SUPPLEMENTAL METHODS

Data Extraction and quality assessment

Hazard ratio (HR) of survival curves, where not reported, was derived from the graph by using the method by Tierney JF et al1. Briefly, Kaplan-Meier curves from each study were read with both Engauge Digitiser and paint.net software to retrieve coordinates (months after randomization on the X axis and cumulative probability on the Y axis) of at least 20 points of each original curve to ensure the best fitting. Subsequently, these values were entered in the calculations spreadsheet provided by the authors to estimate HR and its 95% CI[1].

Pair-wise meta-analyses

All comparisons included in the pair-wise meta-analyses were performed as follows: 1) experimental therapy versus conventional bortezomib-based therapy (with subgroup analyses for class of drugs – bortezomib+HDACi (BORT+HDAC), bortezomib+mAbs (BORT+mAbs), bortezomib+bevacizumab/siltuximab/PLD or subcutaneous bortezomib (BORT+OTHER), carfilzomib (CARF), IMiDs – and for "single" (X +/- DEX, 2 drugs regimen) versus "double" (X + Y +/- DEX, 3 drugs regimen) schedules), and 2) experimental therapy versus conventional IMiDs-based therapy (with subgroup analyses for class of drugs – bortezomib (BORT), IMiDs + mAbs, PIs+mAbs – and for "single" (X +/- DEX, 2 drugs regimen) versus "double" (X + Y +/- DEX, 3 drugs regimen) schedules).

References

1. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.

Supplementary figures legends

Figure S1: funnel plots of studies included in bortezomib and IMiDs pair-wise meta-analysis

Figure S2: forest plots of comparisons between experimental and standard treatments in term of PFS and OS. Bortezomib +/- DEX represents the standard treatment in A (PFS) and C (OS) while IMiDs represent the standard treatment in B (PFS) and D (OS). Subgroups have been made according to the number of drugs (excluding DEX) included in the experimental regimen (one or two) against standard therapy.

Figure S3: forest plots of comparisons between experimental treatment and bortezomib +/- DEX standard treatment in term of overall response rate (ORR, A-B), very good partial response rate (VGPR, C-D) and complete response rate (CR, E-F). Subgroups have been made according to drug classes (A, C, E) or to the number of drugs (excluding DEX) included in the experimental regimen (one or two) against standard therapy (B, D, F).

Figure S4: forest plots of comparisons between experimental treatment and IMiDs standard treatment in term of overall response rate (ORR, A-B), very good partial response rate (VGPR, C-D) and complete response rate (CR, E-F). Subgroups have been made according to drug classes (A, C, E) or to the number of drugs (excluding DEX) included in the experimental regimen (one or two) against standard therapy (B, D, F).

Figure S5: A: network plots of all treatment groups evaluated in the NMA for the analysis of OS, ORR, CR, and safety. B: network plots of all regimens evaluated in the NMA for the analysis PFS, ORR, CR, and safety.

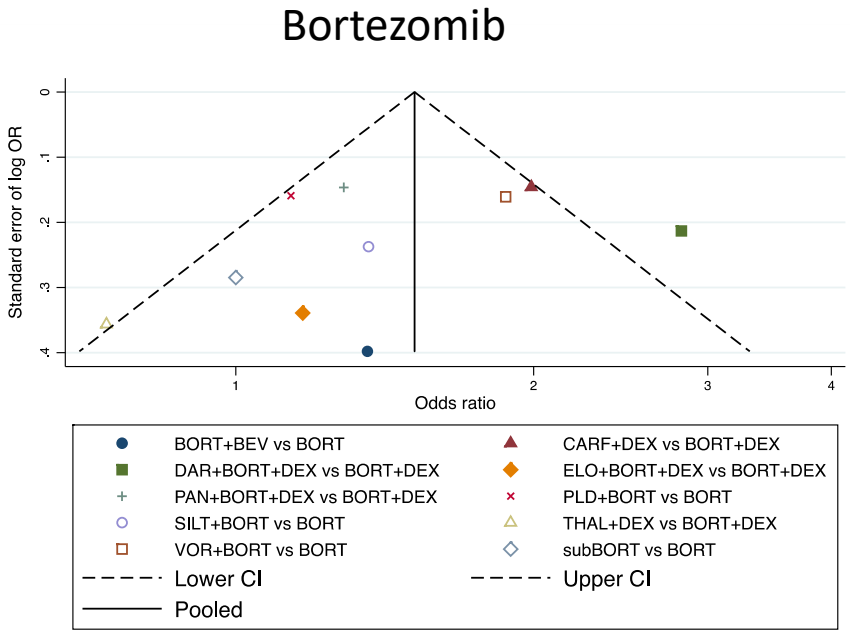
Figure S6: on the upper side, interval plots reporting the effect of each treatment group as compared to all other regimens in term of PFS (left) or OS (right). On the lower side, effect estimates of the treatment in term of overall response rate (column headings being compared to row headings) complete response rate safety (row headings being compared to column headings).

Figure S7: A: probability of each treatment group to rank as the best regimen in term of progression free survival (PFS), overall survival (OS), overall response rate (ORR), complete response rate (CR) and toxicity. B shows all the surface under the cumulative ranking curve (SUCRA) values for each treatment group as regard to PFS, OS, ORR, CR and Toxicity (TOX, in this case the higher is the SUCRA the safer is the regimen for patients). An average SUCRA and the average ranking is further provided. C: probability of being at each rank for all treatment groups evaluated in our analysis.

Figure S8: A: probability of each schedule to rank as the best regimen in term of progression free survival (PFS), overall survival (OS), overall response rate (ORR), complete response rate (CR) and toxicity. B: cumulative ranking probabilities for each regimen evaluated in network meta-analysis as regard to PFS and OS.

Figure S9: A: IF plot evaluating inconsistency and loop-specific heterogeneity for network meta-analysis on progression free survival (PFS) and overall survival (OS) end-points. B: P-scores (frequentist equivalent of surface under the cumulative ranking curve (SUCRA)) for each regimen as regard to PFS, OS, overall response rate (ORR), complete response rate (CR) and toxicity (TOX). An average P-score and the average ranking is further provided.

Figure S1


Bortezomib
Standard error of log OR
0
.1
.2
.3
.4
1
2
3
4
Odds ratio
BORT+BEV vs BORT
DAR+BORT+DEX vs BORT+DEX
PAN+BORT+DEX vs BORT+DEX
SILT+BORT vs BORT
VOR+BORT vs BORT
CARF+DEX vs BORT+DEX
ELO+BORT+DEX vs BORT+DEX
PLD+BORT vs BORT
THAL+DEX vs BORT+DEX
subBORT vs BORT
Lower CI
Upper CI
Pooled

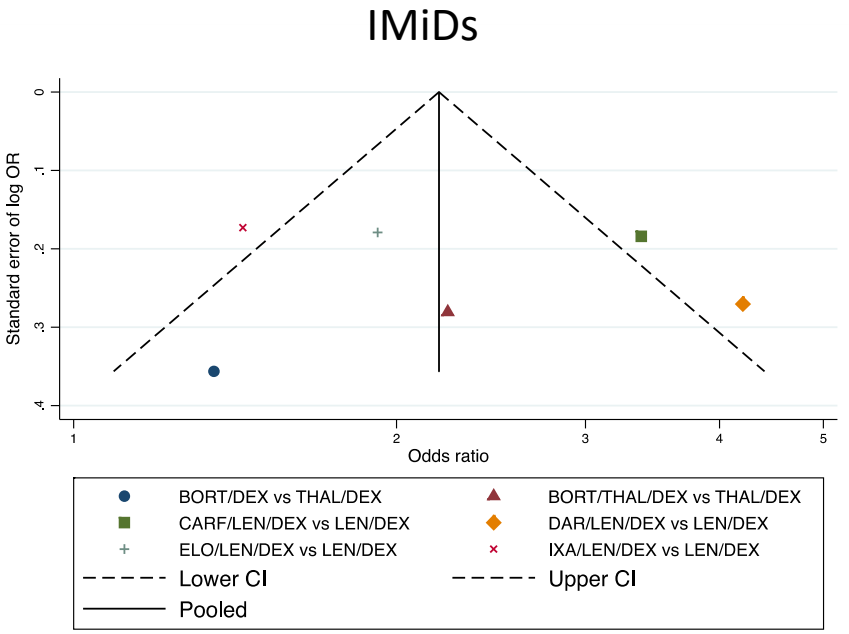

IMiDs
Standard error of log OR
0
.1
.2
.3
.4
1
2
3
4
5
Odds ratio
BORT/DEX vs THAL/DEX
CARF/LEN/DEX vs LEN/DEX
ELO/LEN/DEX vs LEN/DEX
BORT/THAL/DEX vs THAL/DEX
DAR/LEN/DEX vs LEN/DEX
IXA/LEN/DEX vs LEN/DEX
Lower CI
Upper CI
Pooled

