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Perioperative immune checkpoint inhibitor therapy across tumors: Insights and shared lessons from a rapidly evolving field

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Abstract. Björkström K, Matikas A, Svedman FC, Björgvinsson E, Zupancic M, Villabona L, et al. Perioperative immune checkpoint inhibitor therapy across tumors: Insights and shared lessons from a rapidly evolving field. *J Intern Med.* 2026;**299**:538–69.

The integration of immune checkpoint inhibitors into perioperative management marks a major evolution in curative-intent oncology. This review examines the current evidence for perioperative immunotherapy encompassing neoadjuvant, adjuvant, and combined strategies in melanoma and non-melanoma skin cancers, non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), esophageal and gastroesophageal junction cancer, renal cell carcinoma, urothelial carcinoma, head and neck squamous cell carcinoma, colorectal cancer, gynecological malignancies, and hepatocellular carcinoma. Neoadjuvant immunotherapy demonstrates biological advantages by exposing the immune system to intact tumor antigens, consistently improving event-free survival and pathological response rates across tumor types. Notable successes include CheckMate 816 in NSCLC, KEYNOTE-522 in TNBC, and emerging trials in melanoma that show superior outcomes compared to adjuvant-only approaches. Pathological complete response and major pathological response have emerged as robust surrogate endpoints correlating with long-term survival. In contrast, adjuvant immunotherapy shows more variable results, with demonstrated recurrence-free survival benefits but inconsistent overall survival (OS) advantages—particularly concerning given the risk of overtreatment in patients potentially cured by surgery alone. Critical challenges include the absence of predictive biomarkers in most cancer types, immune-related adverse events occurring in up to 30% of patients, substantial healthcare costs, and insufficient OS follow-up duration in many approved indications. Future priorities include biomarker development, adaptive trial designs incorporating response-guided therapy, and long-term toxicity assessment. Although perioperative immunotherapy is reshaping curative-intent cancer treatment, optimal patient selection, treatment sequencing, and safety optimization remain essential for widespread implementation.

Keywords: adjuvant therapy, immune checkpoint inhibitors, neoadjuvant therapy, neoplasms

Abbreviations: AE, adverse event; CC, cervical cancer; cCR, clinical complete response; ccRCC, clear cell renal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; ctDNA, circulating tumor DNA; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DFS, disease-free survival; dMMR, deficient mismatch repair; EC, endometrial cancer; EAU, European Association of Urology; EFS, event-free survival; EMA, European Medicines Agency; FDA, Food and Drug Administration; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; MCC, Merkel

cell carcinoma; MIBC, muscle-invasive bladder cancer; MPR, major pathological response; MSI, microsatellite instability; mUC, metastatic urothelial carcinoma; NED, no evidence of disease; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, overall survival; pCR, pathological complete response; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RCC, renal cell carcinoma; RFS, recurrence-free survival; SOC, standard of care; TIL, tumor infiltrating lymphocytes; TLND, therapeutic lymph node dissection; TNBC, triple-negative breast cancer; UC, urothelial carcinoma

Introduction

The introduction of immune checkpoint inhibitors (ICIs) has fundamentally transformed oncological practice over the past decade, demonstrating remarkable efficacy in the metastatic setting across multiple tumor types. Building on these successes, the focus has progressively shifted toward earlier disease stages, where the immune system may be more intact and responsive. This paradigm shift has led to numerous clinical trials investigating perioperative immunotherapy—encompassing both neoadjuvant and adjuvant strategies—across a diverse spectrum of solid malignancies [1, 2] (Tables 1–4). Neoadjuvant therapy is administered before surgery to reduce tumor burden, whereas adjuvant therapy is given after surgery to eliminate residual microscopic disease.

The biological rationale for perioperative immunotherapy is compelling. In the neoadjuvant setting, the intact tumor provides a rich source of tumor-associated antigens that can prime and activate the immune system before surgical resection [3]. This approach may facilitate immune memory formation and systemic immune activation that could target micrometastatic disease. Additionally, neoadjuvant immunotherapy offers the opportunity to assess treatment response through pathological evaluation, with pathological complete response (pCR) and major pathological response (MPR) emerging as important surrogate endpoints that correlate with long-term outcomes [4–6].

