

Efficacy and Safety of Tucatinib Added to HER2-Directed Therapy in HER2-Positive Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

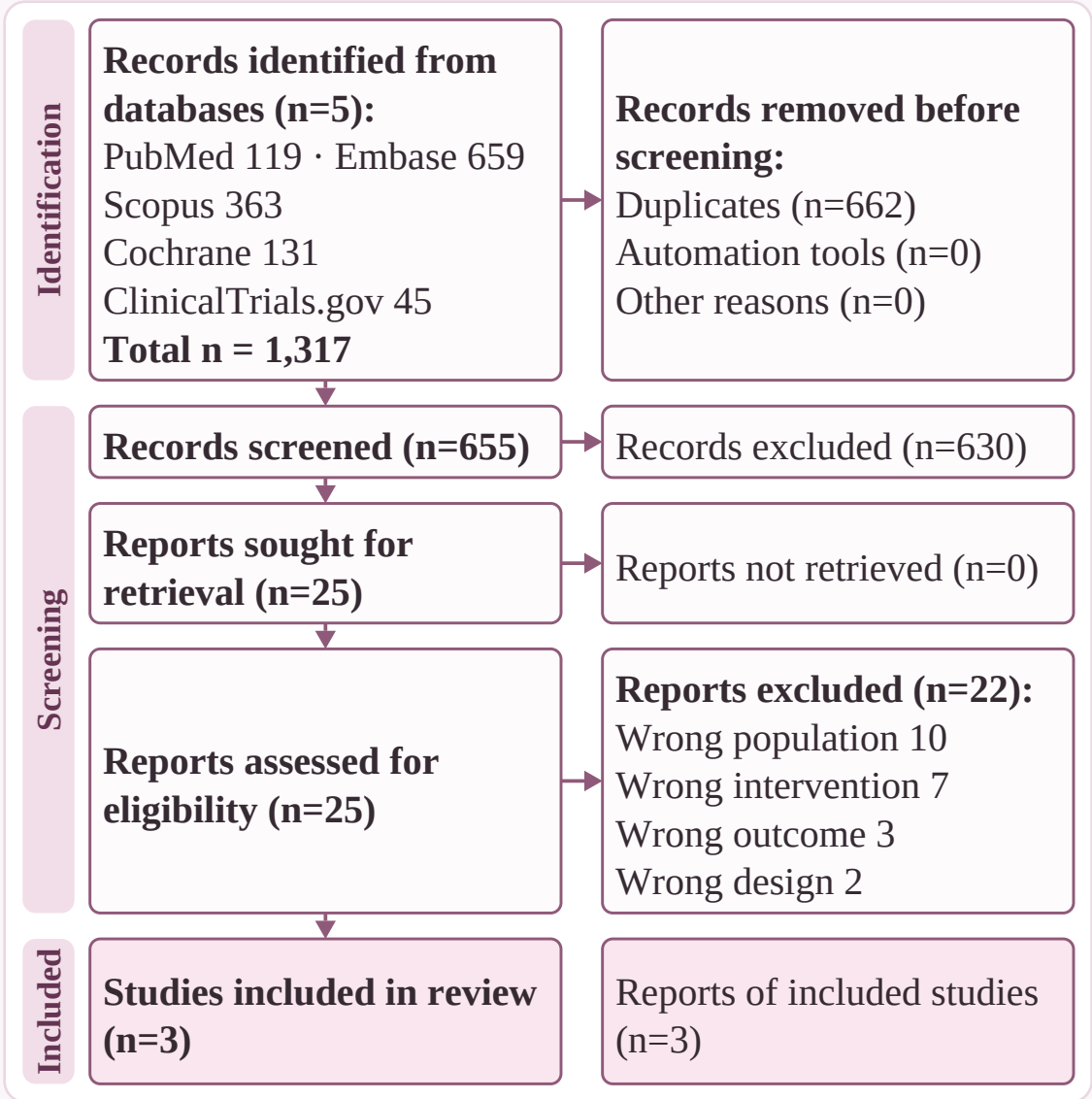
BACKGROUND

Tucatinib, a selective HER2 TKI, was tested on several HER2-directed backbones, but its pooled efficacy and safety, including with brain metastases, were unknown.

