Safety and Efficacy of Immune Checkpoint Inhibitors in Early Triple Negative Breast Cancer: A Systematic Review and Meta-Analysis of Real-World Evidence vs Clinical Trial Data

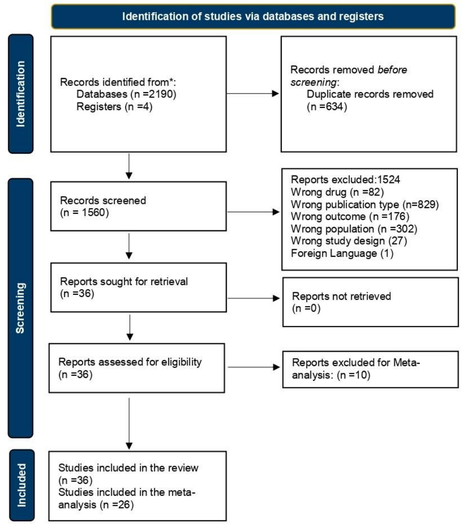
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Background

Immune checkpoint inhibitors (ICIs) in combination with chemotherapy, have markedly transformed the therapeutic alogorithm of high risk early-stage triple-negative breast cancer (eTNBC)[1,3]. Although the safety and efficacy of ICIs have been extensively evaluated in clinical trials (CTs), their toxicity and effectiveness profiles may differ in real-world clinical practice[2,4]. This systematic review and meta-analysis aimed to compare the incidence of all-grade adverse events (AEs), grade ≥3 AEs, treatment related discontinuation, and pathological complete response (pCR) rates across phase I-III CTs and real-world evidence (RWE) in patients with eTNBC receiving neoadjuvant ICIs.

Prisma



Clinical Trials

CTs	Year	Exp	Control	N of patients	Any grade AE exp arm	Grade ≥ 3 AEs	Discont. due to AE	pCR
Keynote 522	2020	Pembrolizumab + Chemo	Placebo + Chemo	784	773	600	199	508
CamRelief	2025	Camrelizumab + Chemo	Placebo + Chemo	222	220	200	41	126
NeoTRIP	2022	Carboplatino + Nab paclitaxel + Atezolizumab	Carboplatino + Nab paclitaxel	138	135	106	35	67
IMpassion031	2020	Atezolizumab + Chemo	Placebo + Chemo	164	115	26	37	95
A-BRAVE	2024	Avelumab	Observation	477	83	10	NA	NA
GeparNuevo	2019	Durvalumab + Chemo	Placebo + Chemo	88	NA	30	20	47
GeparDouze	2024	Atezolizumab + Chemo	Placebo + Chemo	776	768	578	163	489
Keynote 173	2020	Pembrolizumab + Chemo	-	60	NA	54	9	36
Neo N	2024	Nivolumab lead-in group Nivolumab concurrent group	-	108	NA	70	15	27/53 30/55
NeoTENNIS	2024	Toripalimab + Chemo	-	70	70	16	1	39
B-IMMUNE	2023	Durvalumab + Chemo	-	50	39	34	NA	12
IMpassion030	2024	Atezolizumab + Chemo	Placebo + Chemo	1093	1085	593	252	NA
neoTAPPL	2024	Penpulimab + chemo	-	17	17	10	NA	10
BELLINI	2024	Nivo Nivo + Ipi 4 wks Nivo + Ipi 6 wks	-	15	41	8	NA	5
M Marhold et al.	2023	22	11	2	5	5		

Real-world data

RWE studies	Year	N of patients	Any grade AE	Grade ≥ 3 AEs	Discont. due to AE	pCR
C. Connors	2024	86	30	30	NA	51
H. Deng	2024	63	NA	11	NA	22
A. Jayan	2022	233	80	24	32	NA
Y. Aoyama	2025	46	46	37	NA	26
L. Rached	2024	100	99	9	35	58
M. Hofherr	2023	577	217	30	288	219
J. McKeon	2025	40	40	17	8	26
Krishnan J	2025	145	NA	55	NA	94
A. Al-Awadh	2023	32	NA	NA	2	16
D. Loirat	2023	37	37	21	5 (Pembrolizumab)	22
M. de Oliveira Andrade	2025	368	51	50	NA	NA