Adjuvant immunotherapy targets residual disease after surgical resection when tumor burden is minimal [1]. The challenge lies in identifying patients who harbor micrometastatic disease and would benefit from additional treatment, while avoiding overtreatment of those already cured by surgery alone. The development of biomarkers, such as circulating tumor DNA (ctDNA), and the identification of predictive biomarkers, such as microsatellite instability (MSI), represent an area of investigation to better guide patient selection [7].

However, several critical challenges persist. The lack of mature overall survival (OS) data for many approved indications raises questions about the true clinical benefit, particularly given the potential for significant immune-related adverse events (irAEs) and substantial healthcare costs. The risk of overtreatment is particularly concerning in early stage disease, where many patients may already be cured by surgery alone. Additionally, immune-related toxicities can be severe and potentially life-threatening, with some effects being irreversible. Economic considerations also present significant challenges for healthcare systems globally. The high cost of ICIs, combined with their use in earlier disease stages where larger patient populations may be treated, raises important questions about cost-effectiveness.

This comprehensive review examines the current state of perioperative immunotherapy across major solid tumor types, including melanoma, non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), esophageal and gastroesophageal junction (GEJ) cancer, renal cell carcinoma (RCC), urothelial carcinoma (UC), head and neck squamous cell carcinoma (HNSCC), colorectal cancer (CRC), Merkel cell carcinoma (MCC), cutaneous squamous cell carcinoma (cSCC), gynecological malignancies, and hepatocellular carcinoma (HCC). For each tumor type, we analyze the clinical trial evidence supporting current approvals, discuss ongoing challenges and controversies, and highlight future directions for research and clinical practice.

Table 1. *Summary of phase II/III clinical trials evaluating neoadjuvant and/or adjuvant PD-1 and CTLA-4 inhibitors in skin cancers.*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA approval
Cutaneous melanoma (CM)	Adj	aCTLA-4 monotherapy	Adj ipi 10 mg/kg Q3W × 4 ($n = 475$)	Adj placebo ($n = 476$)	CM stage III (AJCC7)	**EORTC 1807** (NCT00636168), RFS, phase III	Improved RFS, DMFS, and OS	NA	2015	Not approved (2025)
CM	Adj	aPD-1 monotherapy	Adj nivo 3 mg/kg Q2W × 25 ($n = 453$)	Adj ipi 10 mg/kg Q3W × 4 ($n = 453$)	CM stage IIIb-c, IV (AJCC7)	**CheckMate-238** (NCT02388906), phase III, RFS	Improved RFS and DMFS, no OS benefit	NA	2017	2018
CM	Adj	aPD-1 monotherapy	Adj pembro 200 mg Q3W × 18 ($n = 647$)	Adj ipi 10 mg/kg Q3W or high-dose interferon ($n = 654$)	CM stage III–IV (AJCC7)	**SWOG S1404** (NCT02506153), phase III, RFS	Improved RFS, no OS benefit	NA	2019	2018
CM	Adj	aPD-1 monotherapy	Adj pembro 200 mg Q3W × 18 ($n = 514$)	Adj placebo ($n = 514$)	CM stage III (AJCC7)	**EORTC 1325/KEYNOTE-054** (NCT02362594), phase III, RFS	Improved RFS and DMFS, OS is awaited	NA	2019	2018
CM	Adj	aPD-1 monotherapy	Adj pembro 200 mg Q3W × 17 ($n = 487$)	Adj placebo ($n = 489$)	CM stage IIB, IIC	**KEYNOTE-716** (NCT03553836), phase IV, RFS	Improved RFS and DMFS, OS is awaited	NA	2021	2022
CM	Adj	aPD-1 monotherapy	Adj nivo 480 mg Q4W × 13 ($n = 487$)	Adj placebo ($n = 489$)	CM stage IIB, IIC	**CheckMate 76K** (NCT04099251), phase III, RFS	Improved RFS and DMFS, OS is awaited	NA	2023	2023
CM	Neoadj	aPD-1 + aCTLA-4	Neoadj nivo 3 mg/kg + ipi 1 mg/kg Q3W × 2 → Adj depending on pR and BRAF status ($n = 99$)	No control arm	CM stage III, clinically detected	**PRADO** (NCT02977052), phase II, pRR	93% RFS at 2 years	MPR: 61%	Not approved (2025), approved in some countries	Not approved (2025), approved in some countries
CM	Neoadj	aPD-1	Neoadj Pembro 200 mg Q3W × 3 → Adj Pembro 200 mg Q3W × 15 ($n = 514$)	Adj pembro 200 mg Q3W × 18 ($n = 514$)	CM stage III–IV, clinically detected	**SWOG S1801** (NCT03698019), phase II, EFS	Improved EFS, OS is awaited	MPR: 52%	Not approved (2025), approved in some countries	Not approved (2025), approved in some countries
CM	Neoadj	aPD-1 + aCTLA-4	Neoadj nivo 240 mg + ipi 80 mg Q3W × 2 → Adj depending on PR and BRAF status ($n = 212$)	Adj nivo 480 mg Q4W × 12 ($n = 211$)	CM stage III, clinically detected	**NADINA** (NCT04949113), phase III, EFS	Improved EFS and DMFS, OS is awaited	MPR: 61%	Not approved (2025), approved in some countries	Not approved (2025), approved in some countries

