Breast Journal Club

PLATINUM-BASED NEOADJUVANT CHEMOTHERAPY IN TRIPLE NEGATIVE BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Study Background

- Triple-negative breast cancer (TNBC) accounts for approximately 10-20% of all breast tumors [1].
- Although TNBC is characterized by aggressive behavior, it is particularly sensitive to cytotoxic chemotherapy (the so called “triple negative paradox”)[2].
- In the neoadjuvant setting, TNBC patients have higher response rates to standard chemotherapy as compared to women affected by hormone receptor-positive breast cancer.

1. Gluz O et al, Ann Oncol. 2009; 2. Carey LA et al, Clin Cancer Res. 2007.

Study Background

- The achievement of pathological complete response (pCR) in TNBC has a strong prognostic value [1,2].
- For this reason, neoadjuvant chemotherapy is considered the preferred approach for TNBC patients, also in the earlier stage [3].
- The role of platinum-based neoadjuvant chemotherapy in TNBC is highly controversial and its use is not endorsed by current guidelines.
- To provide up to date evidence on this controversial topic, we conducted a systematic review and meta-analysis aiming to better elucidate the role of platinum-based neoadjuvant chemotherapy in TNBC patients.

1. Cortazar P, Lancet 2014; 2. von Minckwitz G, J Clin Oncol 2012; 3. Harbeck N, Breast 2017.

Study Design

- Quantitative synthesis of randomized trials evaluating the activity, efficacy and safety of platinum-based (experimental arm) versus platinum-free (control arm) neoadjuvant chemotherapy in TNBC patients.

- The work was done and reported according to the PRISMA guidelines for reporting of systematic reviews.

- A literature search using PubMed, Embase and the Cochrane Library was performed with no date restriction up to October 30th, 2017; abstracts presented at ASCO, SABCS and ESMO meetings were also searched.

Eligibility Criteria

- **Inclusion criteria:**

  a) phase II or III randomized controlled trials (RCTs);
  b) RCTs including TNBC patients who received platinum-based neoadjuvant chemotherapy in the experimental arm and platinum-free neoadjuvant chemotherapy in the control arm;
  c) studies with available information on pCR rates in the experimental and control arms to estimate the odds ratio (OR) and 95% confidence intervals (CI).

- **Exclusion criteria:**

  a) non-randomized controlled trials on this topic;
  b) RCTs investigating platinum-based neoadjuvant chemotherapy in patients with breast cancer subtypes other than TNBC ;
  c) ongoing studies with results not presented or published at the time of the literature search.

Study Objectives and Endpoints

- **Primary objective:** to compare the activity of platinum-based versus platinum-free neoadjuvant chemotherapy in TNBC patients in term of pCR (i.e. ypT0/is pN0).

Four additional analysis were performed, including:

(i) all the RCTs irrespective of the chemotherapy backbone;

(ii) only RCTs in which the same neoadjuvant chemotherapy backbone (with or without a platinum agent) was administered in both treatment arms;

(iii) only RCTs that used the same standard neoadjuvant chemotherapy regimen of weekly paclitaxel (with or without a platinum agent) followed by anthracycline plus cyclophosphamide in both treatment arms.

(iv) a further analysis was performed to assess the benefit of the addition of platinum to a neoadjuvant chemotherapy according to germline *BRCA* mutational status.