Figure S2

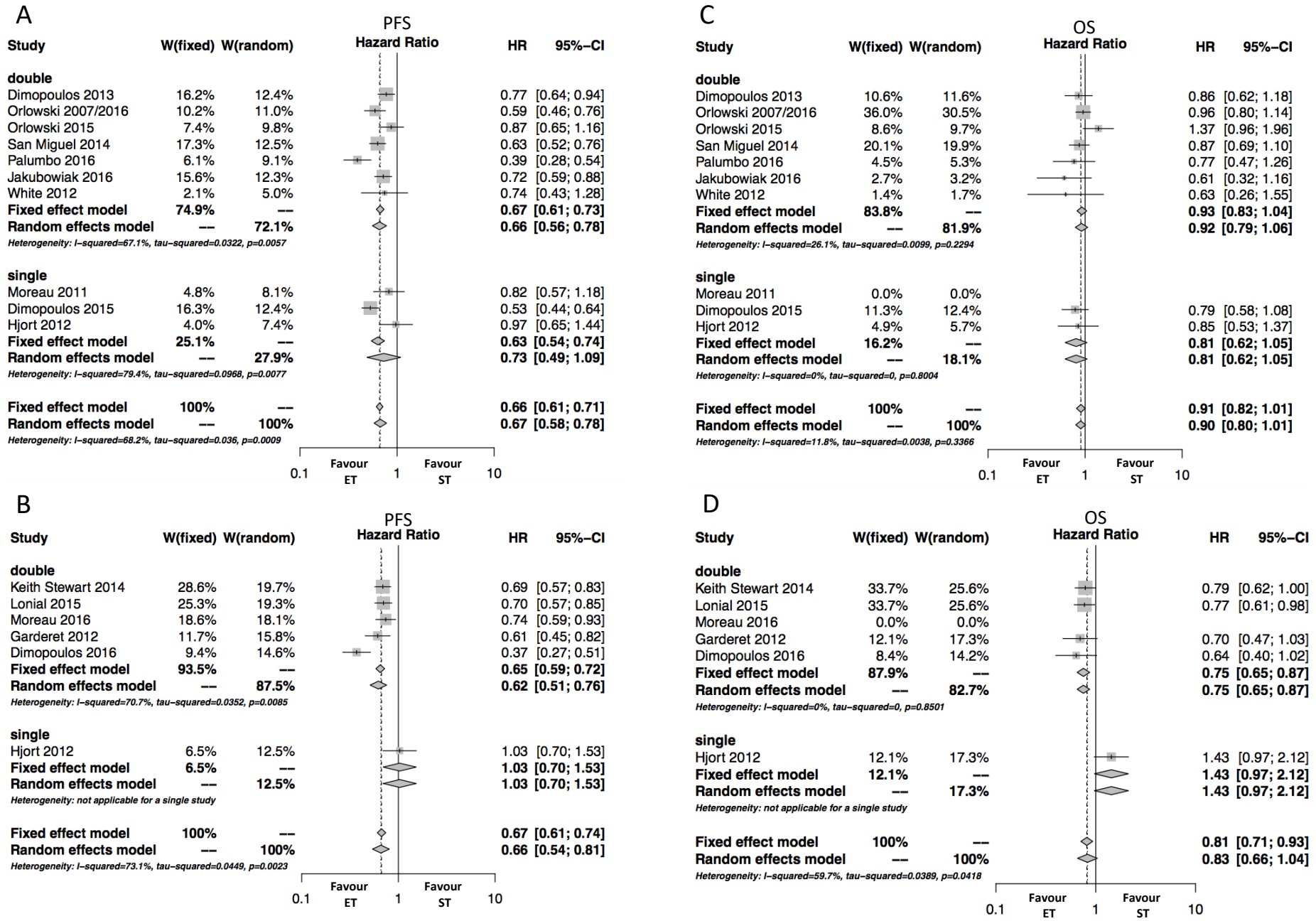

A
PFS
Hazard Ratio
Study W(fixed) W(random) HR 95%–CI
double
Dimopoulos 2013 16.2% 12.4% 0.77 [0.64; 0.94]
Orlowski 2007/2016 10.2% 11.0% 0.59 [0.46; 0.76]
Orlowski 2015 7.4% 9.8% 0.87 [0.65; 1.16]
San Miguel 2014 17.3% 12.5% 0.63 [0.52; 0.76]
Palumbo 2016 6.1% 9.1% 0.39 [0.28; 0.54]
Jakubowiak 2016 15.6% 12.3% 0.72 [0.59; 0.88]
White 2012 2.1% 5.0% 0.74 [0.43; 1.28]
Fixed effect model 74.9% — 0.67 [0.61; 0.73]
Random effects model — 72.1% 0.66 [0.56; 0.78]
Heterogeneity: I–squared=67.1%, tau–squared=0.0322, p=0.0057
single
Moreau 2011 4.8% 8.1% 0.82 [0.57; 1.18]
Dimopoulos 2015 16.3% 12.4% 0.53 [0.44; 0.64]
Hjort 2012 4.0% 7.4% 0.97 [0.65; 1.44]
Fixed effect model 25.1% — 0.63 [0.54; 0.74]
Random effects model — 27.9% 0.73 [0.49; 1.09]
Heterogeneity: I–squared=79.4%, tau–squared=0.0968, p=0.0077
Fixed effect model 100% — 0.66 [0.61; 0.71]
Random effects model — 100% 0.67 [0.58; 0.78]
Heterogeneity: I–squared=68.2%, tau–squared=0.036, p=0.0009
0.1
Favour ET
1
Favour ST
10
C
OS
Hazard Ratio
Study W(fixed) W(random) HR 95%–CI
double
Dimopoulos 2013 10.6% 11.6% 0.86 [0.62; 1.18]
Orlowski 2007/2016 36.0% 30.5% 0.96 [0.80; 1.14]
Orlowski 2015 8.6% 9.7% 1.37 [0.96; 1.96]
San Miguel 2014 20.1% 19.9% 0.87 [0.69; 1.10]
Palumbo 2016 4.5% 5.3% 0.77 [0.47; 1.26]
Jakubowiak 2016 2.7% 3.2% 0.61 [0.32; 1.16]
White 2012 1.4% 1.7% 0.63 [0.26; 1.55]
Fixed effect model 83.8% — 0.93 [0.83; 1.04]
Random effects model — 81.9% 0.92 [0.79; 1.06]
Heterogeneity: I–squared=26.1%, tau–squared=0.0099, p=0.2294
single
Moreau 2011 0.0% 0.0%
Dimopoulos 2015 11.3% 12.4% 0.79 [0.58; 1.08]
Hjort 2012 4.9% 5.7% 0.85 [0.53; 1.37]
Fixed effect model 16.2% — 0.81 [0.62; 1.05]
Random effects model — 18.1% 0.81 [0.62; 1.05]
Heterogeneity: I–squared=0%, tau–squared=0, p=0.8004
Fixed effect model 100% — 0.91 [0.82; 1.01]
Random effects model — 100% 0.90 [0.80; 1.01]
Heterogeneity: I–squared=11.8%, tau–squared=0.0038, p=0.3366
0.1
Favour ET
1
Favour ST
10
B
PFS
Hazard Ratio
Study W(fixed) W(random) HR 95%–CI
double
Keith Stewart 2014 28.6% 19.7% 0.69 [0.57; 0.83]
Lonial 2015 25.3% 19.3% 0.70 [0.57; 0.85]
Moreau 2016 18.6% 18.1% 0.74 [0.59; 0.93]
Garderet 2012 11.7% 15.8% 0.61 [0.45; 0.82]
Dimopoulos 2016 9.4% 14.6% 0.37 [0.27; 0.51]
Fixed effect model 93.5% — 0.65 [0.59; 0.72]
Random effects model — 87.5% 0.62 [0.51; 0.76]
Heterogeneity: I–squared=70.7%, tau–squared=0.0352, p=0.0085
single
Hjort 2012 6.5% 12.5% 1.03 [0.70; 1.53]
Fixed effect model 6.5% — 1.03 [0.70; 1.53]
Random effects model — 12.5% 1.03 [0.70; 1.53]
Heterogeneity: not applicable for a single study
Fixed effect model 100% — 0.67 [0.61; 0.74]
Random effects model — 100% 0.66 [0.54; 0.81]
Heterogeneity: I–squared=73.1%, tau–squared=0.0449, p=0.0023
0.1
Favour ET
1
Favour ST
10
D
OS
Hazard Ratio
Study W(fixed) W(random) HR 95%–CI
double
Keith Stewart 2014 33.7% 25.6% 0.79 [0.62; 1.00]
Lonial 2015 33.7% 25.6% 0.77 [0.61; 0.98]
Moreau 2016 0.0% 0.0%
Garderet 2012 12.1% 17.3% 0.70 [0.47; 1.03]
Dimopoulos 2016 8.4% 14.2% 0.64 [0.40; 1.02]
Fixed effect model 87.9% — 0.75 [0.65; 0.87]
Random effects model — 82.7% 0.75 [0.65; 0.87]
Heterogeneity: I–squared=0%, tau–squared=0, p=0.8501
single
Hjort 2012 12.1% 17.3% 1.43 [0.97; 2.12]
Fixed effect model 12.1% — 1.43 [0.97; 2.12]
Random effects model — 17.3% 1.43 [0.97; 2.12]
Heterogeneity: not applicable for a single study
Fixed effect model 100% — 0.81 [0.71; 0.93]
Random effects model — 100% 0.83 [0.66; 1.04]
Heterogeneity: I–squared=59.7%, tau–squared=0.0389, p=0.0418
0.1
Favour ET
1
Favour ST
10