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Table 1. *(Continued)*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA approval
Merkel cell carcinoma (MCC)	Adj	aPD-1	Adj nivo 480 mg Q4W × 13 ($n = 118$)	Observation ($n = 61$)	MCC any stage, completely resected	**ADMEC-O** (NCT02196961), phase II, DFS	Improved DFS, OS is awaited	NA	Not approved (2025)	Not approved (2025)
MCC	Neoadj	aPD-1	Neoadj nivo 240 mg Q2W × 2 → Adj RT as determined by treating physician ($n = 39$)	No control arm	MCC, stage IIa–IIIB, primary >2 cm, oligomet stage IV	**CheckMate 358** (NCT02488759), phase I/II, safety	RFS: median not reached, 24 months 68.5%. OS: median not reached, 24 months 79.4%	pCR: 46.2%; MPR: 15.4%	Not approved (2025)	Not approved (2025)
Cutaneous squamous cell carcinoma (cSCC)	Adj	aPD-1	Adj pembro 400 mg Q6W × 9	Placebo	High-risk cSCC	**KEYNOTE-630** (NTC03833167), phase III, RFS (was planned to enroll 570 patients)	Stopped for futility after including 436 patients	NA	Not approved (2025)	Not approved (2025)
cSCC	Adj	aPD-1	Adj cemi 350 mg Q3W × 4 → 700 mg Q6W × 6	Placebo	High-risk cSCC	**C-POST trial** (NCT03969004), phase III, DFS	Improved DFS, OS not mature	NA	Approved (2025)	Approved (2025)
cSCC	Neoadj + Adj	aPD-1	Neoadj cemi 350 mg Q3W × 4 → optional Adj cemi 350 mg Q3W × 16 ($n = 16$), Adj radiotherapy ($n = 17$), or observation ($n = 32$)	No control arm	cSCC stage II–IV (M0)	**R2810-ONC-1901** (NCT04154943), phase II, pCR	NA	pCR 51% ($n = 40$), none with recurrences	Not approved (2025)	Not approved (2025)
cSCC	Neoadj + Adj	aPD-1	Neoadj cemi 350 mg Q3W × 2 → Adj cemi 350 mg Q3W, 1 year ($n = 23$)	No control arm	cSCC stage II–IV (M0)	**Neoadj-CESQ** (NCT04632433), phase II, MPR	NA	MPR: 47%; pCR: 39%	Not approved (2025)	Not approved (2025)
cSCC	Neoadj	aPD-1	Neoadj cemi 350 mg Q3W × 2 → adjuvant radiotherapy ($n = 20$)	No control arm	cSCC stage III–IVA in the head and neck area	NCT03565783, phase II, ORR per RECIST 1.1	12-month DFS and OS rates 90% and 95%	MPR 75%	Not approved (2025)	Not approved (2025)

Note: FDA and EMA approval status is indicated for each regimen.