Study Objectives and Endpoints

- **Secondary objectives:**

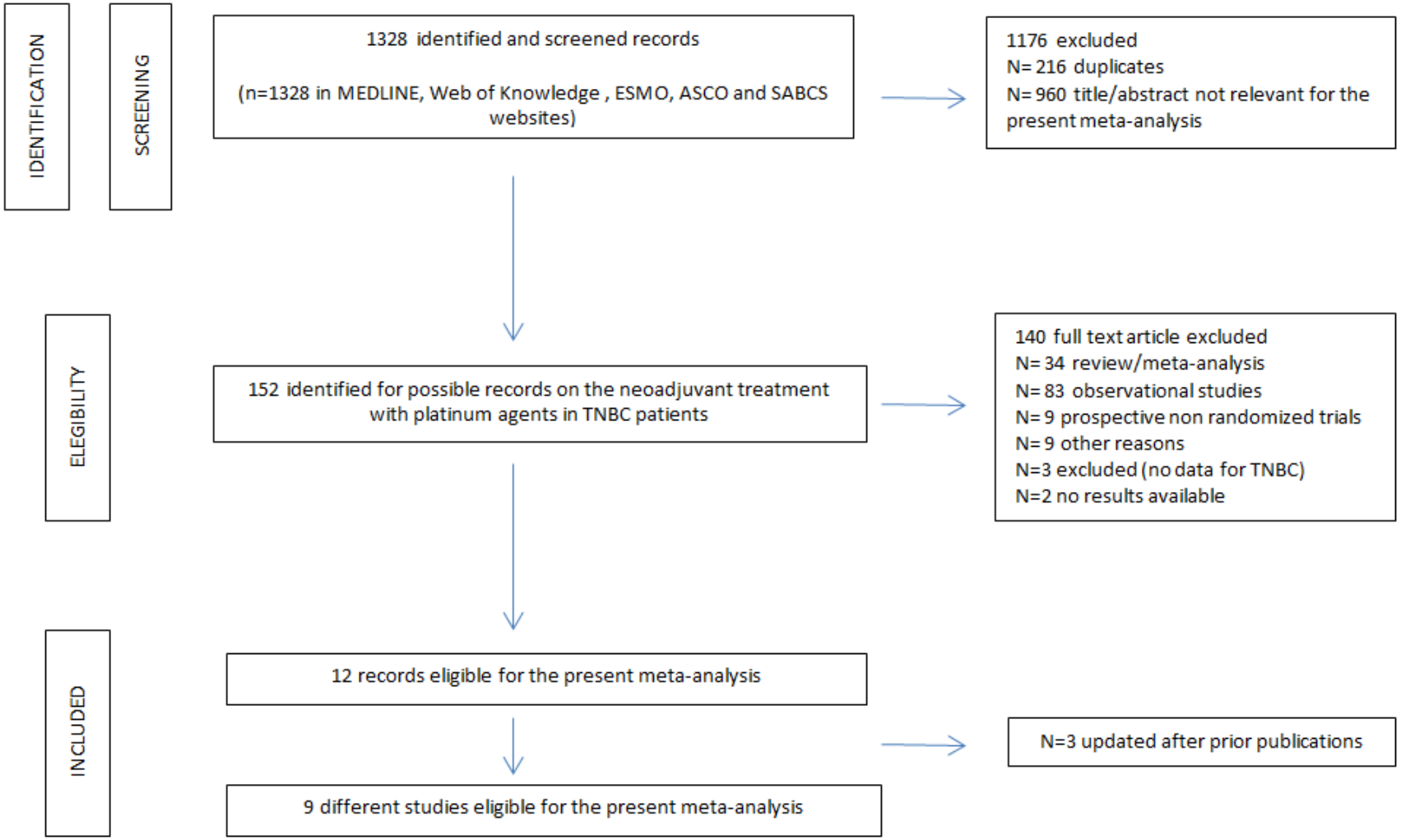
  a) to compare event-free survival (EFS) and overall survival (OS) between the two study arms;

  b) to compare the grade 3 and 4 adverse events (AEs, i.e. neutropenia, anemia, thrombocytopenia and neuropathy)

Statistical Considerations

- ORs and 95% CI were calculated for pCR and grade 3-4 AEs.
- Hazard ratios (HRs) and 95% CI were calculated in terms of EFS and OS.
- In presence of significant heterogeneity among the trials, the method of Der Simonian and Laird using random effect model was performed.
- A visual inspection of the funnel plot and the Harbord's asymmetry test were used to assess the likelihood of publication bias.