Figure S3

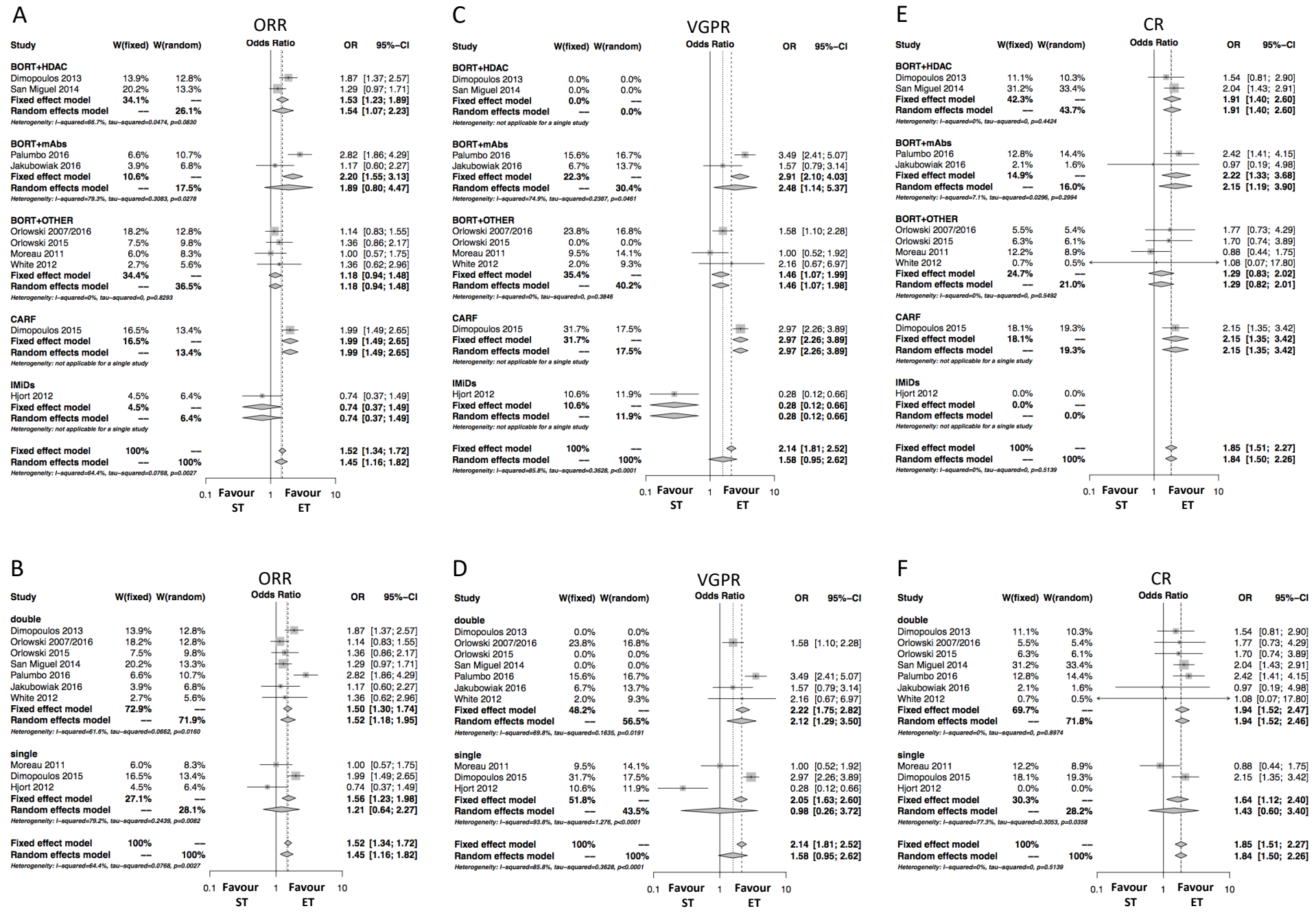
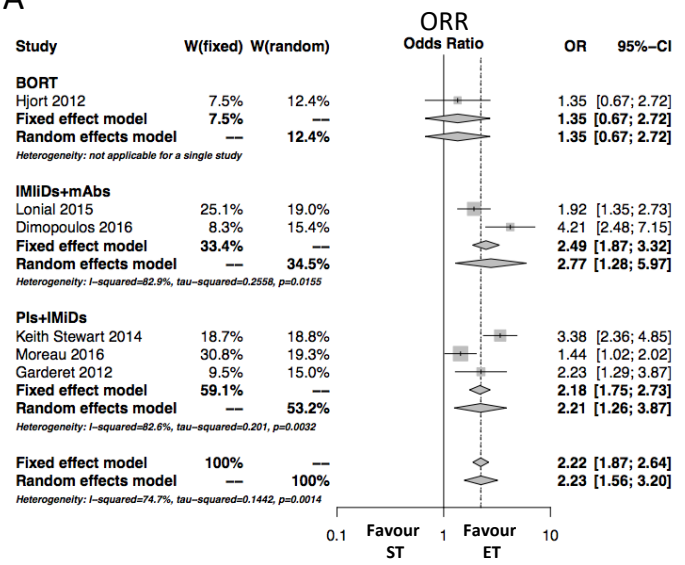
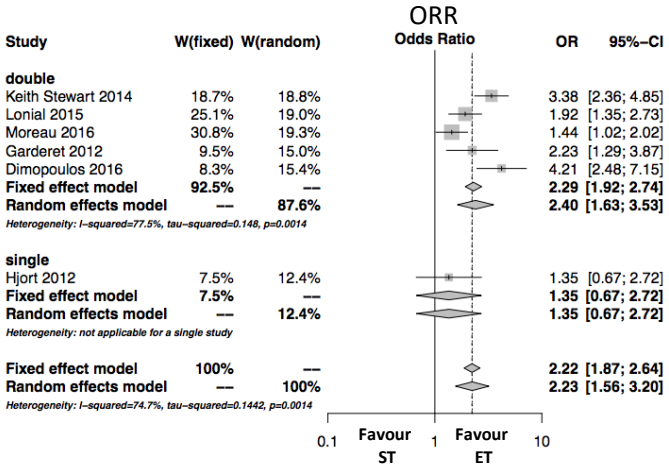

