

CO224

Systematic Literature Review of Efficacy, Health-Related Quality of Life, and Safety of Immunotherapies for Perioperative Treatment of Early-Stage Non-Small Cell Lung Cancer

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CONCLUSIONS

- This SLR underscores the efficacy benefits and safety profiles of immunotherapies for early-stage NSCLC
- Tislelizumab, pembrolizumab, and nivolumab demonstrated EFS and OS benefits in the perioperative setting compared with placebo/control arm, particularly in patients with higher PD-L1 expression (≥1% or ≥50%)
- In the adjuvant setting, immunotherapies did not demonstrate significant effects on OS; except for a subgroup of patients with PD-L1 ≥1% or ≥50% treated with atezolizumab

INTRODUCTION

- Several immunotherapies have recently been approved for the treatment of early-stage non-small cell lung cancer (NSCLC; resectable, stage II–IIIA).¹ Integration of immunotherapy into the perioperative management of NSCLC aims to improve response rates, thereby reducing recurrence and improving long-term survival for patients with early-stage NSCLC
- Perioperative systemic treatments, covering both neoadjuvant (pre-surgical) and adjuvant (post-surgical) therapies, aim to improve outcomes in early-stage, resectable NSCLC.¹ Neoadjuvant treatments are intended to reduce tumor size, making surgery more feasible and potentially more effective, while adjuvant treatments seek to eliminate residual microscopic disease, thereby minimizing the risk of recurrence
- The objective of this systematic literature review (SLR) was to synthesize evidence on the clinical efficacy, safety, and health-related quality of life (HRQoL) of current immunotherapies for the treatment of early-stage NSCLC