Abbreviations: aCTLA-4, CTLA-4 inhibitor; Adj, adjuvant; aPD-1, PD-1 inhibitor; CM, cutaneous melanoma; cSCC, cutaneous squamous cell carcinoma; DFS, disease-free survival; DMFS, distant metastasis-free survival; EFS, event-free survival; EMA, European Medicines Agency; FDA, Food and Drug Administration; ipi, ipilimumab; MPR, major pathologic response (≤10% residual viable tumor after treatment); NA, not applicable; neoadj, neoadjuvant; nivo, nivolumab; ORR, objective response rate (percentage of patients with tumor shrinkage); OS, overall survival; pCR, pathologic complete response (no residual cancer in the tumor sample); pembro, pembrolizumab; PR, pathologic response; pRR, pathologic response rate; RFS, relapse-free survival; RT, radiotherapy.

Table 2. *Summary of phase II/III clinical trials evaluating neoadjuvant and/or adjuvant PD-1 and CTLA-4 inhibitors in respiratory and gastrointestinal cancers.*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
Non-small cell lung cancer (NSCLC)	Adj	aPD-1	Adj pembro 200 mg Q3W × 18 (*n* = 590)	Adj placebo (*n* = 587)	NSCLC stage IB-IIIA (AJCC7)	**KEYNOTE-091** (NCT02504372), phase III, DFS	Improved DFS, no OS benefit	NA	2023	Not approved (2025), approved in some countries
NSCLC	Neoadj + Adj	aPD-1	Neoadj nivo 360 mg Q3W × 3 + chemo → Adj nivo 480 mg Q4W × 13 (*n* = 46)	None	NSCLC stage IIIA (N2) (AJCC 7)	**NADIM I** (NCT03081689), phase II, PFS	3-year OS 81.9%, PFS 69.6%	pCR 63%, MPR 83%	Not approved (2025)	Not approved (2025)
NSCLC	Neoadj + Adj	aPD-1	Neoadj pembro 200 mg Q3W × 4 + chemo → Adj pembro 200 mg Q3W × 13 (*n* = 397)	Neoadj placebo + chemo → Adj placebo (*n* = 400)	NSCLC stage II–IIIB (N2)	**KEYNOTE-671** (NCT03425643), phase III, EFS and OS	Improved EFS and OS	Improved pCR (18.1% vs. 4.0%)	2023	Not approved (2025), approved in some countries
NSCLC	Neoadj + Adj	aPD-L1	Neoadj durva 1500 mg Q3W × 4 + chemo → Adj durva 1500 mg Q4W × 12 (*n* = 400)	Neoadj placebo + chemo → Adj placebo (*n* = 402)	NSCLC stage II–IIIB (N2)	**AEGEAN** (NCT03800134), phase III, EFS and pCR	Improved EFS, OS is awaited	Improved pCR (17.2% vs. 4.3%)	2024	Not approved (2025), approved in some countries
NSCLC	Neoadj + Adj	aPD-1	Neoadj nivo 360 mg Q3W × 3 + chemo → Adj nivo 480 mg Q4W × 13 (*n* = 461)	Neoadj placebo + chemo → Adj placebo (*n* = 458)	NSCLC stage IIA–IIIB	**CheckMate 77T** (NCT04025879), phase III, EFS and OS	Improved EFS, OS is awaited	Improved pCR (25.3% vs. 4.7%)	2024	Not approved (2025), approved in some countries
NSCLC	Neoadj + Adj	aPD-1	Neoadj toripalimab 240 mg Q3W × 3 + chemo → Adj toripalimab 240 mg Q3W × 12 (*n* = 404)	Neoadj chemo + placebo → Adj placebo (*n* = 404)	NSCLC stage II–III	**NEOTORCH** (NCT04158440), phase III, EFS and OS	Improved EFS, OS is awaited	Improved pCR (24% vs. 4%)	Not approved (2025)	Not approved (2025)
NSCLC	Neoadj + Adj	aPD-1	Neoadj tislelizumab 200 mg Q3W × 3 + chemo → Adj tislelizumab 200 mg Q3W × 9 (*n* = 310)	Neoadj chemo + placebo → Adj placebo (*n* = 310)	NSCLC stage II–IIIB	**RATIONALE-315** (NCT04379635), phase III, EFS and OS	Improved EFS and OS	Improved pCR (20% vs. 6%)	Not approved (2025)	Not approved (2025)
NSCLC	Neoadj	aPD-1	Neoadj nivo 360 mg Q3W × 3 + chemo (*n* = 57)	Neoadj chemo alone (*n* = 57)	NSCLC stage IIA–IIIB	**NADIM II** (NCT03838159), phase IIb, EFS	Improved EFS	pCR 36.2% vs. 6.8%	Not approved (2025)	Not approved (2025)