METHODS

- PRISMA 2020; PROSPERO CRD420261482121
- PubMed, Embase, Scopus, Cochrane and ClinicalTrials.gov to Aug 4, 2026
- RCTs in HER2-positive advanced or metastatic breast cancer
- Random-effects HR/RR (RevMan 5.4.1); RoB 2; GRADE

STUDY FLOW / PRISMA 2020



RISK OF BIAS (RoB 2)

Diéras 2026

LOW RISK

Hurvitz 2026

SOME CONCERNS

Murthy 2020

LOW RISK

● Low risk

○ Some concerns

Dots = domains D1 Randomization · D2 Deviations · D3 Missing data · D4 Measurement · D5 Selective reporting

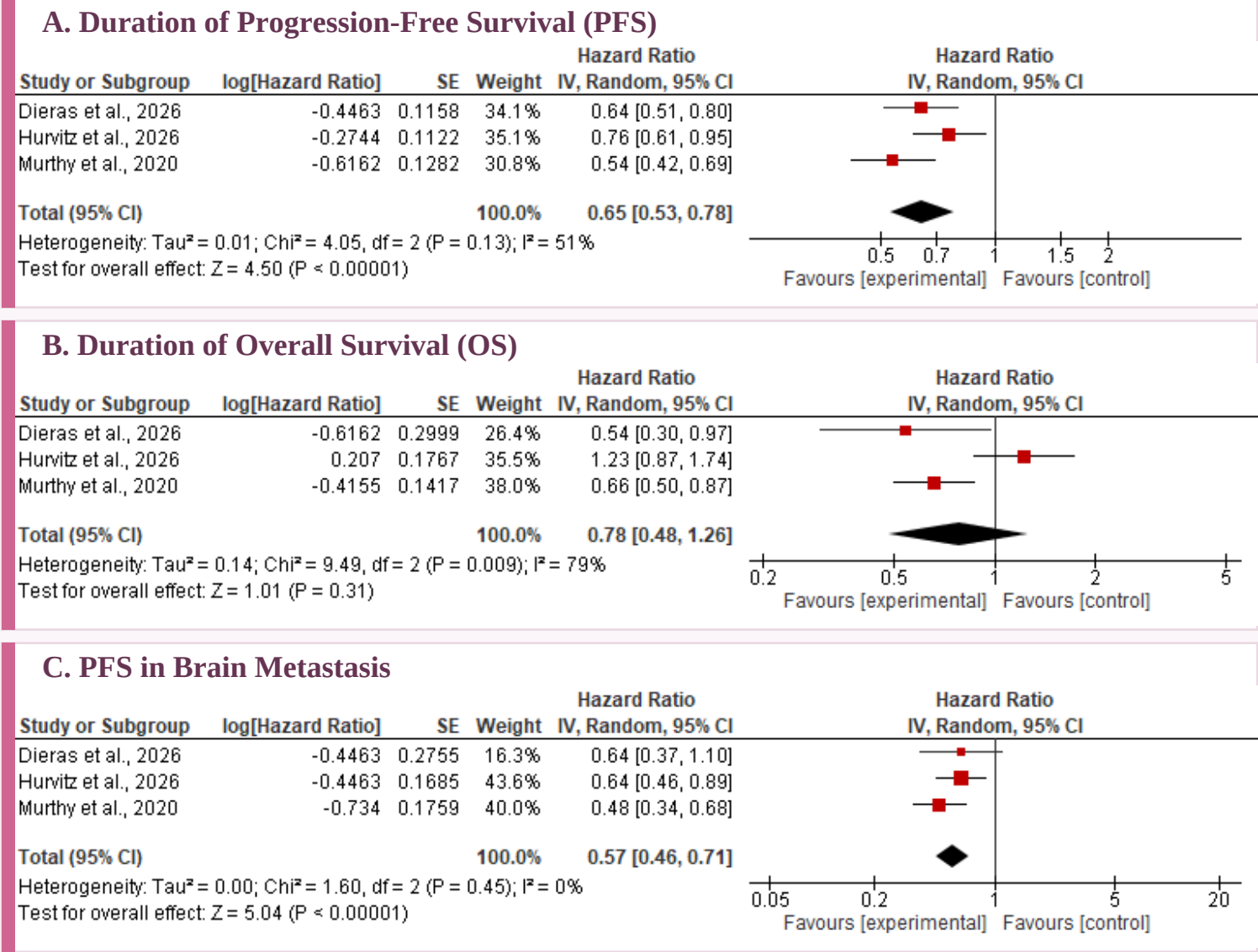
RESULTS AT A GLANCE

- PFS HR 0.65 (0.53–0.78); with brain metastases HR 0.57 (0.46–0.71).
- OS not significant: HR 0.78 (0.48–1.26); low certainty.
- Per 1,000: grade 3+ TEAEs 359 vs 532; AE discontinuation 49 vs 126.

CONCLUSION

Tucatinib prolongs PFS, including with brain metastases, with more GI/liver toxicity and discontinuations. OS benefit was inconsistent across trials.

PRIMARY OUTCOMES



SECONDARY OUTCOMES (SAFETY)

Outcome	Risk ratio (95% CI)	Heterog. (I ²)	P-value	GRADE
Fatigue	1.26 (1.00–1.59)	64%	0.05	●●○○
Decreased appetite	1.48 (1.17–1.88)	25%	0.001	●●●●
Headache	0.99 (0.84–1.17)	0%	0.90	●●●●
Constipation	0.83 (0.68–1.01)	0%	0.06	●●●○
Arthralgia	1.23 (0.69–2.19)	85%	0.48	●●○○

CERTAINTY OF EVIDENCE (GRADE)