Results

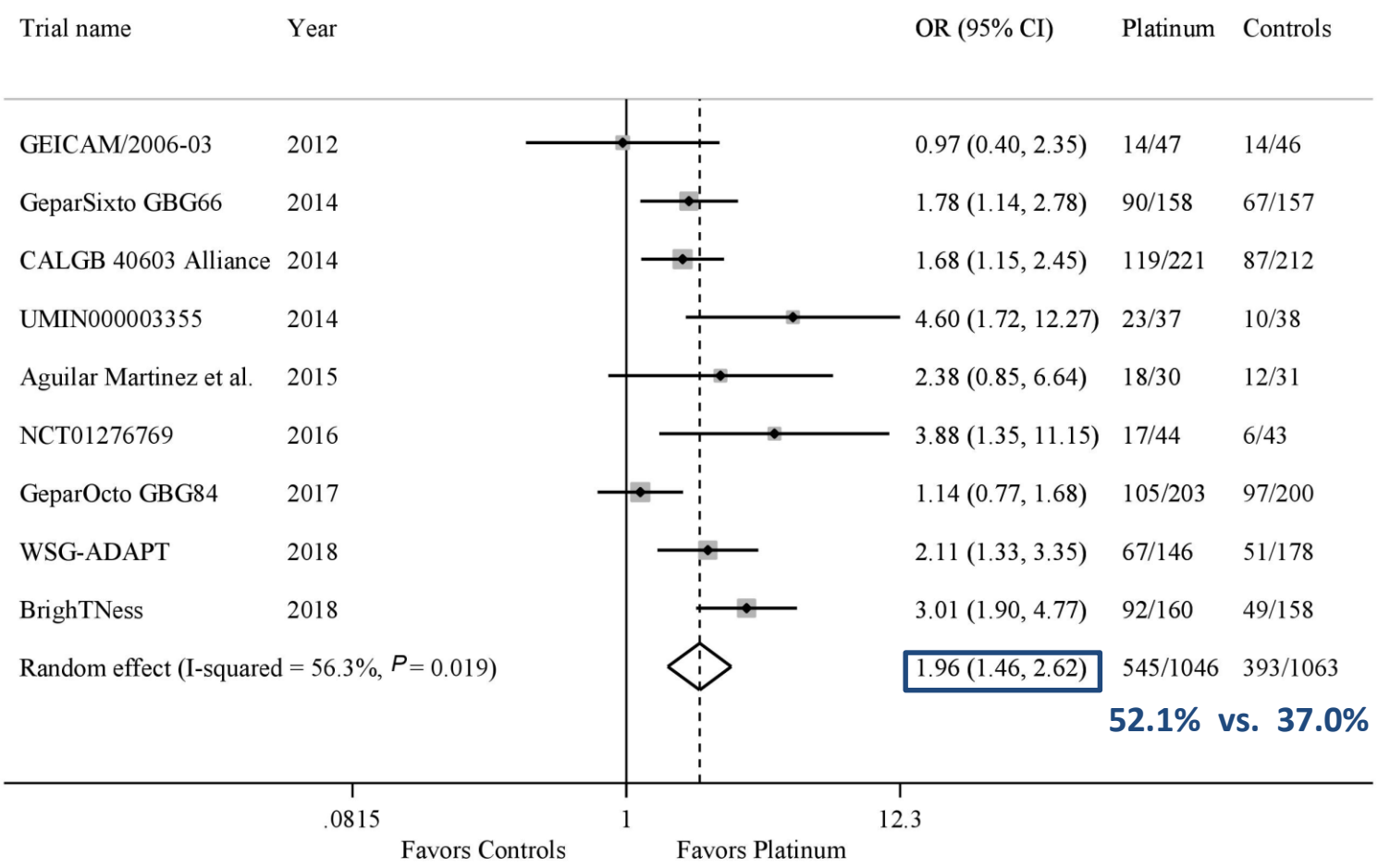

IDENTIFICATION
SCREENING
1328 identified and screened records
(n=1328 in MEDLINE, Web of Knowledge , ESMO, ASCO and SABCS websites)
1176 excluded
N= 216 duplicates
N= 960 title/abstract not relevant for the present meta-analysis
ELEGIBILITY
152 identified for possible records on the neoadjuvant treatment with platinum agents in TNBC patients
140 full text article excluded
N= 34 review/meta-analysis
N= 83 observational studies
N= 9 prospective non randomized trials
N= 9 other reasons
N=3 excluded (no data for TNBC)
N=2 no results available
INCLUDED
12 records eligible for the present meta-analysis
N=3 updated after prior publications
9 different studies eligible for the present meta-analysis