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Table 2. *(Continued)*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
NSCLC	Neoadj	aPD-1	Neoadj nivo 360 mg Q3W × 3 + chemo (*n* = 179)	Neoadj placebo + chemo (*n* = 179)	NSCLC stage IB–IIIA (AJCC7)	**CheckMate-816** (NCT02998528), phase III, EFS and pCR	Improved EFS and OS	Improved pCR (24% vs. 2.2%)	2022	Not approved (2025), approved in some countries
NSCLC	Neoadj	aPD-L1	Neoadj atezo 1200 mg Q3W × 2 (*n* = 181)	No control arm	NSCLC stage IB–IIIB	**LCMC3** (NCT02927301), phase II, MPR	3-year OS 80%	MPR 20%, pCR 6%	Not approved (2025)	Not approved (2025)
NSCLC	Neoadj	aPD-L1	Neoadj atezo 1200 mg Q3W × 4 + chemo (*n* = 30)	No control arm	NSCLC stage IB–IIIA (AJCC7)	NCT02716038, phase II, MPR	3-year OS 77%	MPR 57%, pCR 30%	Not approved (2025)	Not approved (2025)
NSCLC	Neoadj	aPD-1 + aCTLA-4	Neoadj nivo 3 mg/kg Q2W × 3 + ipi 1 mg/kg Q6W × 1 (*n* = 21)	Neoadj nivo 3 mg/kg Q2W × 3 (*n* = 23)	NSCLC stage I–IIIA (AJCC7)	**NeoadjSTAR** (NCT03158129), phase II, MPR	Median OS and RFS not reached	MPR 50% (nivo + ipi) vs. 24% (nivo), pCR 38% vs. 10%	Not approved (2025)	Not approved (2025)
Head and neck squamous cell carcinoma (HNSCC)	Adj	aPD-L1	Adj. atezo 1200 mg Q3W × 16 (*n* = 203)	Adj placebo (*n* = 203)	Stage IVa or IVb HNSCC (stage III for HPV+ OPSCC); CR, PR, or SD after definitive multimodal treatment	**IMvoke010** (NTC03452137), phase III, INV-assessed EFS	No EFS or OS benefit.	NA	Not approved (2025)	Not approved (2025)
HNSCC	Adj	aPD-1	Adj. nivo, 240 mg Q2W × 1 → nivo 360 mg Q3W × 3 + SOC (RT + chemo) → nivo 480 mg Q4W × 6 (*n* = 332)	Adj. SOC (RT ± chemo) (*n* = 334)	High-risk HNSCC-treated by primary surgery, stage III–IV, cisplatin eligible	NIVOPOSTOP (NCT03576417), phase III, DFS	Improved DFS, a trend toward improved OS	NA	Not approved (2025)	Not approved (2025)
HNSCC	Neoadj	aPD-1	Neoadj nivo, 240 mg Q2W × 2, surgery planned by d29 (*n* = 52, 26 HPV-pos, 26 HPV-neg)	No control arm	Stage III–IVa, HPV+/HPV−	**CheckMate 358** (NCT02488759), phase I/II, safety and tolerability	Surgery not delayed	pPR: HPV+: 24%/HPV−: 6%	Not approved (2025)	Not approved (2025)

