3280a kappa-chain, dimer OR MPDL3280A OR MPDL-3280A OR Tecentriq OR RG7446 OR RG-7446) Sort by: Most Recent*	1,136
#5	*Search: "durvalumab" [Supplementary Concept] OR (MEDI4736 OR MEDI-4736 OR Imfinzi) Sort by: Most Recent*	545
#6	*Search: "pembrolizumab" [Supplementary Concept] OR (SCH-900475 OR Keytruda MK-3475 OR lambrolizumab) Sort by: Most Recent*	4,086
#7	*Search: "Nivolumab" [Mesh] OR (Opdivo OR ONO-4538 OR ONO 4538 OR ONO4538 OR MDX-1106 OR MDX 1106 OR MDX1106 OR BMS-936558 OR BMS 936558 OR BMS936558) Sort by: Most Recent*	5,147
#8	*Search: "Ipilimumab" [Mesh] OR (Anti-CTLA-4 MAb Ipilimumab OR Anti CTLA 4 MAb Ipilimumab OR Ipilimumab, Anti-CTLA-4 MAb OR Yervoy OR MDX 010 MDX010 OR MDX-010 OR MDX-CTLA-4 OR MDX CTLA 4) Sort by: Most Recent*	10,061
#9	*Search: #4 OR #5 OR #6 OR #7 OR #8*	16,32
#10	*Search: #3 AND #9*	**383**

Table S2. Search strategy for EMBASE (1980 to 17 July 2020)

SEARCH	*QUERY*	*RESULTS*
#1.	*small cell lung cancer'/exp OR 'small cell lung cancer'*	154,361
#2.	*Sclc*	13,126
#3.	*'pembrolizumab'/exp OR 'pembrolizumab'*	15,875
#4.	*'nivolumab'/exp OR 'nivolumab'*	18,248
#5.	*'ipilimumab'/exp OR 'ipilimumab'*	14,42
#6.	*'durvalumab'/exp OR 'durvalumab'*	3,771
#7.	*'atezolizumab'/exp OR 'atezolizumab'*	5,578
#8.	*chemo naïve' OR untreated OR 'un-treated' OR 'not treated' OR 'first line' OR '1st line' OR '1st-line'*	394,911
#9.	*#1 OR #2*	155,621
#10.	*#8 AND #9*	13,699
#11.	*#3 OR #4 OR #5 OR #6 OR #7*	34,146
#12.	*#10 AND #11*	1,503
#13.	*#12 AND 'randomized controlled trial'/de*	**320**