Outcome	Placebo per 1,000	Tucatinib per 1,000 (95% CI)	Relative effect (95% CI)	Patients (studies)	GRADE
EFFICACY OUTCOMES (time-to-event)					
PFS	—	—	HR 0.65 (0.53–0.78)	3 RCTs	●●●●
Overall survival	—	—	HR 0.78 (0.48–1.26)	3 RCTs	●●○○ ^a
PFS, brain mets	—	—	HR 0.57 (0.46–0.71)	3 RCTs	●●●●
SAFETY OUTCOMES (dichotomous)					
Any TEAE	977	987 (968–1,000)	RR 1.01 (0.99–1.04)	1,715	●●●○ ^b
Grade 3+ TEAE	359	532 (403–704)	RR 1.48 (1.12–1.96)	1,715	●●●○ ^c
AE discontinuation	49	126 (88–181)	RR 2.57 (1.79–3.68)	1,715	●●●●
Nausea	367	496 (445–551)	RR 1.35 (1.21–1.50)	1,715	●●●●
Diarrhea	442	715 (587–870)	RR 1.62 (1.33–1.97)	1,715	●●●○ ^d
Vomiting	179	290 (222–378)	RR 1.62 (1.24–2.11)	1,715	●●●●
Raised ALT	101	286 (183–448)	RR 2.84 (1.82–4.44)	1,715	●●●○ ^e
Raised AST	127	274 (208–360)	RR 2.15 (1.63–2.83)	1,715	●●●●

Dots: 4 high, 3 moderate, 2 low. a: inconsistency and imprecision; b–e: inconsistency (I² 69–85%). Pink = significant.

LIMITATIONS

- Only 3 RCTs with different HER2 backbones and treatment lines.
- Substantial heterogeneity for OS (I² = 79%) and several toxicity outcomes (I² = 64–85%).
- Hurvitz 2026 had some concerns for selection of the reported result (D5).
- OS benefit was significant only without Hurvitz 2026; longer follow-up is needed.
- Fewer than 10 studies, so publication bias could not be assessed.