(*Continued*)

Table 2. *(Continued)*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
HNSCC	Neoadj	aPD-1 + aCTLA-4	Neoadj nivo 240 mg Q2W × 2 (*n* = 6, phase I) OR neoadj nivo 240 mg + ipi 1 mg/kg Q2W × 1 + nivo 240 mg Q2W × 1 (*n* = 26, phase II)	No control arm	T2-4, N0-3, M0 primary/recurrent	**IMCISION** (NCT03003637), phase I/II, feasibility to resect no later than week 6 (phase I), pRR (phase II)	Surgery not delayed/suspended	MPR: mono nivo 17%, ipi + nivo: 35%	Not approved (2025)	Not approved (2025)
HNSCC	Neoadj	aPD-1	Neoadj pembro 200 mg Q2W × 2 → Adj pembro 200 mg Q3W × 15 + SOC (RT ± chemo) (*n* = 357)	Adj. SOC (RT ± chemo) (*n* = 357)	Stage III or IVa	**KEYNOTE-689** (NCT03765918), phase III, EFS	Improved EFS, a trend toward improved OS	Improved mPR	Approved (2025)	Approved (2025)
Esophageal and gastroesophageal junction (GEJ) cancer	Adj	aPD1	Adj nivo 240 mg Q2W × 8 + 480 mg × 8 (*n* = 532)	Adj placebo (*n* = 262)	Resected (R0) after chemoradiotherapy stage II–III (AJCC7)	**CheckMate-577** (NCT02743494), phase III, DSF	Improved DSF, OS is awaited	NA	2021	2021
Gastric and GEJ cancer	Neoadj + Adj	aPD1 + aCTLA-4	Neoadj nivo 240 mg Q2W × 6 + ipi 1 mg/kg Q6W × 2 → Adj nivo 480 mg Q4W × 9 by "investigator decision" (*n* = 32)	No control arm	Resectable stage T2-4, N0-N+, M0, dMMR MSI-H	**GERCOR NeoadjNIPIGA** (NCT04006262), phase II, pCR	Limited data (1 death occurred)	pCR: 59%	Not approved but used in some countries	Not approved but used in some countries
Gastric and GEJ cancer	Neoadj + Adj	aPD-L1	Neoadj durva 1500 mg Q4W × 2 + chemotherapy × 2 → Adj durva 1500 mg Q4W × 12 + chemotherapy × 2	Placebo	Resectable stage II–IVA Adenocarcinoma	**MATTERHORN** (NCT04592913), phase III, EFS	Improved EFS, OS improvement not reached as of now	pCR: 19.2%	Not approved (2025)	Not approved (2025)

(Continued)

