Meta-Analysis of different treatments for platinum-resistant ovarian cancer (PROC)

Based on 7 clinical trials

By Siddhartha Sen

Background & Objective

- To perform meta-analysis i.e. to systematically combine results from multiple independent studies to reach more generalizable conclusions than any single study can offer.

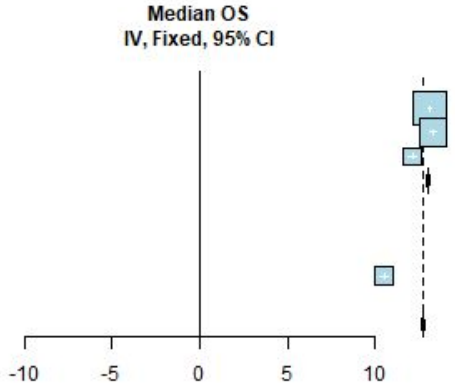
- We summarized different kinds of outcomes for eg Overall Survival, Progression Free Survival and Objective Response Rate from 7 clinical trials evaluating different treatments in PROC compared to different kinds of single-agent chemotherapies.

Methodology

- Software : R (packages - meta, readxl, dplyr)
- Models : Fixed Effect and Random Effects model.

Forest plot for Fixed effects model for Overall Survival

Study or Subgroup	Median OS	SE	Weight	Median OS IV, Fixed, 95% CI
Comparator = chemotherapy				
JAVELIN Ovarian 200	13.1000	0.0696	42.7%	13.10 [12.96; 13.24]
AURELIA	13.3000	0.0818	30.9%	13.30 [13.14; 13.46]
NINJA	12.1000	0.1270	12.8%	12.10 [11.85; 12.35]
Total (95% CI)			**86.4%**	**13.02 [12.93; 13.12]**
Heterogeneity: $Tau^2 = 0.3972$; $Chi^2 = 65.51$, df = 2 ($P < 0.0001$); $I^2 = 96.9\%$				
Comparator = placebo+AUC2-carboplatin				
OVATURE	10.5200	0.1234	13.6%	10.52 [10.28; 10.76]
Total (95% CI)			**100.0%**	**12.68 [12.59; 12.77]**



Heterogeneity: $Tau^2 = 1.6006$; $Chi^2 = 421.22$, df = 3 ($P < 0.0001$); $I^2 = 99.3\%$
Test for overall effect: Z = 278.92 (P = 0)
Test for overall effect: Z = 19.31 ($P < 0.0001$)
Test for subgroup differences: $Chi^2 = 355.72$, df = 1 ($P < 0.0001$)

Interpretations

Comparator = Chemotherapy

- Studies: JAVELIN Ovarian 200, AURELIA, NINJA
  Combined Median OS (Fixed Effects Model): 13.02 months (95% CI: 12.93 to 13.12)

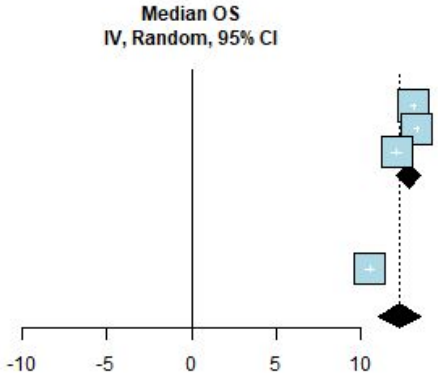
- Heterogeneity: I^2 = 96.9% → indicates substantial variability between these studies.

Comparator = Placebo + AUC2-carboplatin

- Study: OVATURE
  Median OS: 10.52 months (95% CI: 10.28 to 10.76)
- Pooled Median OS (across all 4 studies): 12.68 months
- The large I^2 values (96.9% and 99.3%) suggest significant heterogeneity across studies.

Forest plot for Random effects model for Overall Survival

Study or Subgroup	Median OS	SE	Weight	Median OS IV, Random, 95% CI
Comparator = chemotherapy				
JAVELIN Ovarian 200	13.1000	0.0696	25.1%	13.10 [12.96; 13.24]
AURELIA	13.3000	0.0818	25.1%	13.30 [13.14; 13.46]
NINJA	12.1000	0.1270	24.9%	12.10 [11.85; 12.35]
Total (95% CI)			**75.1%**	**12.84 [12.12; 13.56]**
Heterogeneity: $Tau^2 = 0.3972$; $Chi^2 = 65.51$, df = 2 ($P < 0.0001$); $I^2 = 96.9\%$				
Comparator = placebo+AUC2-carboplatin				
OVATURE	10.5200	0.1234	24.9%	10.52 [10.28; 10.76]
Total (95% CI)			**100.0%**	**12.26 [11.01; 13.50]**