Figure S1. PRISMA flow-chart of study selection

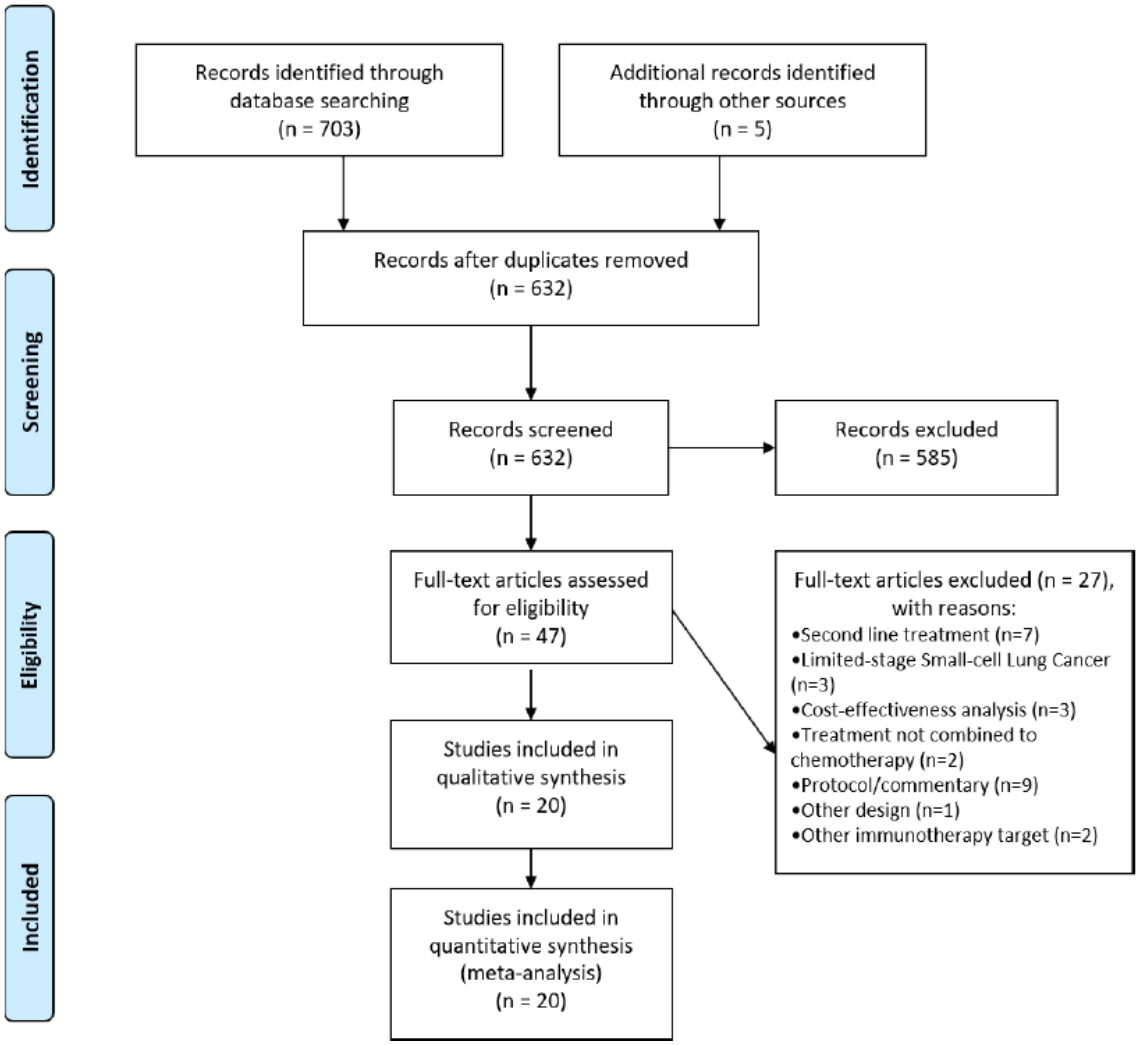


Figure S2. Risk of bias summary: authors' judgements about risk of bias for each included study