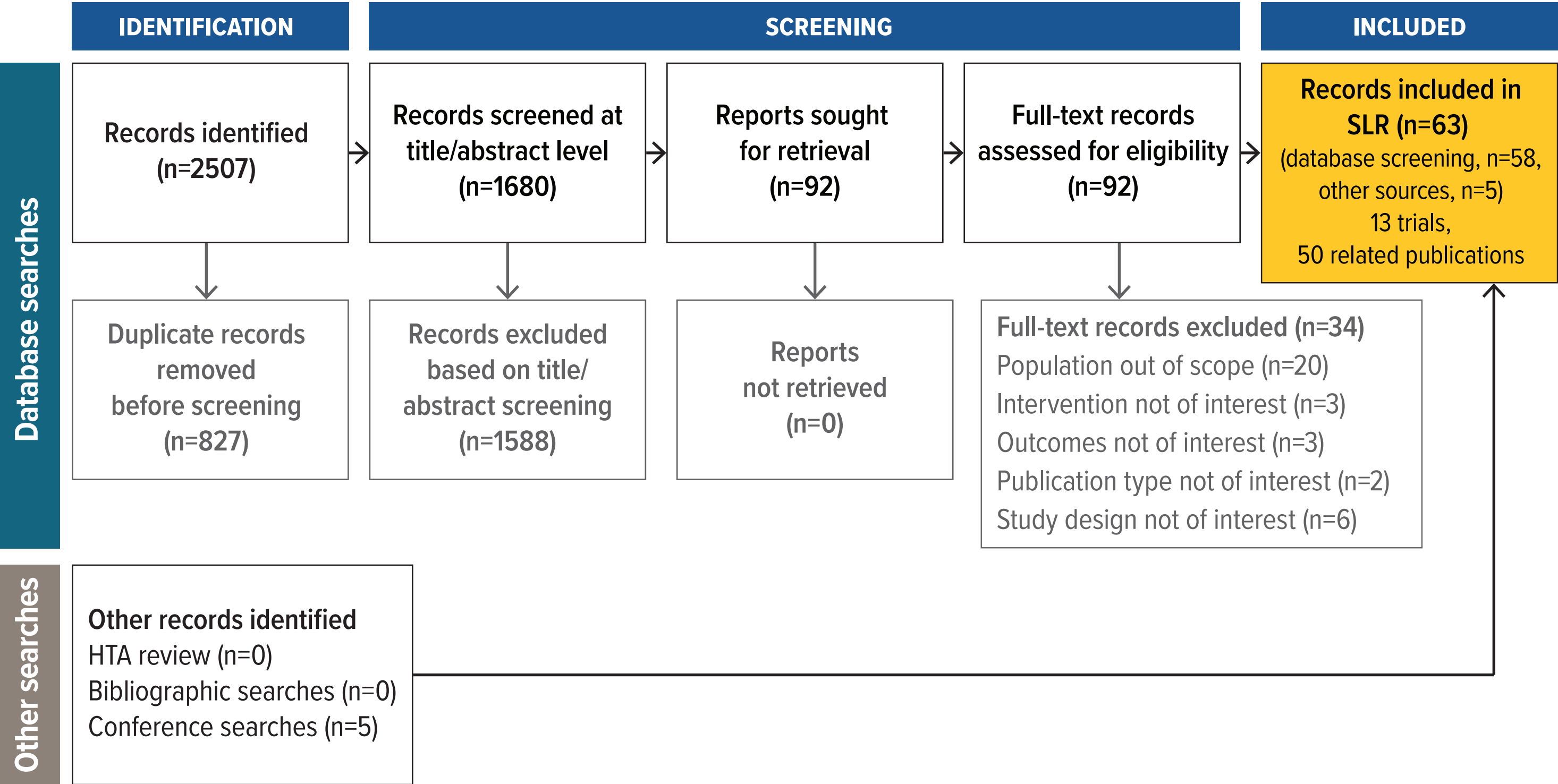
METHODS

- The SLR was conducted according to the standards set forth in the Cochrane Handbook for Systematic Reviews of Interventions, as well as the high-quality standards required by the National Institute for Health and Care Excellence
- Evidence was gathered from randomized controlled trials evaluating immunotherapy interventions on survival, response, surgical outcomes, safety, and HRQoL in patients with stage II-IIIA NSCLC
- Searches were run on September 18, 2024, in MEDLINE, MEDLINE In-Process, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. The search was limited to studies from the start of 2013 to September 2024 and supplemented with grey literature searches conducted in September 2024 across clinical trials registry database (clinicaltrials.gov), conference proceedings from the past 2 years (2022–2024), regulatory documents, health technology assessments, and recently published SLRs (2021–2024)
- Articles were screened by two independent reviewers, with discrepancies resolved by a third reviewer

RESULTS

- After deduplication, 1680 records were screened at title and abstract level. Of these, 92 records were sought for retrieval and screened at full-text level
- Following the full-text review, 58 records reporting on clinical outcomes from electronic databases were deemed eligible for inclusion. Five records reporting on clinical outcomes were included from grey literature searches
- A total of 63 records reporting on 13 unique clinical trials (phase 2 or 3) were included and categorized into perioperative (n=7), neoadjuvant (n=3), and adjuvant (n=3) settings (**Figure 1**)

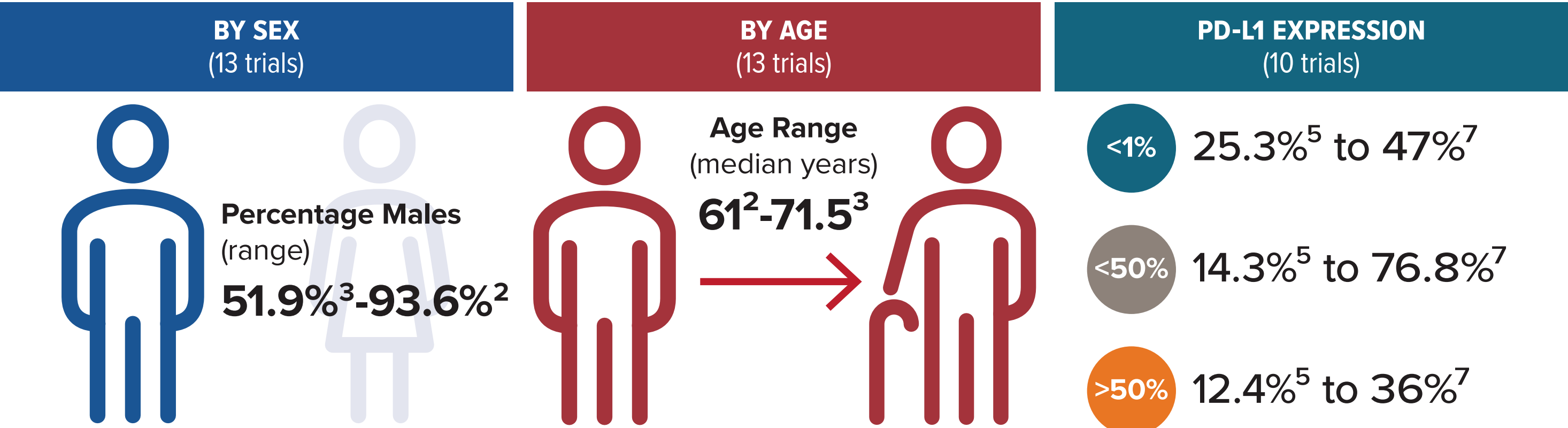
Figure 1. PRISMA Diagram



Abbreviations: HTA, health technology assessment; SLR, systematic literature review.