A
ORR
Study W(fixed) W(random) OR 95%−CI
BORT+HDAC
Dimopoulos 2013 13.9% 12.8% 1.87 [1.37; 2.57]
San Miguel 2014 20.2% 13.3% 1.29 [0.97; 1.71]
Fixed effect model 34.1% — 1.53 [1.23; 1.89]
Random effects model — 26.1% 1.54 [1.07; 2.23]
Heterogeneity: I−squared=66.7%, tau−squared=0.0474, p=0.0830
BORT+mAbs
Palumbo 2016 6.6% 10.7% 2.82 [1.86; 4.29]
Jakubowiak 2016 3.9% 6.8% 1.17 [0.60; 2.27]
Fixed effect model 10.6% — 2.20 [1.55; 3.13]
Random effects model — 17.5% 1.89 [0.80; 4.47]
Heterogeneity: I−squared=79.3%, tau−squared=0.3083, p=0.0278
BORT+OTHER
Orlowski 2007/2016 18.2% 12.8% 1.14 [0.83; 1.55]
Orlowski 2015 7.5% 9.8% 1.36 [0.86; 2.17]
Moreau 2011 6.0% 8.3% 1.00 [0.57; 1.75]
White 2012 2.7% 5.6% 1.36 [0.62; 2.96]
Fixed effect model 34.4% — 1.18 [0.94; 1.48]
Random effects model — 36.5% 1.18 [0.94; 1.48]
Heterogeneity: I−squared=0%, tau−squared=0, p=0.8293
CARF
Dimopoulos 2015 16.5% 13.4% 1.99 [1.49; 2.65]
Fixed effect model 16.5% — 1.99 [1.49; 2.65]
Random effects model — 13.4% 1.99 [1.49; 2.65]
Heterogeneity: not applicable for a single study
IMiDs
Hjort 2012 4.5% 6.4% 0.74 [0.37; 1.49]
Fixed effect model 4.5% — 0.74 [0.37; 1.49]
Random effects model — 6.4% 0.74 [0.37; 1.49]
Heterogeneity: not applicable for a single study
Fixed effect model 100% — 1.52 [1.34; 1.72]
Random effects model — 100% 1.45 [1.16; 1.82]
Heterogeneity: I−squared=64.4%, tau−squared=0.0768, p=0.0027
Odds Ratio
0.1 Favour ST 1 Favour ET 10
C
VGPR
Study W(fixed) W(random) OR 95%−CI
BORT+HDAC
Dimopoulos 2013 0.0% 0.0%
San Miguel 2014 0.0% 0.0%
Fixed effect model 0.0% —
Random effects model — 0.0%
Heterogeneity: not applicable for a single study
BORT+mAbs
Palumbo 2016 15.6% 16.7% 3.49 [2.41; 5.07]
Jakubowiak 2016 6.7% 13.7% 1.57 [0.79; 3.14]
Fixed effect model 22.3% — 2.91 [2.10; 4.03]
Random effects model — 30.4% 2.48 [1.14; 5.37]
Heterogeneity: I−squared=74.9%, tau−squared=0.2387, p=0.0461
BORT+OTHER
Orlowski 2007/2016 23.8% 16.8% 1.58 [1.10; 2.28]
Orlowski 2015 0.0% 0.0%
Moreau 2011 9.5% 14.1% 1.00 [0.52; 1.92]
White 2012 2.0% 9.3% 2.16 [0.67; 6.97]
Fixed effect model 35.4% — 1.46 [1.07; 1.99]
Random effects model — 40.2% 1.46 [1.07; 1.98]
Heterogeneity: I−squared=0%, tau−squared=0, p=0.3846
CARF
Dimopoulos 2015 31.7% 17.5% 2.97 [2.26; 3.89]
Fixed effect model 31.7% — 2.97 [2.26; 3.89]
Random effects model — 17.5% 2.97 [2.26; 3.89]
Heterogeneity: not applicable for a single study
IMiDs
Hjort 2012 10.6% 11.9% 0.28 [0.12; 0.66]
Fixed effect model 10.6% — 0.28 [0.12; 0.66]
Random effects model — 11.9% 0.28 [0.12; 0.66]
Heterogeneity: not applicable for a single study
Fixed effect model 100% — 2.14 [1.81; 2.52]
Random effects model — 100% 1.58 [0.95; 2.62]
Heterogeneity: I−squared=85.8%, tau−squared=0.3628, p<0.0001
Odds Ratio
0.1 Favour ST 1 Favour ET 10
E
CR
Study W(fixed) W(random) OR 95%−CI
BORT+HDAC
Dimopoulos 2013 11.1% 10.3% 1.54 [0.81; 2.90]
San Miguel 2014 31.2% 33.4% 2.04 [1.43; 2.91]
Fixed effect model 42.3% — 1.91 [1.40; 2.60]
Random effects model — 43.7% 1.91 [1.40; 2.60]
Heterogeneity: I−squared=0%, tau−squared=0, p=0.4424
BORT+mAbs
Palumbo 2016 12.8% 14.4% 2.42 [1.41; 4.15]
Jakubowiak 2016 2.1% 1.6% 0.97 [0.19; 4.98]
Fixed effect model 14.9% — 2.22 [1.33; 3.68]
Random effects model — 16.0% 2.15 [1.19; 3.90]
Heterogeneity: I−squared=7.1%, tau−squared=0.0296, p=0.2994
BORT+OTHER
Orlowski 2007/2016 5.5% 5.4% 1.77 [0.73; 4.29]
Orlowski 2015 6.3% 6.1% 1.70 [0.74; 3.89]
Moreau 2011 12.2% 8.9% 0.88 [0.44; 1.75]
White 2012 0.7% 0.5% 1.08 [0.07; 17.80]
Fixed effect model 24.7% — 1.29 [0.83; 2.02]
Random effects model — 21.0% 1.29 [0.82; 2.01]
Heterogeneity: I−squared=0%, tau−squared=0, p=0.5492
CARF
Dimopoulos 2015 18.1% 19.3% 2.15 [1.35; 3.42]
Fixed effect model 18.1% — 2.15 [1.35; 3.42]
Random effects model — 19.3% 2.15 [1.35; 3.42]
Heterogeneity: not applicable for a single study
IMiDs
Hjort 2012 0.0% 0.0%
Fixed effect model 0.0% —
Random effects model — 0.0%
Heterogeneity: not applicable for a single study
Fixed effect model 100% — 1.85 [1.51; 2.27]
Random effects model — 100% 1.84 [1.50; 2.26]
Heterogeneity: I−squared=0%, tau−squared=0, p=0.5139
Odds Ratio
0.1 Favour ST 1 Favour ET 10
B
ORR
Study W(fixed) W(random) OR 95%−CI
double
Dimopoulos 2013 13.9% 12.8% 1.87 [1.37; 2.57]
Orlowski 2007/2016 18.2% 12.8% 1.14 [0.83; 1.55]
Orlowski 2015 7.5% 9.8% 1.36 [0.86; 2.17]
San Miguel 2014 20.2% 13.3% 1.29 [0.97; 1.71]
Palumbo 2016 6.6% 10.7% 2.82 [1.86; 4.29]
Jakubowiak 2016 3.9% 6.8% 1.17 [0.60; 2.27]
White 2012 2.7% 5.6% 1.36 [0.62; 2.96]
Fixed effect model 72.9% — 1.50 [1.30; 1.74]
Random effects model — 71.9% 1.52 [1.18; 1.95]
Heterogeneity: I−squared=61.6%, tau−squared=0.0662, p=0.0160
single
Moreau 2011 6.0% 8.3% 1.00 [0.57; 1.75]
Dimopoulos 2015 16.5% 13.4% 1.99 [1.49; 2.65]
Hjort 2012 4.5% 6.4% 0.74 [0.37; 1.49]
Fixed effect model 27.1% — 1.56 [1.23; 1.98]
Random effects model — 28.1% 1.21 [0.64; 2.27]
Heterogeneity: I−squared=79.2%, tau−squared=0.2439, p=0.0082
Fixed effect model 100% — 1.52 [1.34; 1.72]
Random effects model — 100% 1.45 [1.16; 1.82]
Heterogeneity: I−squared=64.4%, tau−squared=0.0768, p=0.0027
Odds Ratio
0.1 Favour ST 1 Favour ET 10
D
VGPR
Study W(fixed) W(random) OR 95%−CI
double
Dimopoulos 2013 0.0% 0.0%
Orlowski 2007/2016 23.8% 16.8% 1.58 [1.10; 2.28]
Orlowski 2015 0.0% 0.0%
San Miguel 2014 0.0% 0.0%
Palumbo 2016 15.6% 16.7% 3.49 [2.41; 5.07]
Jakubowiak 2016 6.7% 13.7% 1.57 [0.79; 3.14]
White 2012 2.0% 9.3% 2.16 [0.67; 6.97]
Fixed effect model 48.2% — 2.22 [1.75; 2.82]
Random effects model — 56.5% 2.12 [1.29; 3.50]
Heterogeneity: I−squared=69.8%, tau−squared=0.1635, p=0.0191
single
Moreau 2011 9.5% 14.1% 1.00 [0.52; 1.92]
Dimopoulos 2015 31.7% 17.5% 2.97 [2.26; 3.89]
Hjort 2012 10.6% 11.9% 0.28 [0.12; 0.66]
Fixed effect model 51.8% — 2.05 [1.63; 2.60]
Random effects model — 43.5% 0.98 [0.26; 3.72]
Heterogeneity: I−squared=93.8%, tau−squared=1.276, p<0.0001
Fixed effect model 100% — 2.14 [1.81; 2.52]
Random effects model — 100% 1.58 [0.95; 2.62]
Heterogeneity: I−squared=85.8%, tau−squared=0.3628, p<0.0001
Odds Ratio
0.1 Favour ST 1 Favour ET 10
F
CR
Study W(fixed) W(random) OR 95%−CI
double
Dimopoulos 2013 11.1% 10.3% 1.54 [0.81; 2.90]
Orlowski 2007/2016 5.5% 5.4% 1.77 [0.73; 4.29]
Orlowski 2015 6.3% 6.1% 1.70 [0.74; 3.89]
San Miguel 2014 31.2% 33.4% 2.04 [1.43; 2.91]
Palumbo 2016 12.8% 14.4% 2.42 [1.41; 4.15]
Jakubowiak 2016 2.1% 1.6% 0.97 [0.19; 4.98]
White 2012 0.7% 0.5% 1.08 [0.07; 17.80]
Fixed effect model 69.7% — 1.94 [1.52; 2.47]
Random effects model — 71.8% 1.94 [1.52; 2.46]
Heterogeneity: I−squared=0%, tau−squared=0, p=0.8974
single
Moreau 2011 12.2% 8.9% 0.88 [0.44; 1.75]
Dimopoulos 2015 18.1% 19.3% 2.15 [1.35; 3.42]
Hjort 2012 0.0% 0.0%
Fixed effect model 30.3% — 1.64 [1.12; 2.40]
Random effects model — 28.2% 1.43 [0.60; 3.40]
Heterogeneity: I−squared=77.3%, tau−squared=0.3053, p=0.0358
Fixed effect model 100% — 1.85 [1.51; 2.27]
Random effects model — 100% 1.84 [1.50; 2.26]
Heterogeneity: I−squared=0%, tau−squared=0, p=0.5139
Odds Ratio
0.1 Favour ST 1 Favour ET 10