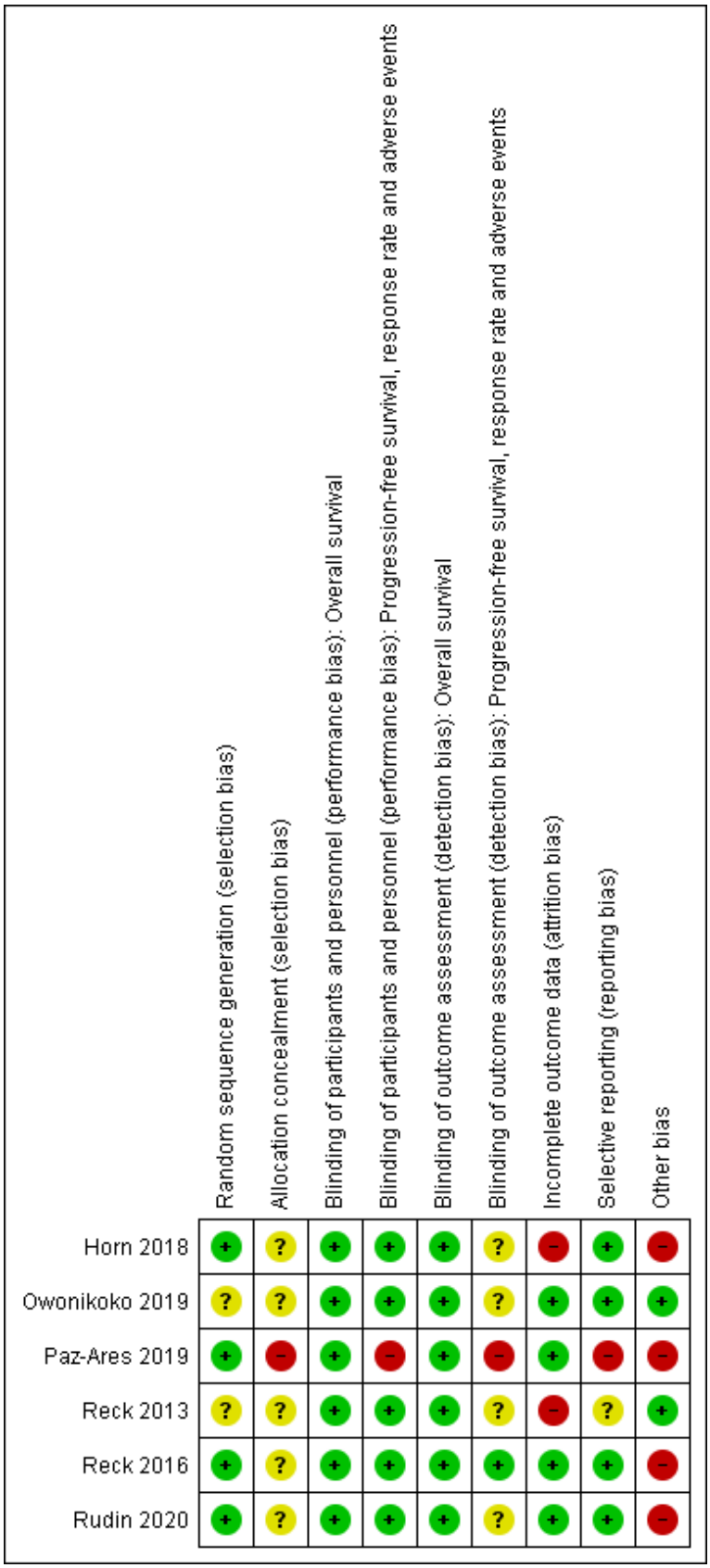
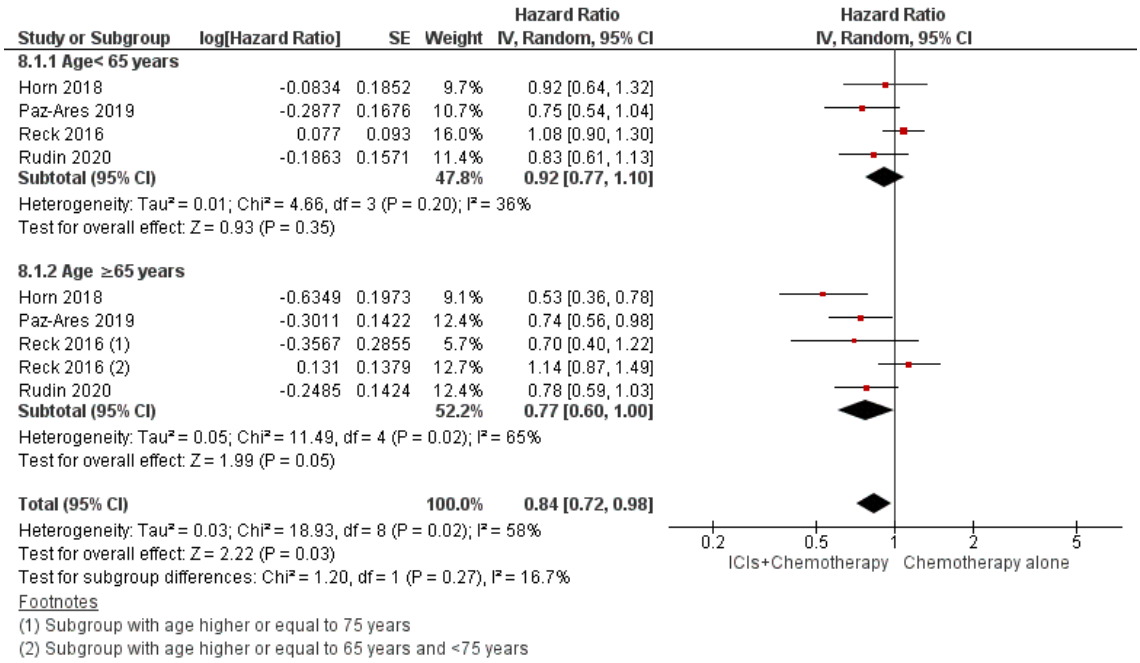


Figure S3. Subgroup analysis by age (age <65 years/≥65 years). Forest plot comparison of adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; IV, inverse variance; SE standard error.