Heterogeneity: $Tau^2 = 1.6006$; $Chi^2 = 421.22$, df = 3 ($P < 0.0001$); $I^2 = 99.3\%$
Test for overall effect: Z = 278.92 (P = 0)
Test for overall effect: Z = 19.31 (P < 0.0001)
Test for subgroup differences: $Chi^2 = 35.71$, df = 1 ($P < 0.0001$)

Interpretations

1. Comparator = Chemotherapy

- Studies: JAVELIN Ovarian 200, AURELIA, NINJA
  Pooled Median OS: 12.84 months (95% CI: 12.12 to 13.56)

- Heterogeneity: $Tau^2 = 0.3972$, $Chi^2 = 65.51$ ($P < 0.0001$)
  $I^2 = 96.9\%$ → high heterogeneity among these studies

2. Comparator = Placebo + AUC2-carboplatin (OVATURE)

- Median OS: 10.52 months (95% CI: 10.28 to 10.76)
- Pooled Median OS: 12.26 months (95% CI: 11.01 to 13.50)
- $I^2 = 99.3\%$ → extreme heterogeneity

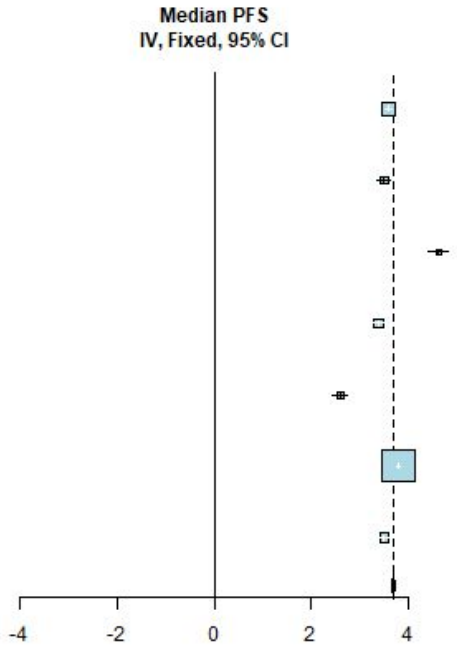
Conclusion

The random effects model accounts for between-study variability, leading to wider, more cautious confidence intervals.

High heterogeneity ($I^2 > 96\%$) makes random effects more appropriate here, as it does not assume that all studies estimate the same underlying effect.

Forest plot for Fixed effect model for Progression Free Survival

Study or Subgroup	Median PFS	SE	Weight	Median PFS IV, Fixed, 95% CI
Comparator = PLD				
CORAIL	3.6000	0.0379	13.6%	3.60 [3.53; 3.67]
Comparator = PLD				
JAVELIN Ovarian 200	3.5000	0.0714	3.8%	3.50 [3.36; 3.64]
Comparator = placebo+AUC2-carboplatin				
OVATURE	4.6300	0.1044	1.8%	4.63 [4.43; 4.83]
Comparator = single-agent chemotherapy				
AURELIA	3.4000	0.0576	5.9%	3.40 [3.29; 3.51]
Comparator = Placebo+Chemotherapy				
PENELOPE	2.6000	0.0794	3.1%	2.60 [2.44; 2.76]
Comparator = chemotherapy(gemcitabine [GEM]or PLD)				
NINJA	3.8000	0.0171	66.9%	3.80 [3.77; 3.83]
Comparator = chemotherapy				
FORWARD I	3.5000	0.0628	5.0%	3.50 [3.38; 3.62]
Total (95% CI)			**100.0%**	**3.70 [3.67; 3.73]**



Heterogeneity: $Tau^2 = 0.3469$; $Chi^2 = 357.63$, df = 6 ($P < 0.0001$); $I^2 = 98.3\%$
Test for overall effect: $Z = 265.01$ ($P = 0$)
Test for overall effect: $Z = 15.95$ ($P < 0.0001$)
Test for subgroup differences: $Chi^2 = 357.63$, df = 6 ($P < 0.0001$)

Interpretations

- Pooled Median PFS: 3.70 months. 95% CI: [3.67 to 3.73]
- $Tau^2 = 0.3469$, $Chi^2 = 357.63$ (df = 6, $P < 0.0001$) - Significant heterogeneity , $I^2 = 98.3\%$ - Very high heterogeneity → results vary substantially across studies, $Chi^2 = 357.63$, $P < 0.0001$ shows significant variation between comparator types.