Figure S4

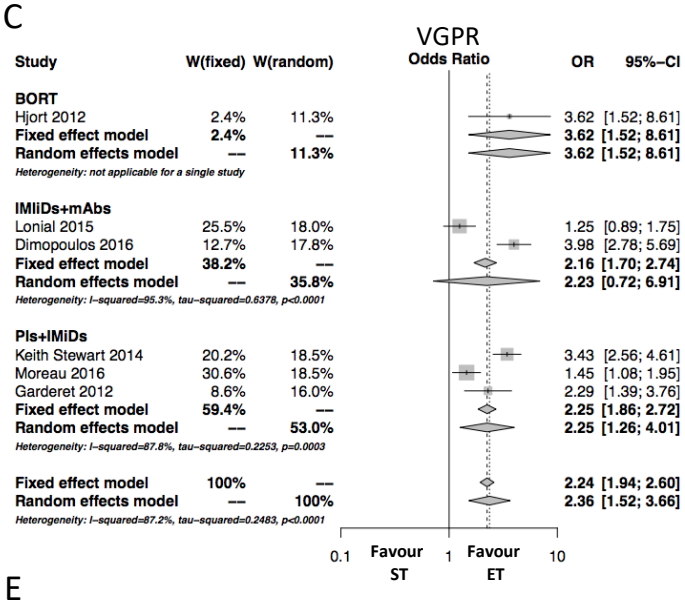
A



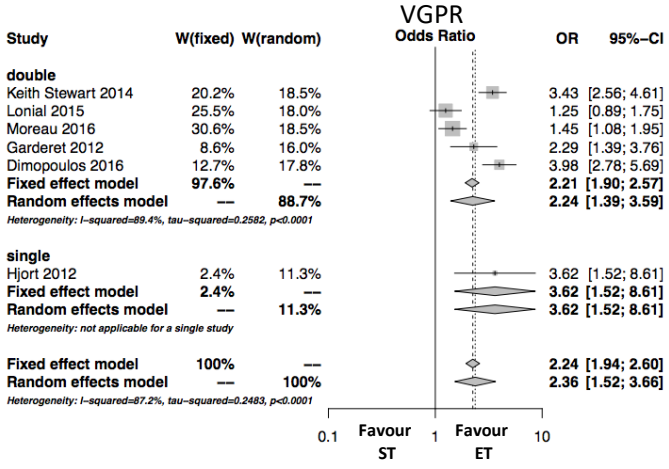
B



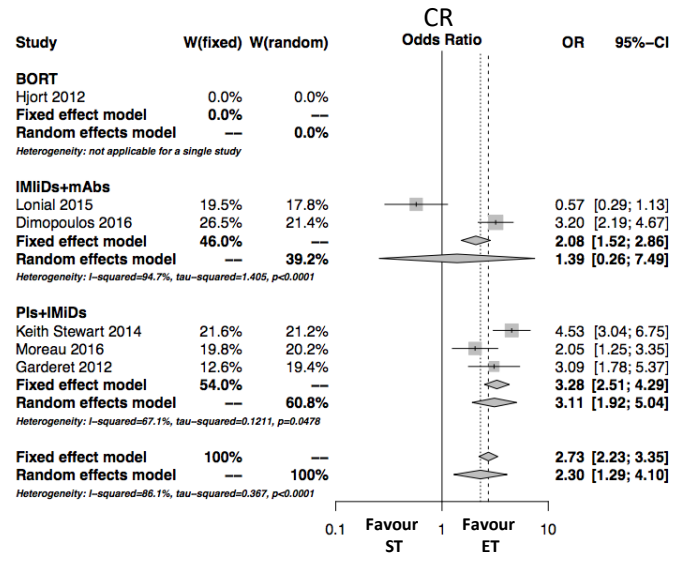
C



D



E



F

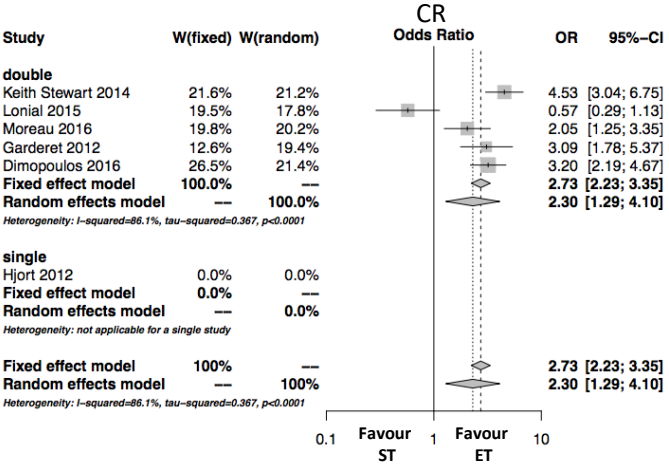


Figure S5

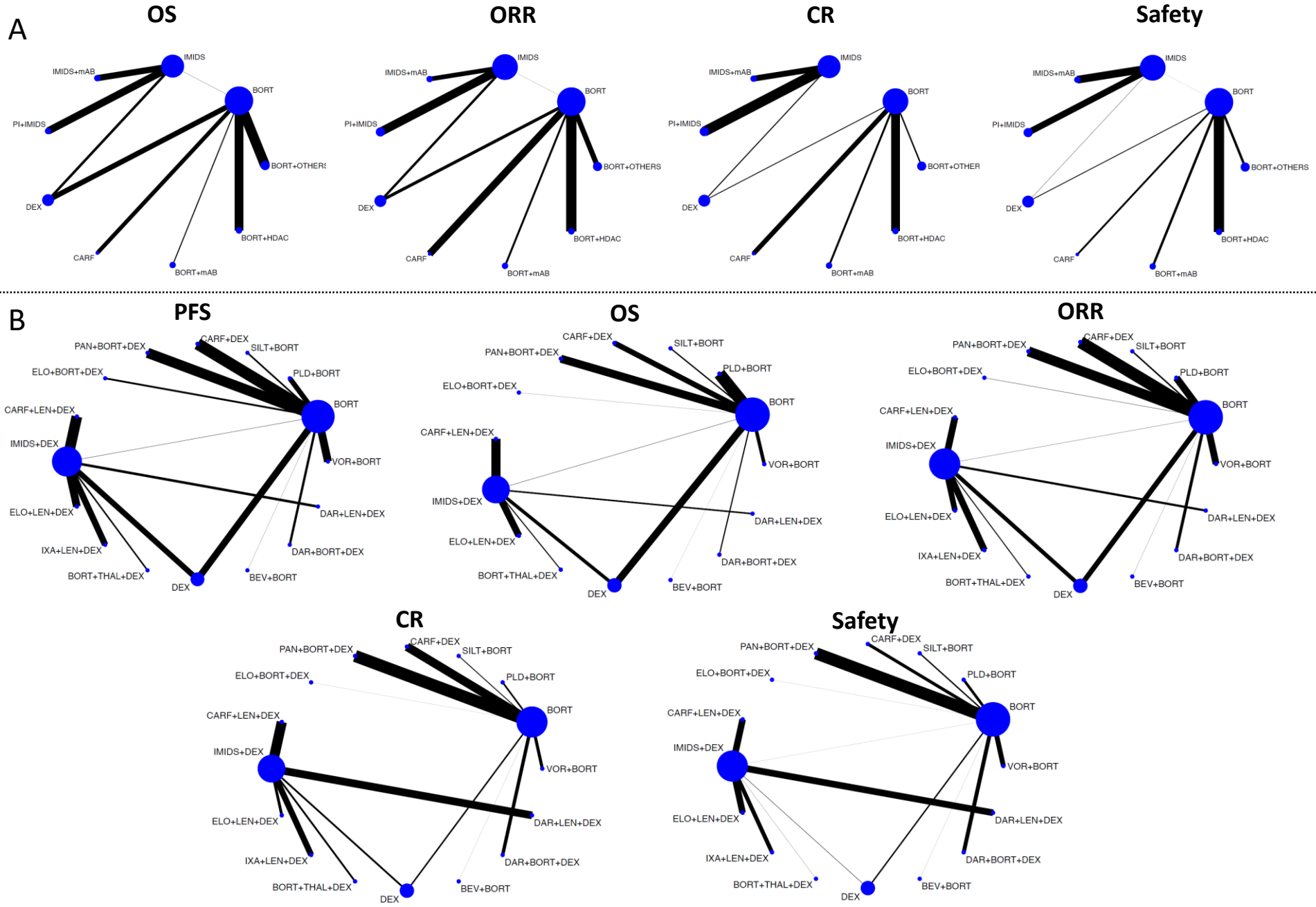
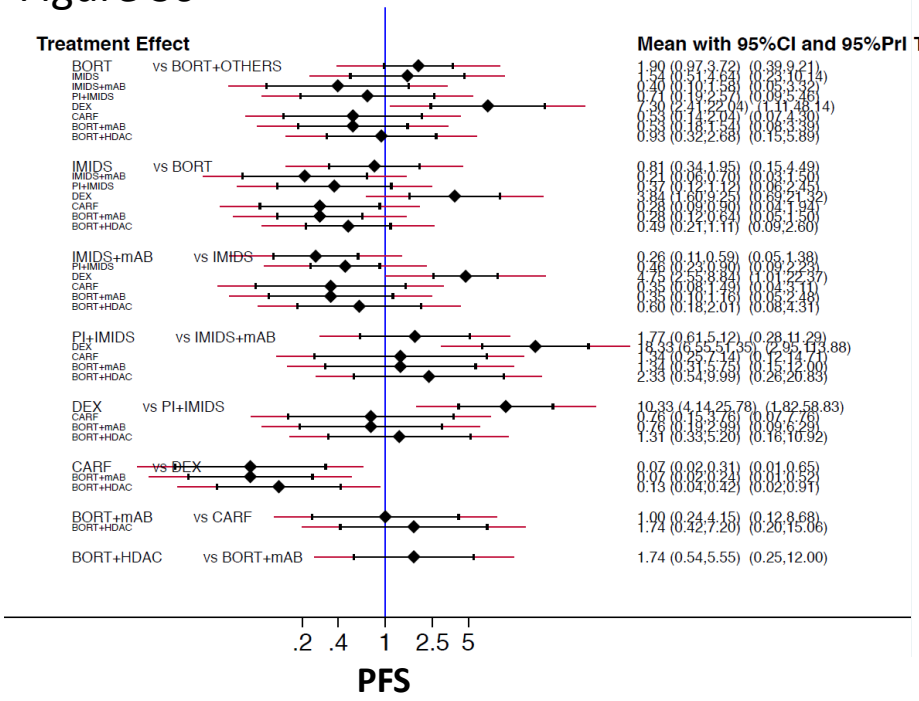
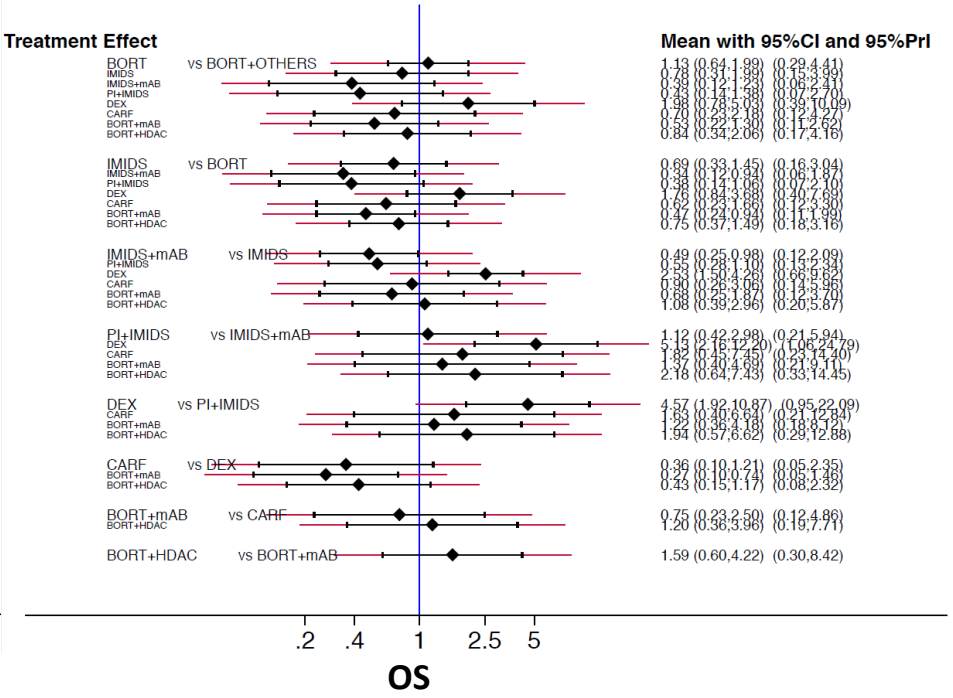

A
OS
ORR
CR
Safety
IMIDS
IMIDS+mAB
PI+IMIDS
DEX
CARF
BORT
BORT+OTHERS
BORT+HDAC
BORT+mAB
B
PFS
OS
ORR
CR
Safety
PAN+BORT+DEX
CARF+DEX
SILT+BORT
ELO+BORT+DEX
PLD+BORT
CARF+LEN+DEX
IMIDS+DEX
VOR+BORT
DAR+LEN+DEX
ELO+LEN+DEX
IXA+LEN+DEX
DAR+BORT+DEX
BORT+THAL+DEX
BEV+BORT

Figure S6





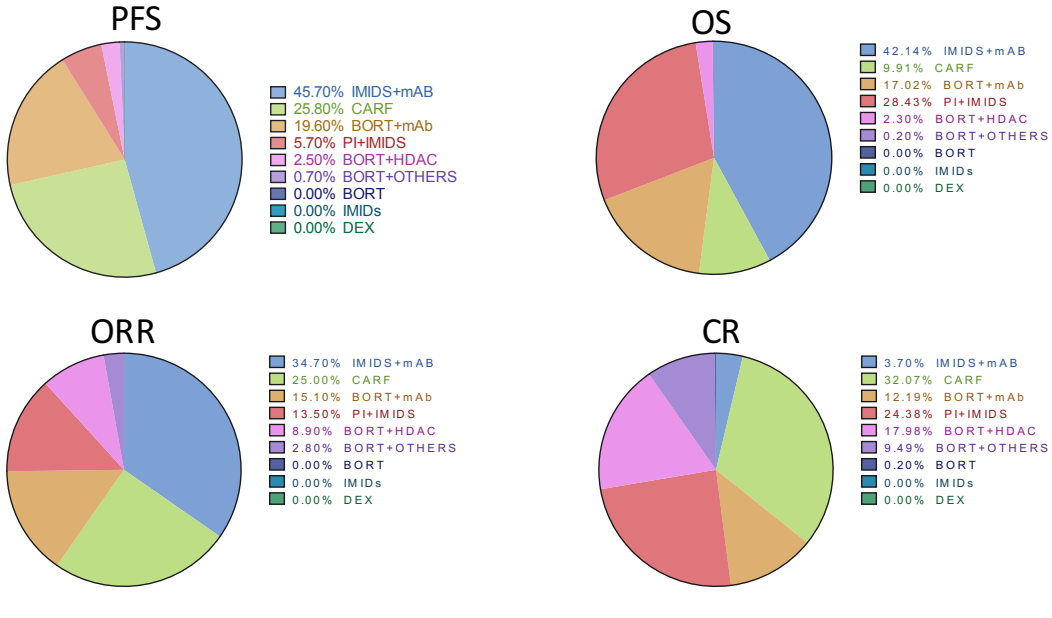
ORR

IMIDS+mAB	1.44 (0.05,45.45)	1.72 (0.08,34.79)	1.65 (0.18,14.72)	2.37 (0.12,47.97)	3.50 (0.20,60.17)	5.73 (0.48,68.63)	8.05 (1.48,43.89)	60.45 (7.21,506.90)
9.06 (0.03,2945.02)	CARF	1.19 (0.06,22.55)	1.14 (0.04,31.39)	1.65 (0.09,31.10)	2.44 (0.15,38.86)	3.98 (0.36,43.82)	5.59 (0.28,113.17)	42.01 (2.08,849.81)