Footnotes

(1) Subgroup with age higher or equal to 75 years

(2) Subgroup with age higher or equal to 65 years and <75 years

Figure S4. Subgroup analysis by sex (male/female). Forest plot comparison of adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; IV, inverse variance; SE, standard error.

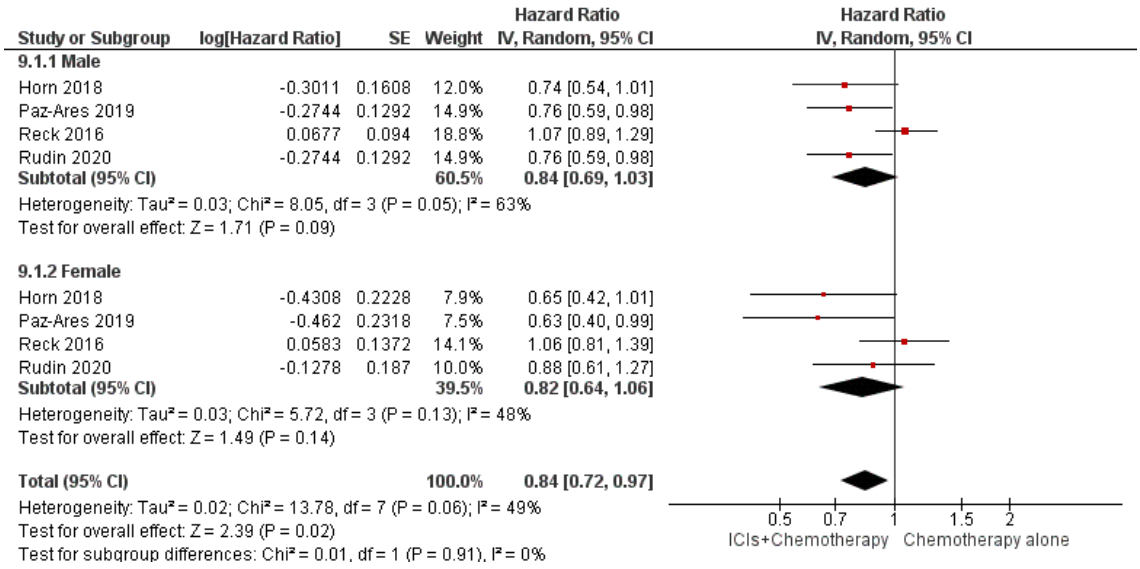
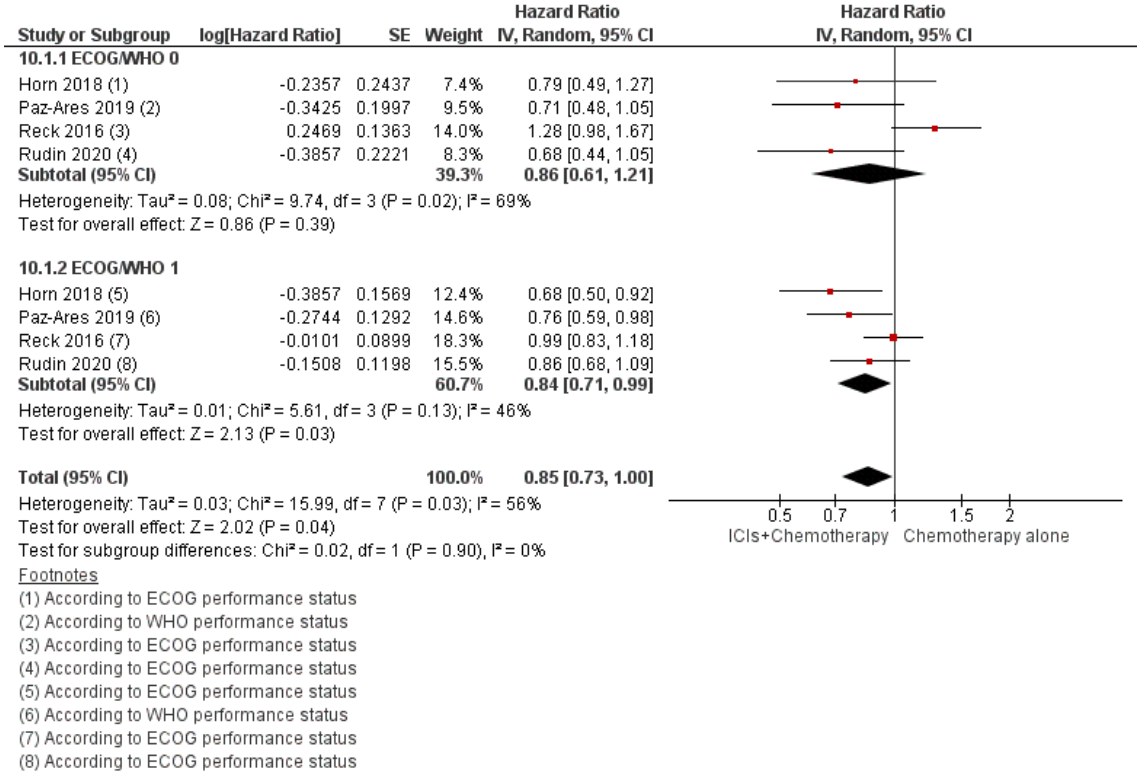