Study and Patient Characteristics (Figure 2)

Figure 2. Key Patient Characteristics at Baseline



Abbreviation: PD-L1, programmed death ligand-1.

Overall Survival

- In the perioperative setting, median overall survival (OS) was not reached in any of the trials. However, tislelizumab (hazard ratio [HR]: 0.62, 95% confidence interval [CI]: 0.39–0.98),^{8,9} pembrolizumab (HR: 0.73, 95% CI: 0.54–0.99),¹⁰ and nivolumab (HR: 0.43, 95% CI: 0.19–0.98)⁷ demonstrated OS benefits against placebo
 - The survival benefit with pembrolizumab was significant in PD-L1 ≥1% and PD-L1 ≥50% subgroups, but not in PD-L1 <1% and PD-L1 1%–49% subgroups.¹¹ The survival benefit with nivolumab was observed in PD-L1 ≥1% patients but not in PD-L1-negative subgroups⁷
- In the neoadjuvant setting, nivolumab plus chemotherapy showed OS (HR: 0.57, 95% CI: 0.38–0.87) benefit over chemotherapy alone¹²
 - Survival benefit was also demonstrated in patients with positive PD-L1 but not in patients with negative PD-L1¹³
- In the adjuvant setting, pembrolizumab, atezolizumab, and canakinumab did not demonstrate any significant OS benefits over the comparator^{5,14,15}
 - Patients with PD-L1 of 50% or more showed a survival benefit with atezolizumab compared with best supportive care (BSC) (HR: 0.42; 95% CI: 0.23–0.78) as well as patients with PD-L1 of 1% or more (HR: 0.67; 95% CI: 0.45–0.98), while no significant benefit was observed in patients with PD-L1 of 1–49% or negative PD-L1¹⁵

Event-Free Survival

- In the perioperative setting, nivolumab (HR: 0.58, 95% CI: 0.42–0.81), pembrolizumab (HR: 0.58, 95% CI: 0.46–0.72), and tislelizumab (HR: 0.56, 95% CI: 0.40–0.79) demonstrated event-free survival (EFS) benefit over placebo in the overall trial population. The benefit was also demonstrated in patients with PD-L1 ≥1%, while no EFS benefit was observed in patients with PD-L1 <1% compared with the placebo arm^{6,8,10}
- In the neoadjuvant setting, nivolumab plus chemotherapy improved EFS compared with chemotherapy alone in the overall population (HR: 0.63, 97.38% CI: 0.43–0.91) and in patients with PD-L1 ≥1% (HR: 0.41, 95% CI: 0.24–0.70) and PD-L1 ≥50% (HR: 0.24, 95% CI: 0.10–0.61)¹²

Disease-Free Survival

- In the adjuvant setting, atezolizumab (HR: 0.81, 95% CI: 0.67–0.99)⁴ and pembrolizumab (HR: 0.76, 95% CI: 0.63–0.91) demonstrated a disease-free survival (DFS) benefit for the intervention over placebo/BSC in the overall trial population
- DFS benefit was also observed in patients with PD-L1 ≥50% in the IMPower010 trial (HR: 0.43, 95% CI: 0.27–0.68),⁴ but not in PEARLS/KEYNOTE-091 (HR: 0.82, 95% CI: 0.57–1.18)¹⁴
- In CANOPY-A,⁵ post-surgery canakinumab was compared with placebo, showing no statistically significant DFS benefit for the overall population (HR: 0.94, 95% CI: 0.78–1.14) or for any of the subgroups based on disease stage, ECOG PS, histology, and PD-L1 expression levels