4.68 (0.02,892.12)	0.52 (0.01,34.92)	BORT+mAB	0.96 (0.06,16.48)	1.38 (0.13,15.20)	2.04 (0.23,18.23)	3.33 (0.61,18.19)	4.68 (0.39,56.16)	35.18 (2.93,421.66)
5.13 (0.22,118.35)	0.57 (0.00,154.89)	1.10 (0.01,172.53)	PI+IMIDS	1.44 (0.08,24.72)	2.13 (0.15,30.69)	3.48 (0.35,34.06)	4.88 (1.22,19.51)	36.69 (5.56,242.29)
6.22 (0.03,1183.35)	0.69 (0.01,46.30)	1.33 (0.04,41.47)	1.21 (0.01,190.59)	BORT+HDAC	1.48 (0.17,13.21)	2.42 (0.44,13.17)	3.39 (0.28,40.68)	25.50 (2.13,305.43)
4.36 (0.03,685.10)	0.48 (0.01,25.59)	0.93 (0.04,21.64)	0.85 (0.01,109.52)	0.70 (0.03,16.24)	BORT+OTHERS	1.63 (0.41,6.53)	2.30 (0.23,22.50)	17.25 (1.76,168.96)
1.98 (0.02,207.36)	0.22 (0.01,6.81)	0.42 (0.04,4.83)	0.39 (0.00,32.55)	0.32 (0.03,3.62)	0.45 (0.06,3.33)	BORT	1.41 (0.23,8.62)	10.55 (1.72,64.73)
0.55 (0.05,6.20)	0.06 (0.00,11.46)	0.12 (0.00,12.23)	0.11 (0.01,0.77)	0.09 (0.00,9.19)	0.13 (0.00,10.56)	0.28 (0.01,14.53)	IMIDS	7.51 (2.08,27.08)
0.02 (0.00,0.54)	0.00 (0.00,0.34)	0.01 (0.00,0.34)	0.00 (0.00,0.08)	0.00 (0.00,0.25)	0.01 (0.00,0.29)	0.01 (0.00,0.37)	0.04 (0.01,0.31)	DEX