Figure S5. Subgroup analysis by baseline functional status. Forest plot comparison of adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IV, inverse variance; SE, standard error; WHO, World Health Organization.



Footnotes

(1) According to ECOG performance status
(2) According to WHO performance status
(3) According to ECOG performance status
(4) According to ECOG performance status
(5) According to ECOG performance status
(6) According to WHO performance status
(7) According to ECOG performance status
(8) According to ECOG performance status

Figure S6. Subgroup analysis by serum lactate dehydrogenase (LDH). Forest plot comparison of adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; IV, inverse variance; SE, standard error.

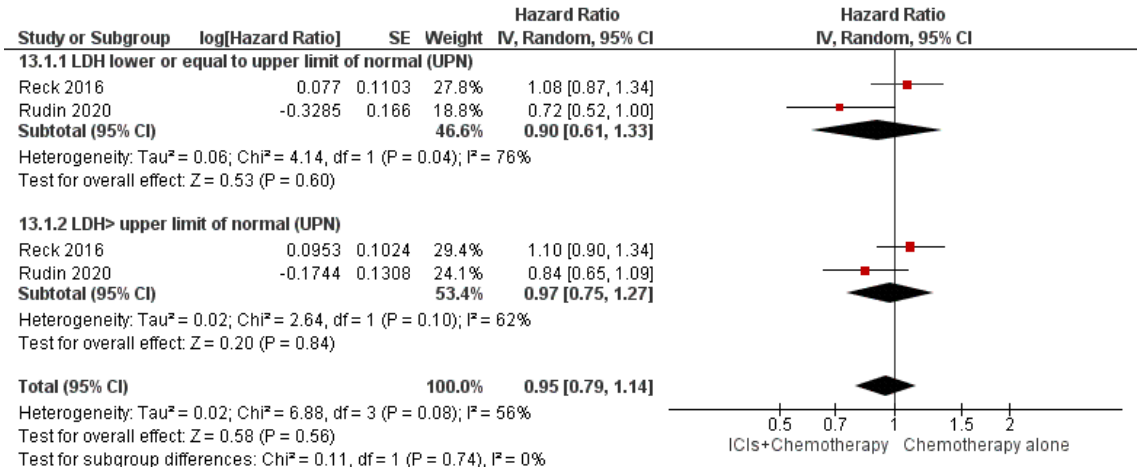


Figure S7. Subgroup analysis by brain metastasis at baseline. Forest plot comparison of adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; IV, inverse variance; SE, standard error.