Forest plot for Random effects model for Progression Free Survival

Study or Subgroup	Median PFS	SE	Weight	Median PFS IV, Random, 95% CI
Comparator = PLD				
CORAIL	3.6000	0.0379	14.4%	3.60 [3.53; 3.67]
Comparator = PLD				
JAVELIN Ovarian 200	3.5000	0.0714	14.3%	3.50 [3.36; 3.64]
Comparator = placebo+AUC2-carboplatin				
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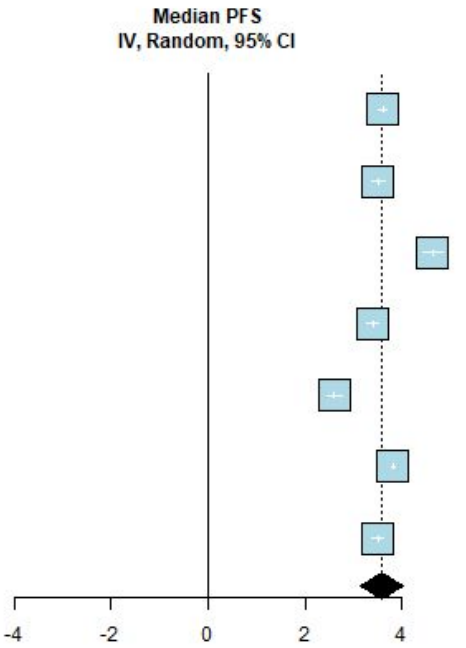
NINJA	3.8000	0.0171	14.5%	3.80 [3.77; 3.83]
Comparator = chemotherapy				
FORWARD I	3.5000	0.0628	14.3%	3.50 [3.38; 3.62]
Total (95% CI)			**100.0%**	**3.57 [3.13; 4.01]**



Heterogeneity: $Tau^2 = 0.3469$; $Chi^2 = 357.63$, df = 6 ($P < 0.0001$); $I^2 = 98.3\%$
Test for overall effect: $Z = 265.01$ ($P = 0$)
Test for overall effect: $Z = 15.95$ ($P < 0.0001$)
Test for subgroup differences: $Chi^2 = 357.63$, df = 6 ($P < 0.0001$)

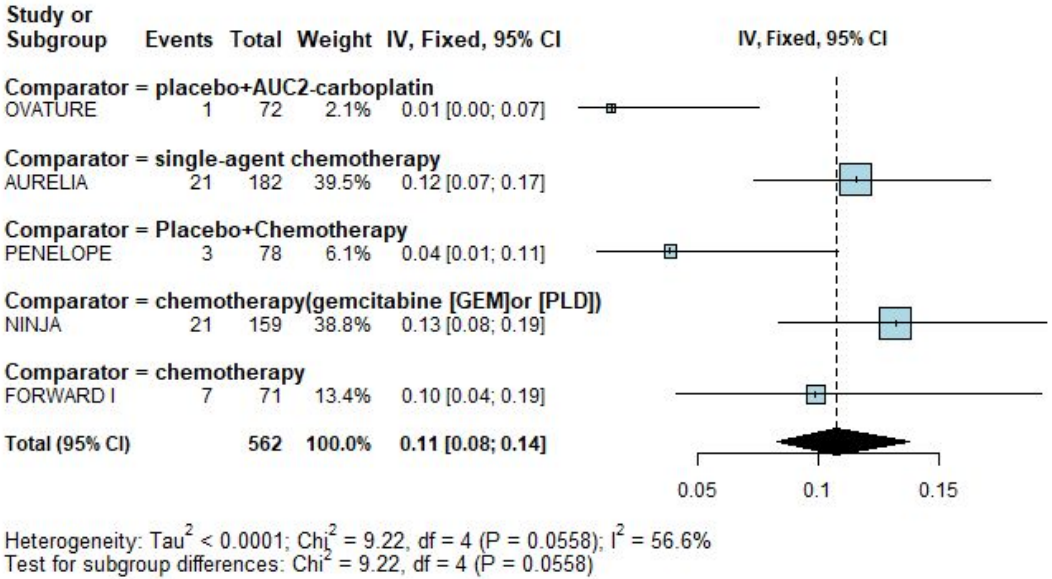
Interpretations

- Pooled Median PFS: 3.57 months. 95% CI: [3.13, 4.01], this wider CI reflects uncertainty from inter-study differences, which are accounted for in the random model.
- $Tau^2 = 0.3469$, $Z = 15.95$, $P < 0.0001$ → PFS differences are highly significant overall. $Chi^2 = 357.63$, $df = 6$, $P < 0.0001$ → Strong evidence that PFS varies significantly across comparator types.