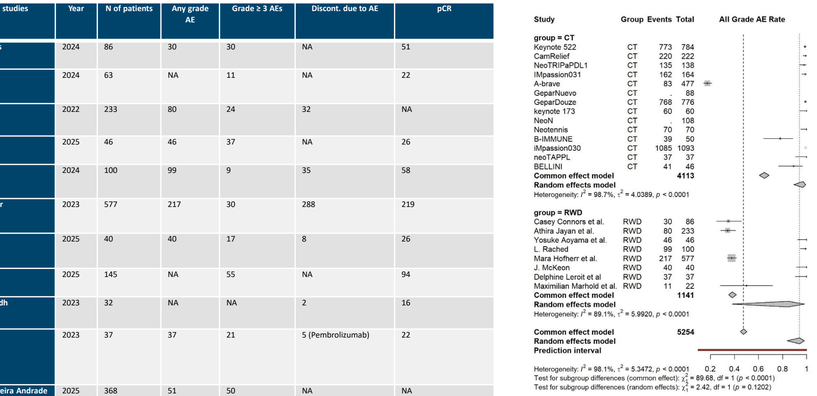
Materials and Methods

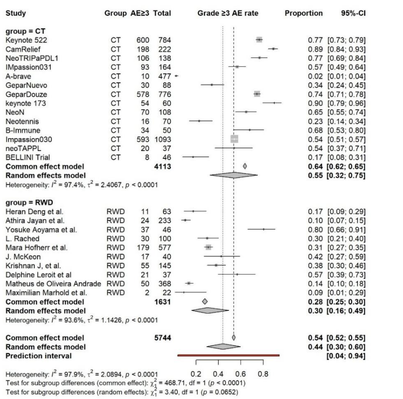
Fourteen clinical trials and twelve real-world evidence studies were included in the analysis. Incidence of all-grade AEs, grade ≥3 AEs, treatment related discontinuation and pCR rate were collected. Proportions were logit-transformed to stabilize variances and pooled using a random-effects model with Hartung-Knapp adjustment. Subgroup differences between RWE and CTs were evaluated using the Q-test for subgroup analysis. Separate analyses were conducted for pCR, overall AEs, grade ≥3 AEs and treatment discontinuation to explore consistency of findings across different outcomes.

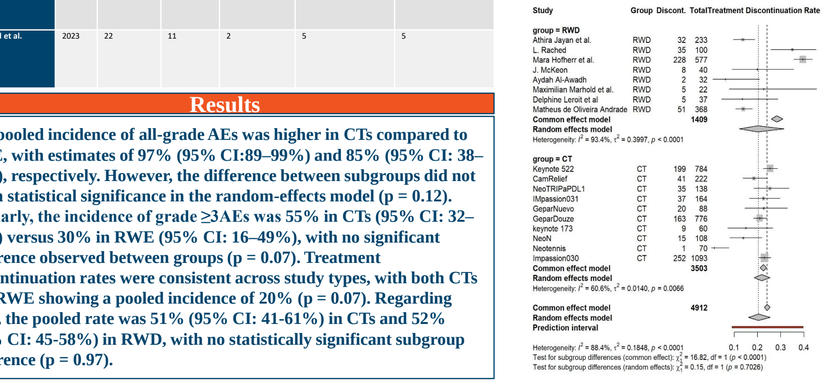
Results

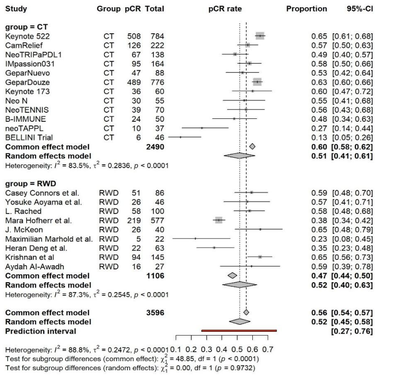
The pooled incidence of all-grade AEs was higher in CTs compared to RWE, with estimates of 97% (95% CI:89–99%) and 85% (95% CI: 38–98%), respectively. However, the difference between subgroups did not reach statistical significance in the random-effects model (p = 0.12). Similarly, the incidence of grade ≥3AEs was 55% in CTs (95% CI: 32–75%) versus 30% in RWE (95% CI: 16–49%), with no significant difference observed between groups (p = 0.07). Treatment discontinuation rates were consistent across study types, with both CTs and RWE showing a pooled incidence of 20% (p = 0.07). Regarding pCR, the pooled rate was 51% (95% CI: 41-61%) in CTs and 52% (95% CI: 45-58%) in RWD, with no statistically significant subgroup difference (p = 0.97).

Forest plots









Conclusions

The incidence and severity of adverse events and pCR rates, were comparable between randomized clinical trials and real-world evidence, indicating that immunotherapy maintains consistent safety and effectiveness profiles across both contexts. These results reinforce the external validity of trial-derived data for application in routine clinical practice. Ongoing post-marketing surveillance and standardized reporting remain crucial to ensurepatient safety, optimize outcomes, and inform evidence-based treatment decisions.

Limitations

The comparison between CTs and real-world studies is limited by inherent heterogeneity in study design, populations and follow-up, as well ad by inconsistent reporting of adverse events (AEs, TRAEs, IRAEs)

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