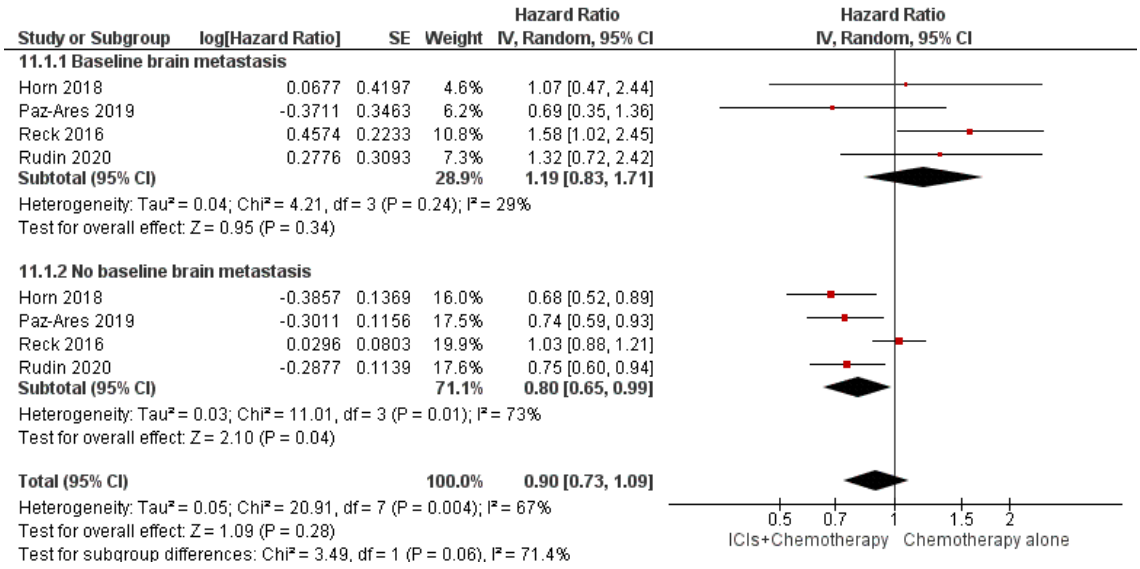


Figure S8. Subgroup analysis by baseline liver metastasis. Forest plot comparison of adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; IV, inverse variance; SE, standard error.

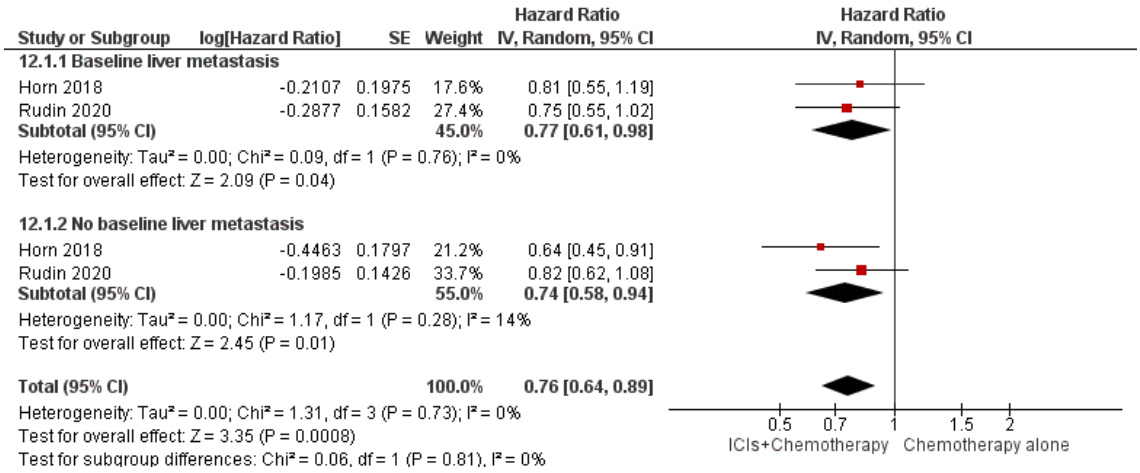


Figure S9. Subgroup analysis in longer-term survival. Forest plot comparison of adverse event rate in patients receiving chemotherapy plus immune checkpoint inhibitors (ICIs) versus chemotherapy alone or combined with placebo. CI, confidence interval; M-H, Mantel-Haenszel.