Conclusion

Median PFS ranges across studies from 2.60 to 4.63 months, showing considerable variation. Random effects model provides a more conservative, cautious estimate. High heterogeneity ($I^2 = 98.3\%$) validates the choice of random effects model. The subgroup differences are statistically significant, meaning treatment comparator type does impact PFS outcome.

Forest plot for Fixed effect model for Objective Response Rate

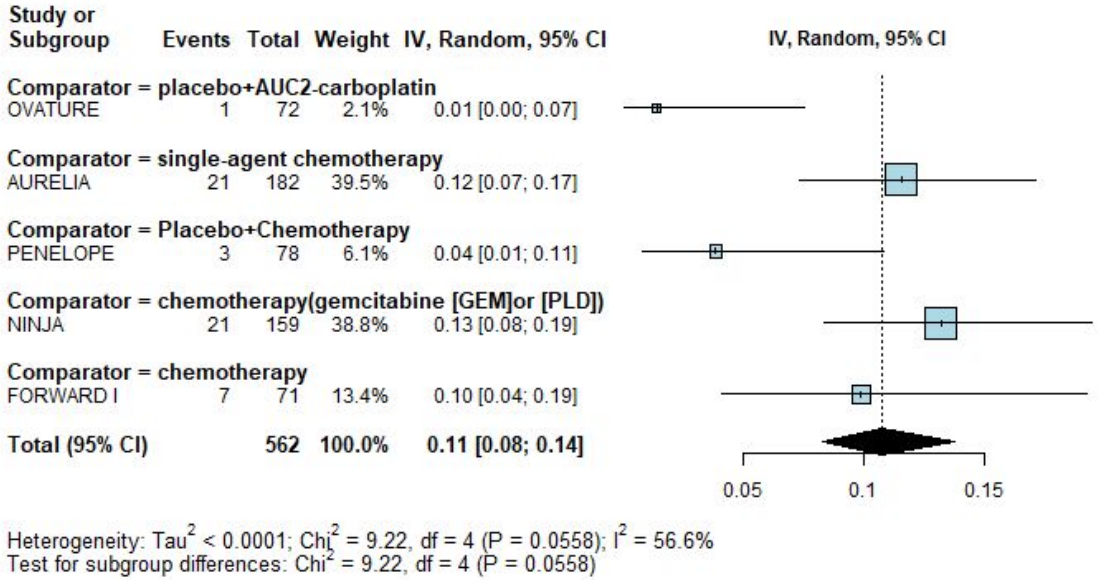


Heterogeneity: $Tau^2 < 0.0001$; $Chi^2 = 9.22$, df = 4 (P = 0.0558); $I^2 = 56.6\%$
Test for subgroup differences: $Chi^2 = 9.22$, df = 4 (P = 0.0558)

Interpretations

- Pooled ORR across all studies = 0.11 (or 11%). This means, on average, 11% of patients across these control/comparator arms experienced an objective tumor response.
- Chi^2 = 9.22, df = 4, P = 0.0558 - Just on the edge of statistical significance - mild variability between studies. I^2 = 56.6% - Moderate heterogeneity - ~57% of variation due to study differences.
- Chi^2 = 9.22, df = 4, P = 0.0558 - No statistically significant subgroup difference, but borderline (suggests possible trends).

Forest plot for Random effect model for Objective Response Rate



Interpretations

- Pooled ORR (random effects): 0.11 (i.e., 11%). 95% Confidence Interval: [0.08, 0.14], Tau^2 = < 0.0001 shows very low between-study variance, Chi^2 = 9.22, df = 4, P = 0.0558 shows borderline heterogeneity, I^2 = 56.6% indicates Moderate heterogeneity, Chi^2 = 9.22, P = 0.0558. Subgroup differences are suggestive, but not statistically significant (P just above 0.05)

Conclusion

Control arms across studies had low ORRs, ranging 1% to 13%. Random effects model confirms the pooled ORR to be ~11%, with slightly wider CI than fixed-effects, to account for inter-study variability. Moderate heterogeneity (I^2 = 56.6%) suggests differences between studies (treatment types, populations, assessment methods), but not extreme. No significant subgroup differences, but the P = 0.0558 indicates possible trends worth exploring further (e.g., certain comparator regimens having consistently lower ORR).