Major Pathological Response and Pathologic Complete Response

- All interventions (nivolumab, durvalumab, pembrolizumab, tislelizumab) in the perioperative setting improved major pathological response (MPR) and pathologic complete response (pCR) outcomes compared with placebo/control arm
- Nivolumab plus chemotherapy in the neoadjuvant setting improved MPR and pCR outcomes compared with chemotherapy alone¹²
- Among patients treated with perioperative and neoadjuvant nivolumab, MPR and pCR were higher in patients with positive PD-L1 expression (≥1%) than in patients with negative PD-L1 expression (<1%)^{6,12}

Safety

- Immunotherapy combined with chemotherapy in the perioperative setting generally led to higher incidences of grade ≥3 adverse events (AEs) and treatment-related AEs (TRAEs) compared with placebo/chemotherapy, particularly during the neoadjuvant phase. Nivolumab, durvalumab, and toripalimab were associated with increased serious AEs (SAEs) compared with placebo/control arms
- Adding nivolumab to chemotherapy in the neoadjuvant phase did not significantly increase AEs or SAEs and generally had similar or lower TRAEs, particularly in PD-L1 ≥1% and patients undergoing definitive surgery subgroups. Pembrolizumab had a lower incidence of grade ≥3 AEs compared with canakinumab alone, but this was not observed for TRAEs
- In the adjuvant setting, safety events were generally lower compared with neoadjuvant and perioperative treatments, with pembrolizumab and atezolizumab presenting slightly higher rates of grade ≥3 AEs and TRAEs compared with placebo/BSC

Health-Related Quality of Life

- In the perioperative setting, patients receiving nivolumab plus chemotherapy had numerically longer median time to definitive deterioration (TTDD) on the EQ-5D-3L utility index scale compared with placebo and significantly longer median TTDD on the EQ-5D visual analogue, NSCLC-SAQ, and FACT-L LCS scales^{6,16}
- In the neoadjuvant setting, there was no significant difference in HRQoL for patients receiving nivolumab plus chemotherapy or chemotherapy alone¹⁷

Strengths and Limitations of the Evidence Base

- While this SLR provides valuable insights into the efficacy and safety of various treatments in the perioperative, neoadjuvant, and adjuvant settings, there are limitations related to trial design, point of randomization (pre vs post surgery), limited QoL data, and variations in outcomes across settings (EFS in perioperative and neoadjuvant trials as a surrogate measure of OS, while DFS is used in adjuvant trials)
- In oncology, improvements in survival are the gold standard for assessing new therapies. However, in this SLR, OS was only presented in seven trials. Additionally, there was limited availability of HRQoL evidence, restricting our understanding of the patient experience and the broader impact of the treatments beyond clinical efficacy and safety metrics

Table 1. Summary of Interventions and Comparators

Trial Name	Tislelizumab	Pembrolizumab	Nivolumab	Durvalumab	Atezolizumab	Canakinumab	Toripalimab	Placebo	CT Alone	Other
Perioperative Setting										
NEOTORCH ²	–	–	–	–	–	–	Yes	Yes	–	–
CheckMate 77T ³	–	–	Yes	–	–	–	–	Yes	–	–
NADIM II ⁷	–	–	Yes	–	–	–	–	–	Yes	–
AEGEAN ⁸	–	–	–	Yes	–	–	–	Yes	–	–
NEOSTAR ⁹	–	–	Yes	–	–	–	–	–	–	Yes ^a
KEYNOTE-671 ¹⁰	–	Yes	–	–	–	–	–	Yes	–	–
RATIONALE-315 ⁸	Yes	–	–	–	–	–	–	Yes	–	–
Neoadjuvant Setting										
CANOPY-N ²⁰	–	Yes	–	–	–	Yes	–	–	–	Yes ^b
CheckMate 816 ²¹	–	–	Yes	–	–	–	–	–	Yes	–
NeoCOAST ³	–	–	–	Yes	–	–	–	–	–	Yes ^c
Adjuvant Setting										
CANOPY-A ⁵	–	–	–	–	–	Yes	–	Yes	–	–
IMPower010 ⁴	–	–	–	–	Yes	–	–	–	–	Yes ^d
PEARLS/KEYNOTE-091 ¹⁴	–	Yes	–	–	–	–	–	Yes	–	–

^aNeoadjuvant ipilimumab plus nivolumab followed by surgical resection and adjuvant standard of care. ^bCanakinumab plus pembrolizumab. ^cDurvalumab in combination with other therapies (oleclumab, monalizumab, or danvatrisen). ^dBest supportive care. **Abbreviation:** CT, chemotherapy.

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DISCLOSURES

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