CR

Figure S7

A



B

	PFS	OS	ORR	CR	TOX	average	ranking
IMIDs+mAb	86.4	85.9	79	41.3	69.3	**72.38**	1
PI+IMIDs	65.1	81.3	68.1	67.5	58.6	**68.12**	2
BORT+mAb	76.7	73.2	68.2	63.1	47.3	**65.7**	3
CARF	75	56.1	69.6	72.7	26	**59.88**	4
IMIDs	28.3	47.5	25.2	28.3	74.2	**40.7**	5
BORT+HDAC	52.2	45.2	59.9	18	13.7	**37.8**	6
BORT+OTHERS	48.5	34.4	48.5	9.5	21.5	**32.48**	7
BORT	17.9	23.6	31.2	0.2	39.7	**22.52**	8
DEX	0	2.8	0.4	0	99.7	**20.58**	9

C

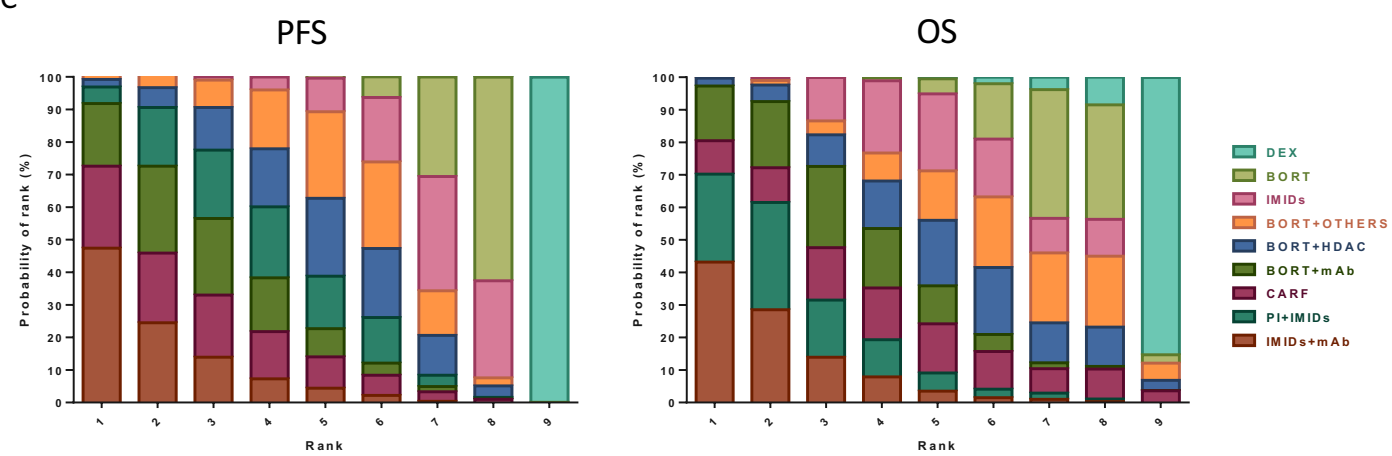
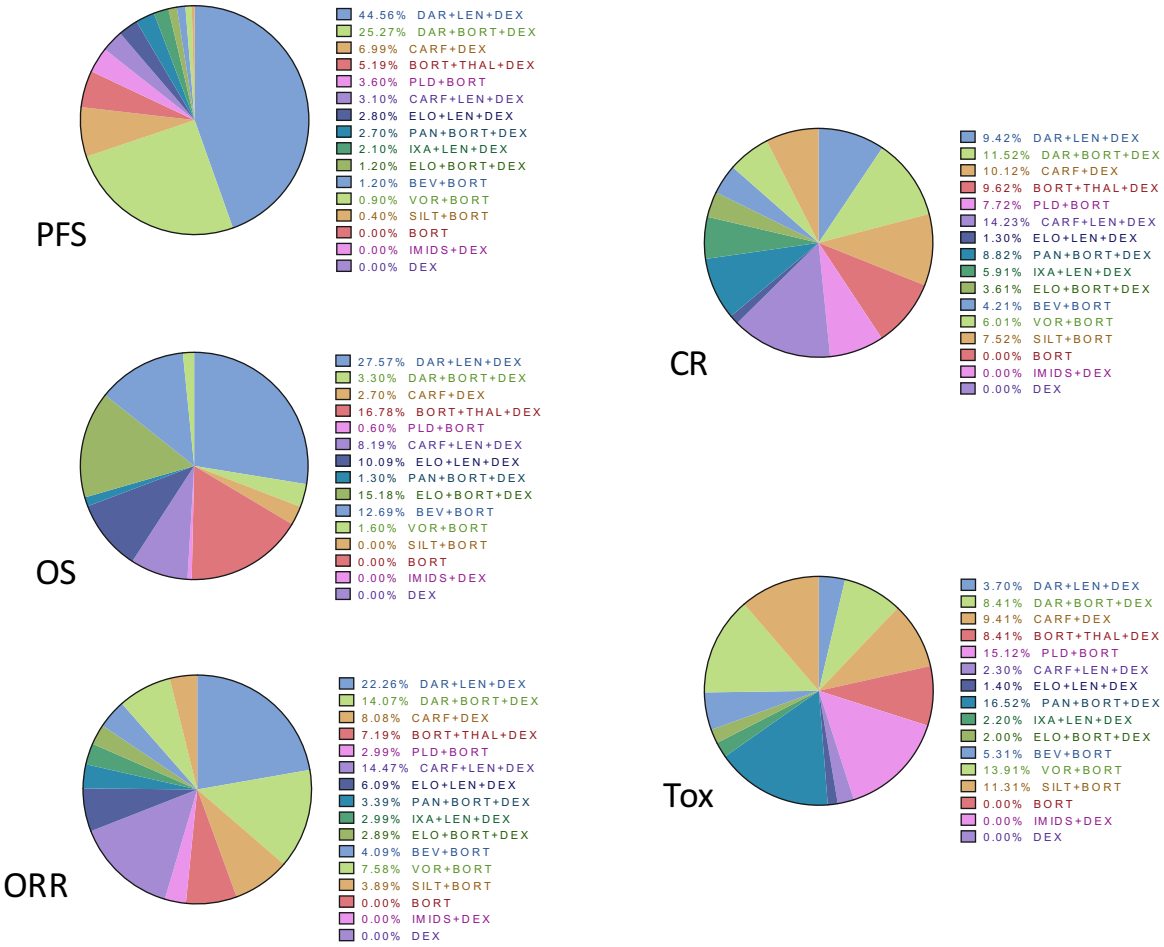


Figure S8

A


PFS
44.56% DAR+LEN+DEX
25.27% DAR+BORT+DEX
6.99% CARF+DEX
5.19% BORT+THAL+DEX
3.60% PLD+BORT
3.10% CARF+LEN+DEX
2.80% ELO+LEN+DEX
2.70% PAN+BORT+DEX
2.10% IXA+LEN+DEX
1.20% ELO+BORT+DEX
1.20% BEV+BORT
0.90% VOR+BORT
0.40% SILT+BORT
0.00% BORT
0.00% IMIDS+DEX
0.00% DEX
CR
9.42% DAR+LEN+DEX
11.52% DAR+BORT+DEX
10.12% CARF+DEX
9.62% BORT+THAL+DEX
7.72% PLD+BORT
14.23% CARF+LEN+DEX
1.30% ELO+LEN+DEX
8.82% PAN+BORT+DEX
5.91% IXA+LEN+DEX
3.61% ELO+BORT+DEX
4.21% BEV+BORT
6.01% VOR+BORT
7.52% SILT+BORT
0.00% BORT
0.00% IMIDS+DEX
0.00% DEX
OS
27.57% DAR+LEN+DEX
3.30% DAR+BORT+DEX
2.70% CARF+DEX
16.78% BORT+THAL+DEX
0.60% PLD+BORT
8.19% CARF+LEN+DEX
10.09% ELO+LEN+DEX
1.30% PAN+BORT+DEX
15.18% ELO+BORT+DEX
12.69% BEV+BORT
1.60% VOR+BORT
0.00% SILT+BORT
0.00% BORT
0.00% IMIDS+DEX
0.00% DEX
Tox
3.70% DAR+LEN+DEX
8.41% DAR+BORT+DEX
9.41% CARF+DEX
8.41% BORT+THAL+DEX
15.12% PLD+BORT
2.30% CARF+LEN+DEX
1.40% ELO+LEN+DEX
16.52% PAN+BORT+DEX
2.20% IXA+LEN+DEX
2.00% ELO+BORT+DEX
5.31% BEV+BORT
13.91% VOR+BORT
11.31% SILT+BORT
0.00% BORT
0.00% IMIDS+DEX
0.00% DEX
ORR
22.26% DAR+LEN+DEX
14.07% DAR+BORT+DEX
8.08% CARF+DEX
7.19% BORT+THAL+DEX
2.99% PLD+BORT
14.47% CARF+LEN+DEX
6.09% ELO+LEN+DEX
3.39% PAN+BORT+DEX
2.99% IXA+LEN+DEX
2.89% ELO+BORT+DEX
4.09% BEV+BORT
7.58% VOR+BORT
3.89% SILT+BORT
0.00% BORT
0.00% IMIDS+DEX
0.00% DEX