Characteristics of the studies

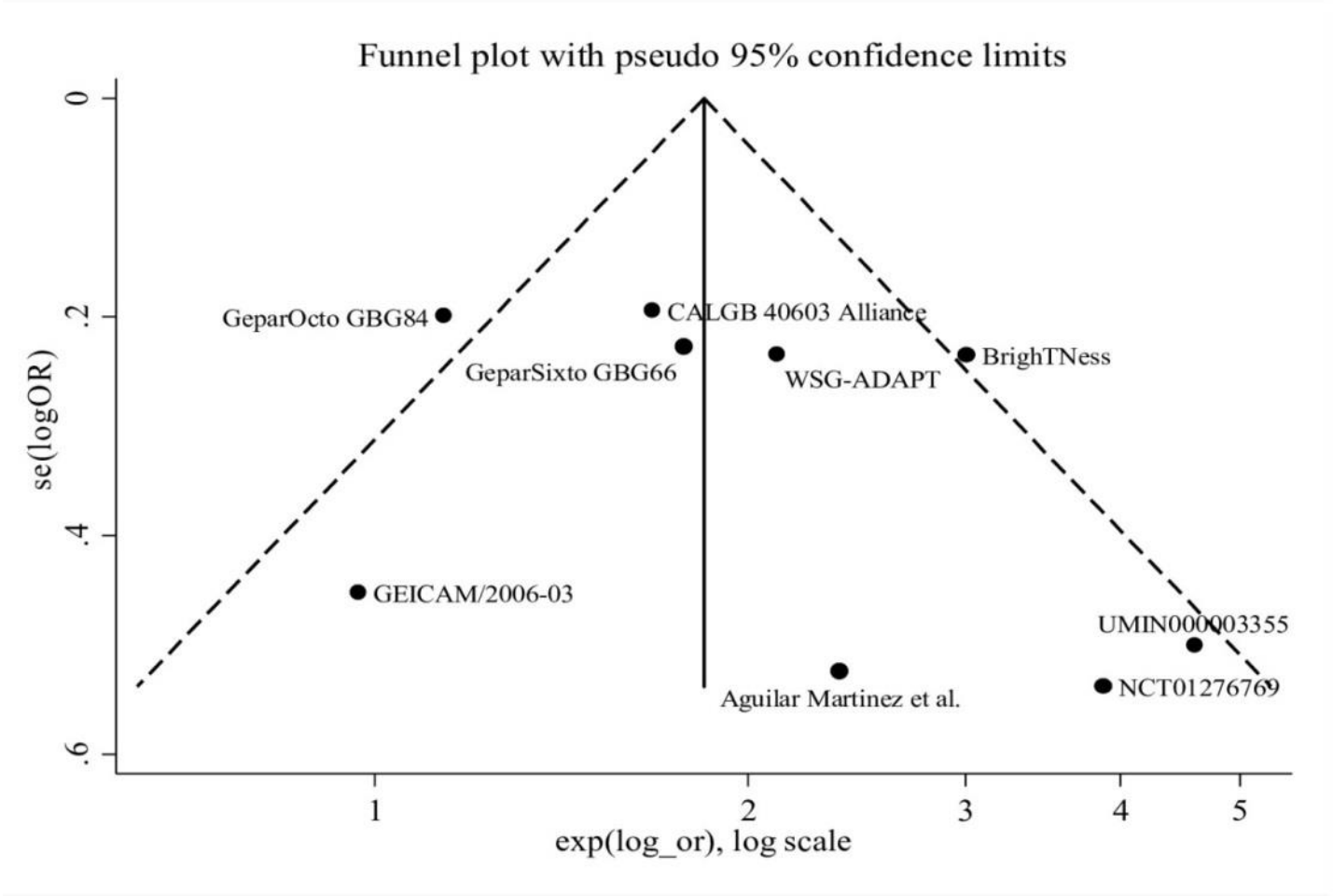
Study	Study design	Treatment arms	TNBC patients, N
GEICAM/2006-03	Phase II	EC–DCb	47
		EC–D	46
GeparSixto GBG66	Phase II	P + Dox + Bev + Cb	158
		P + Dox + Bev	157
CALGB 40603 Alliance	Phase II	P + Cb ±Bev → ddAC	221
		P± Bev → ddAC	212
UMIN000003355	Phase II	PCb → CEF	37
		P → CEF	38
Aguilar Martinez	Phase II	Cis + P → Cis + Dox	30
		P → FAC	31
NCT01276769	Phase II	PCb	44
		EP	43
GeparOcto GBG84	Phase III	PDoxCb	203
		ddEPC	200
WSG-ADAPT	Phase II	Nab-P + Cb	146
		Nab-P + Gem	178
BrighTNess	Phase III	P+Cb → AC	160
		P → AC	158

Results:

pCR in all the studies

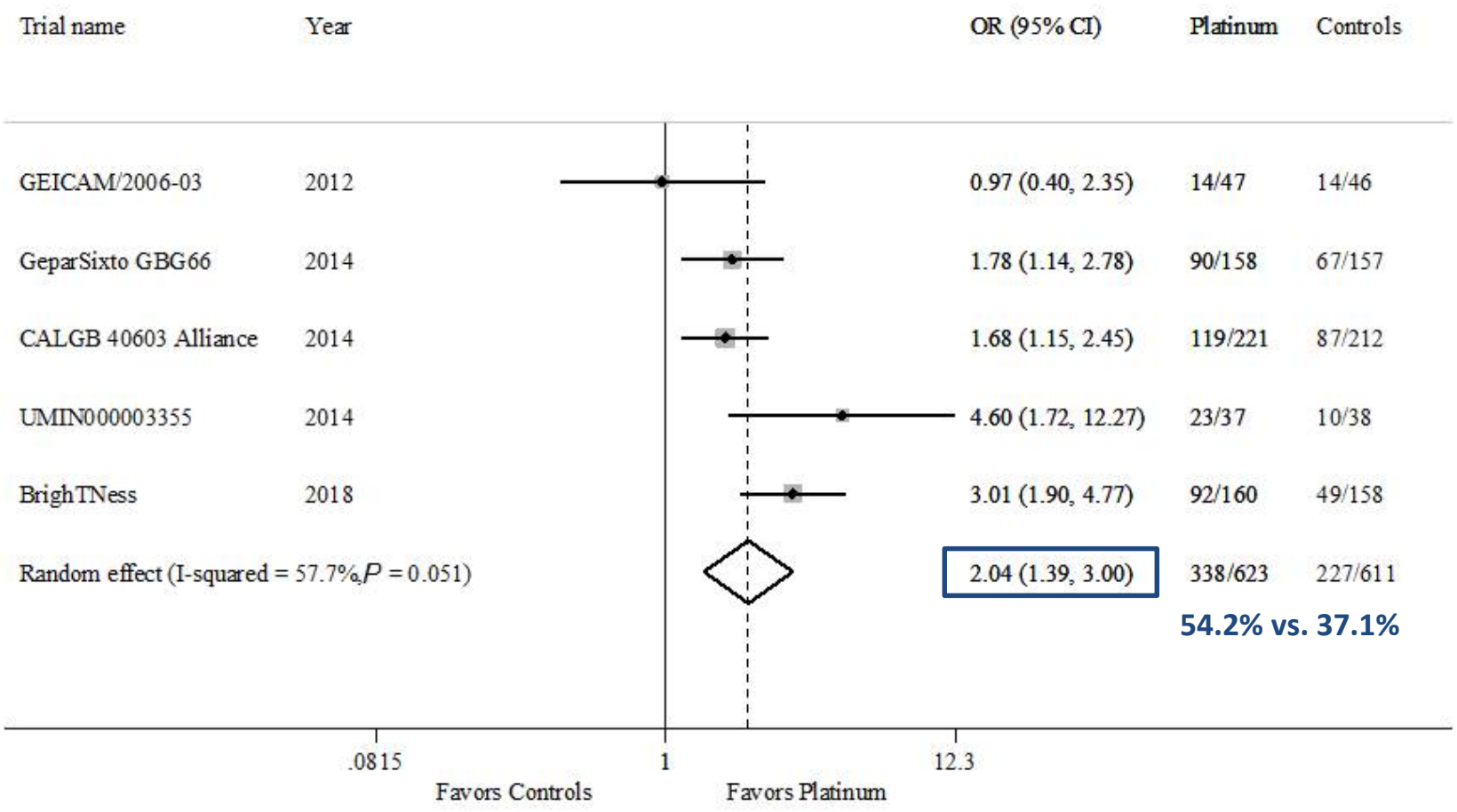


Results


Funnel plot with pseudo 95% confidence limits
se(logOR)
0
.2
.4
.6
GeparOcto GBG84
CALGB 40603 Alliance
GeparSixto GBG66
WSG-ADAPT
BrighTNess
GEICAM/2006-03
UMIN000003355
NCT01276769
Aguilar Martinez et al.
1
2
3
4
5
exp(log_or), log scale

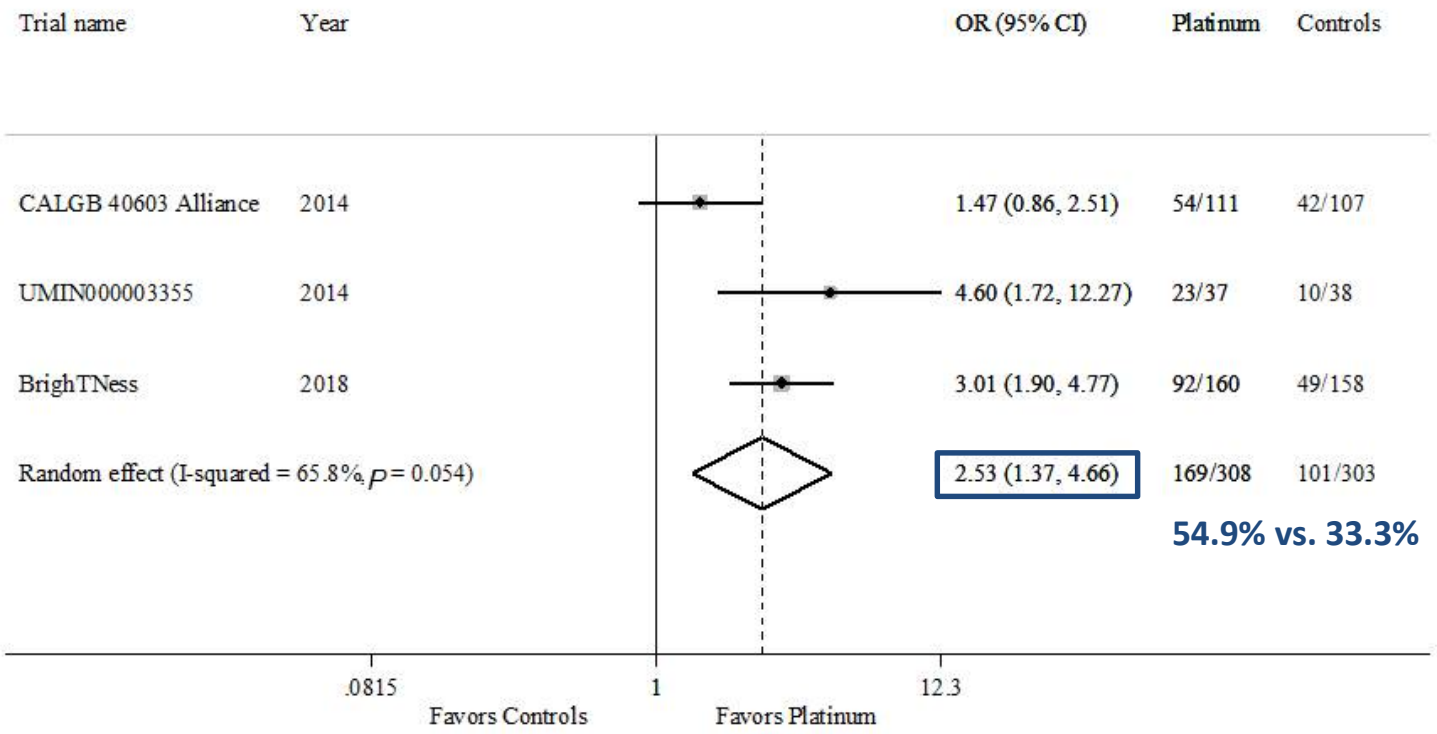
Results:

RCTs with the same CT backbone

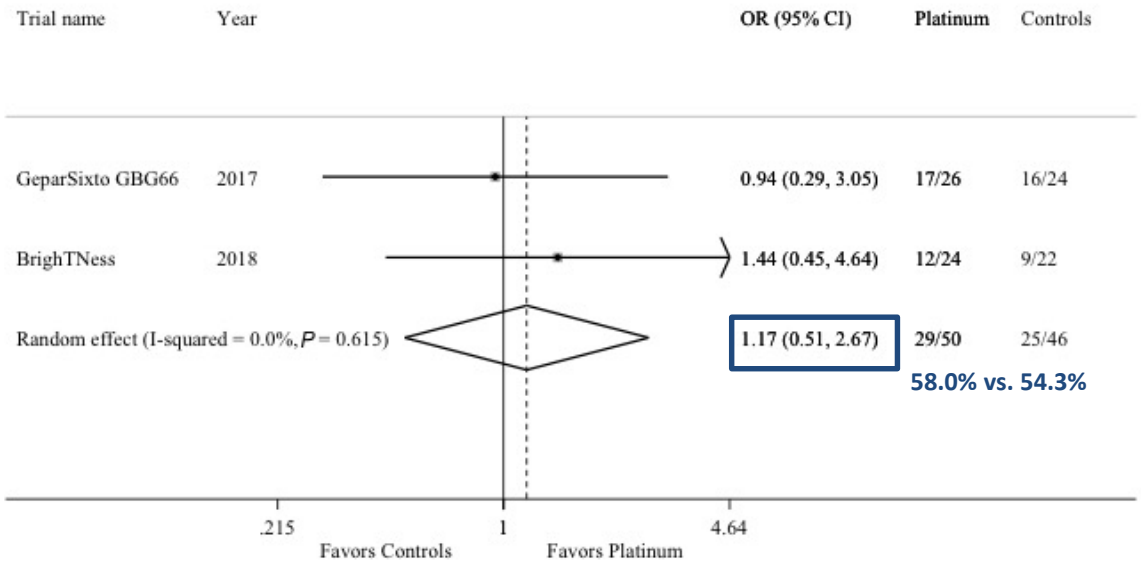


Results

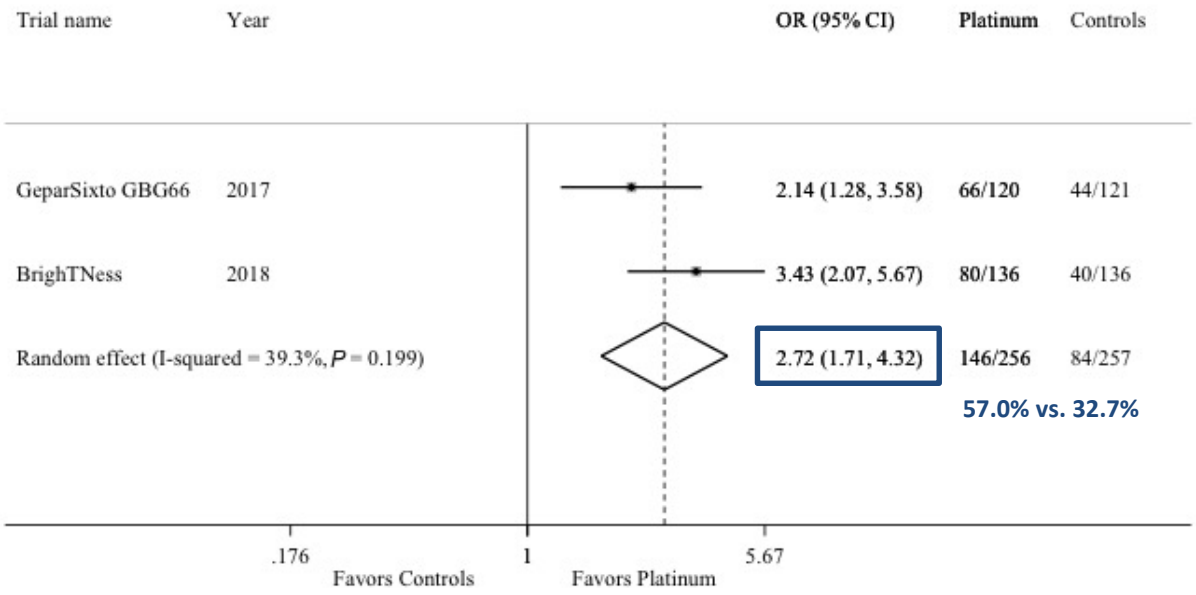
RCTs with the same standard anthracycline- and taxane-based CT