B

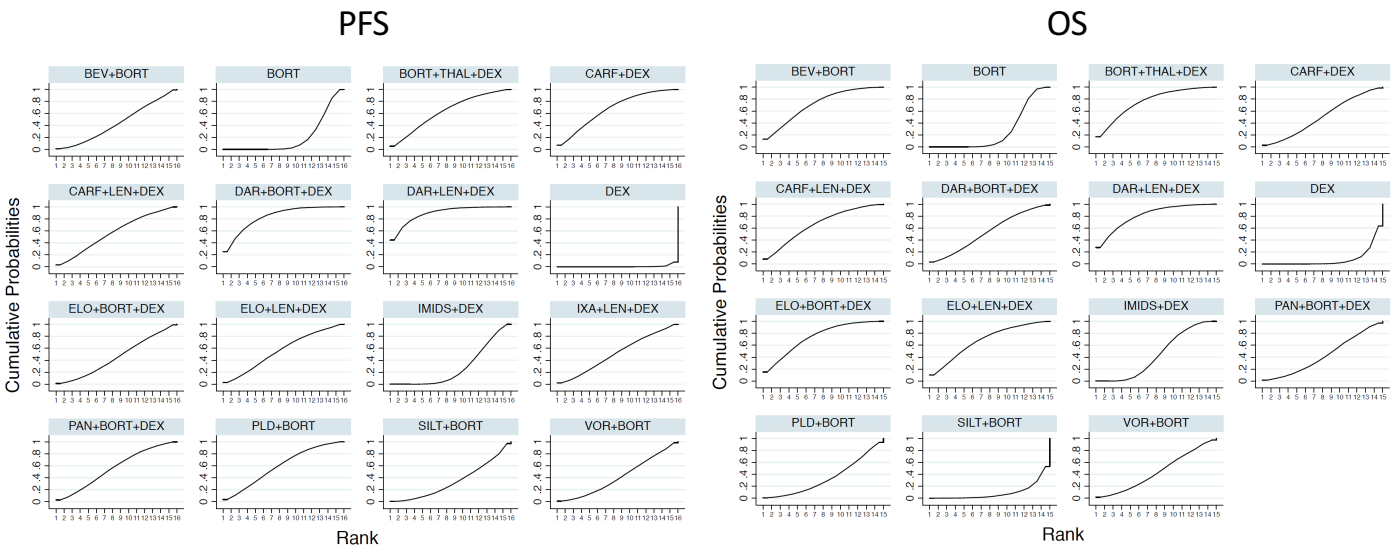
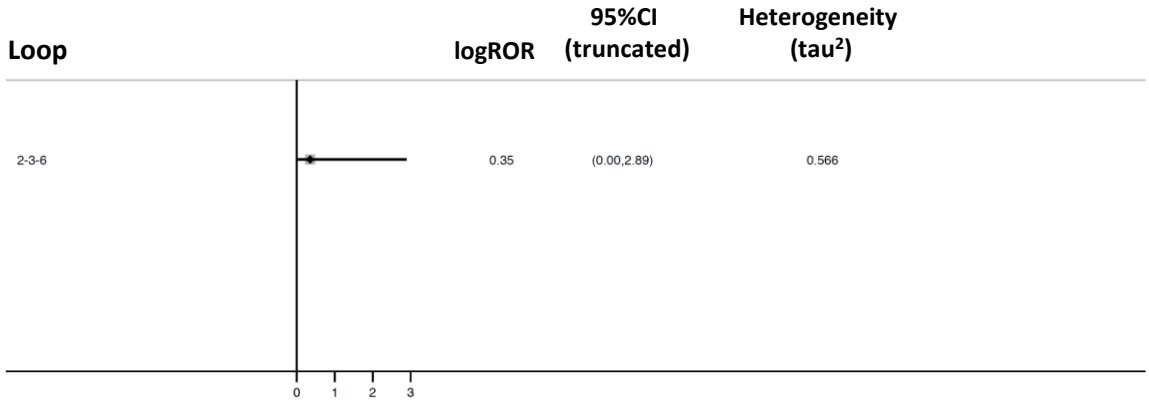

PFS
OS
BEV+BORT
BORT
BORT+THAL+DEX
CARF+DEX
CARF+LEN+DEX
DAR+BORT+DEX
DAR+LEN+DEX
DEX
ELO+BORT+DEX
ELO+LEN+DEX
IMIDS+DEX
IXA+LEN+DEX
PAN+BORT+DEX
PLD+BORT
SILT+BORT
VOR+BORT
Cumulative Probabilities
Rank

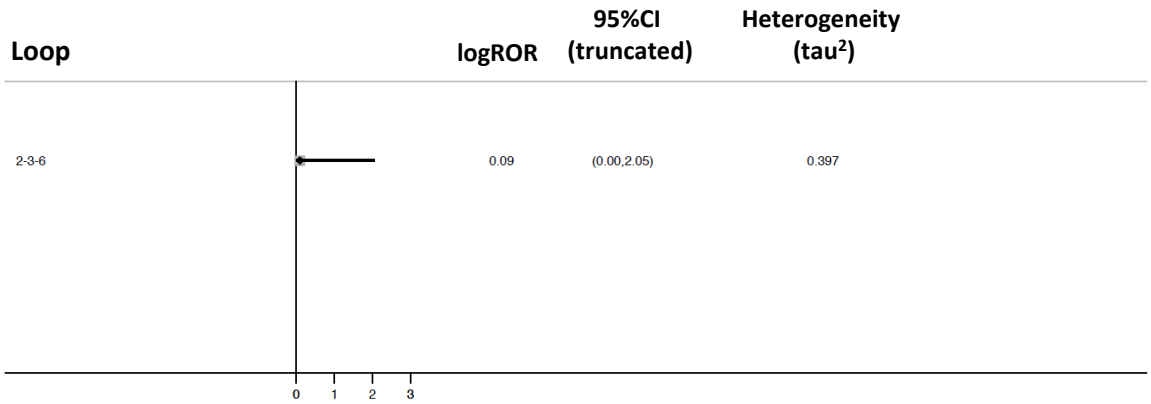
Figure S9

A

PFS



OS



B

	PFS	OS	ORR	CR	TOX	average	ranking
DAR+IMiDs+DEX	0.898	0.826	0.764	0.624	0.553	**0.733**	1
CARF+IMiDs+DEX	0.571	0.695	0.712	0.695	0.604	**0.6554**	2
DAR+BORT+DEX	0.835	0.536	0.71	0.661	0.386	**0.6256**	3
BORT+IMiDs+DEX	0.65	0.777	0.592	0.611	0.429	**0.6118**	4
CARF+DEX	0.672	0.519	0.608	0.633	0.364	**0.5592**	5
ELO+IMiDs+DEX	0.561	0.716	0.547	0.24	0.684	**0.5496**	6
IXA+IMiDs+DEX	0.522		0.456	0.516	0.64	**0.5335**	7
ELO+BORT+DEX	0.462	0.708	0.438	0.443	0.605	**0.5312**	8
BEV+BORT	0.444	0.658	0.486	0.475	0.455	**0.5036**	9
PAN+BORT+DEX	0.556	0.424	0.468	0.621	0.284	**0.4706**	10
VOR+BORT	0.411	0.438	0.589	0.549	0.311	**0.4596**	11
PLD+BORT	0.598	0.328	0.428	0.584	0.296	**0.4468**	12
IMiDs+/-DEX	0.283	0.463	0.309	0.322	0.661	**0.4076**	13
SILT+BORT	0.335	0.08	0.486	0.574	0.336	**0.3622**	14
BORT+/-DEX	0.197	0.259	0.357	0.417	0.454	**0.3368**	15
DEX	0.006	0.071	0.051	0.037	0.94	**0.221**	16