Results



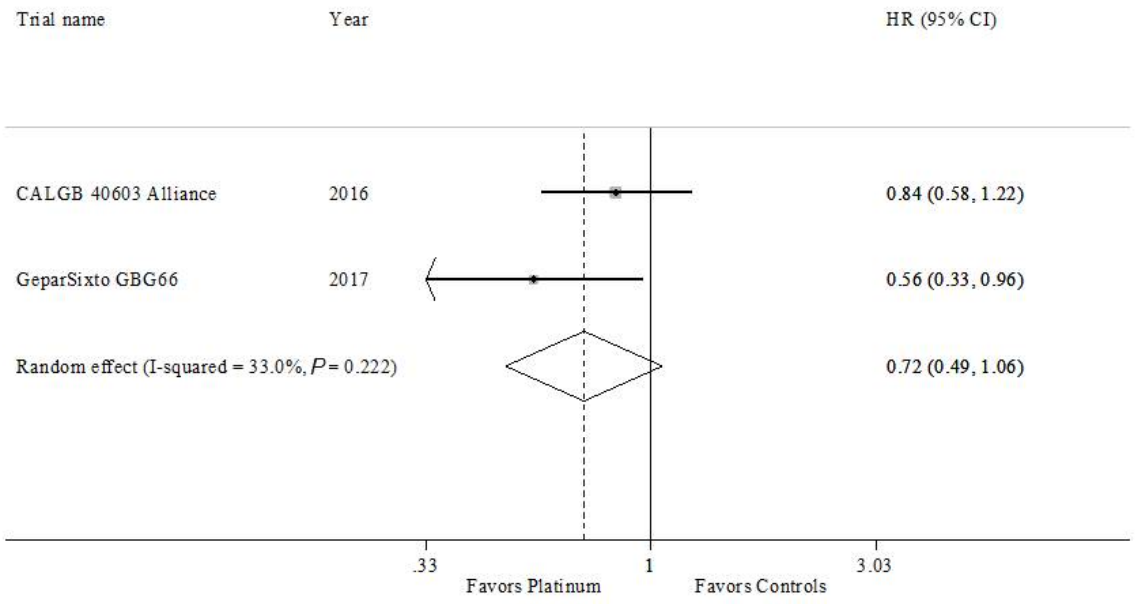
BRCA-mutated patients



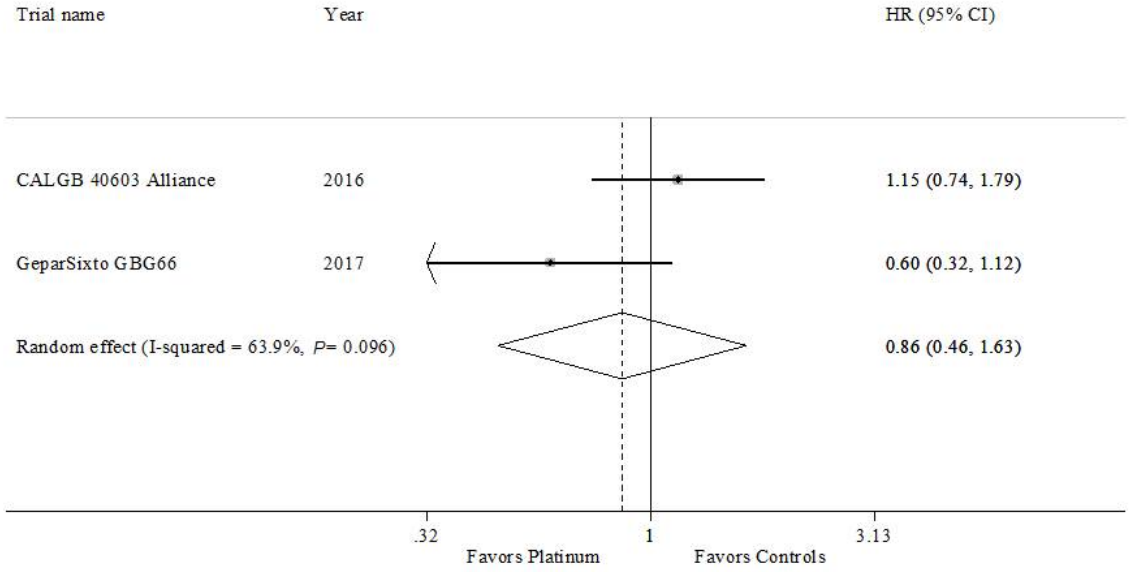
BRCA-negative patients

Results

Event-free survival

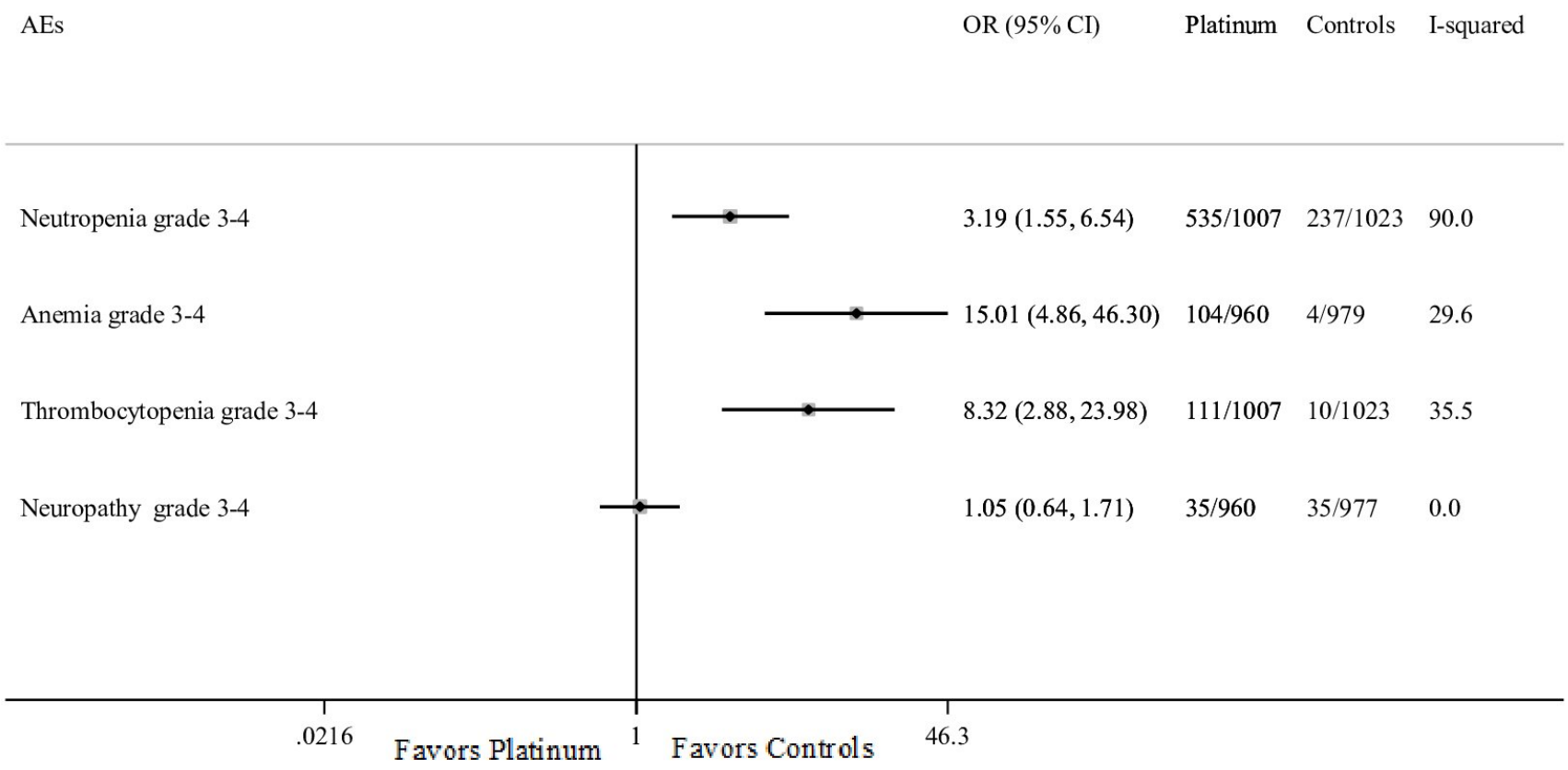


Overall survival



Results:

Safety profile overview



Conclusions

- Our meta-analysis showed that platinum-based neoadjuvant chemotherapy was associated with significant increased pCR rates in TNBC patients at the cost of higher risk of hematological toxicities.

- The addition of platinum agents to standard anthracycline-taxane-based neoadjuvant chemotherapy may be considered an option in unselected TNBC patients.

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REVIEW

Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis

F. Poggio[1,2], M. Bruzzone[3], M. Ceppi[3], N. F. Pondé[1], G. La Valle[4], L. Del Mastro[5,6], E. de Azambuja[1] & M. Lambertini[1,7*]

Nelle donne con carcinoma mammario TRIPLO NEGATIVO (recettori ormonali negativi ed HER2-negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, è raccomandabile l'aggiunta del platino ad uno schema standard con antracicline e taxani rispetto alla sola chemioterapia a base di antracicline e taxani?

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne con carcinoma mammario triplo negativo (recettori ormonali negativi ed HER2 negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, l'aggiunta del platino ad uno schema standard con antracicline e taxani può essere preso in considerazione.	**Positiva debole**