Table 2. *(Continued)*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
Hepatocellular carcinoma (HCC)	Adj	aPD-L1	Adj. atezo 1200 mg + bevacizumab 15 mg/kg Q3W × 17 ($n = 334$)	Active surveillance ($n = 334$)	High-risk surgically resected or ablated HCC	**IMbrave050** (NCT04102098), phase III, RFS	No RFS benefit.	NA	Not approved (2025)	Not approved (2025)
HCC	Neoadj + Adj	aPD1 + aCTLA-4	Neoadj nivo 240 mg Q2W × 3 → Adj nivo 480 mg Q4W × 26 ($n = 13$)	Neoadj nivo 240 mg Q2W × 3 + ipi 1 mg/kg x 1 → Adj nivo 480 mg Q4W × 26 + ipi 1 mg/kg Q6W × 4 ($n = 14$)	Resectable HCC	NCT03222076, phase II, tolerability, ORR, PFS	No difference in PFS (HR 0.99). ORR 23% with nivo, ORR 0% with nivo + ipi	NA	Not approved (2025)	Not approved (2025)
HCC	Neoadj	aPD1	Neoadj cemi Q3W × 2 → resection	No control arm	Resectable HCC.	NCT03916627, phase II, ORR, significant tumor necrosis	ORR 15%	20% had significant tumor necrosis	Not approved (2025)	Not approved (2025)
Colorectal cancer (dMMR/MSI-H)	Neoadj	aPD-1 + aCTLA-4	Neoadj nivo 3 mg/kg Day 1 + 15, ipi 1 mg/kg Day 1 ($n = 113$)	No control arm	Colon adenocarcinoma dMMR, T4, T3, N+	**NICHE-2** (NCT03026140), phase II. Safety + DFS-3 years	DFS = 100% median follow-up 26.2 (9.1–65.3) months	pCR = 68% (≤10% residual viable cells)	Not approved (2025)	Not approved (2025)
Colorectal cancer (dMMR/MSI-H)	Neoadj	aPD-1	Neoadj dostarlimab 500 mg Q3W × 9 = 6 months, $n = 48$	No control arm	Rectal adenocarcinoma dMMR stage 2 + 3	NTC04165772, phase II, cCR, pCR	cCR at 6 months = 100% ($n = 42$); DFS = 100% at 0.3–50.5 months	NA	Not approved (2025)	Not approved (2025)

Note: FDA and EMA approval status is indicated for each regimen.

Abbreviations: aCTLA-4, CTLA-4 inhibitor; Adj, adjuvant; aPD-1, PD-1 inhibitor; aPD-L1, PD-L1 inhibitor; atezo, atezolizumab; cemi, cemiplimab; chemo, chemotherapy; CR, complete response; DFS, disease-free survival; dMMR, mismatch repair-deficient; durva, durvalumab; EFS, event-free survival; EMA, European Medicines Agency; FDA, Food and Drug Administration; GEJ, gastroesophageal junction; HNSCC, head and neck squamous cell carcinoma; ipi, ipilimumab; NA, not applicable; MPR, major pathologic response (≤10% residual viable tumor after treatment); neoadj, neoadjuvant; nivo, nivolumab; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathologic complete response (no residual cancer in the tumor sample); PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PR, partial response; pRR, pathologic response rate; RFS, relapse-free survival; RT, radiotherapy; SD, stable disease; SOC, standard of care.

Table 3. *Summary of phase I–III clinical trials evaluating neoadjuvant and/or adjuvant PD-1 and PD-L1 inhibitors in female-specific cancers.*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
Triple-negative breast cancer (TNBC)	Adj	aPD-L1	Adj atezo 840 mg Q2W × 10 + chemo, followed by only atezo 1200 mg Q3W for 1 year (*n* = 1101)	Adj chemo (*n* = 1098)	TNBC stage II–III	**ALEXANDRA/IMPassion030** (NCT03498716), phase III, invasive DFS	No improvement in DFS	NA	Not approved (2025)	Not approved (2025)
TNBC	Adj	aPD-L1	Adj ave 10 mg/kg Q2W monotherapy for 1 year, after Neoadj chemo (*n* = 235)	Observation (*n* = 231)	TNBC w/any non-pCR after neoadj, or pN2, pT1-2N1, pT3N0	**A-BRAVE** (NCT02926196), phase III, DFS	No improvement in DFS, but improved OS mainly in the neoadj-treated patients stratum	NA	Not approved (2025)	Not approved (2025)
TNBC	Neoadj + Adj	aPD-1	Neoadj pembro 200 mg Q3W × 8 + chemo → adj pembro 200 mg Q3W × 9 (*n* = 784)	Neoadj chemo (*n* = 390)	TNBC cT2-4N0-2 or cT1cN1-2	**KEYNOTE-522** (NCT03036488), phase III, co-primary endpoints: pCR, EFS	Improved EFS, DDFS, and OS	Improved pCR	2021	2022
TNBC	Neoadj + Adj	aPD-L1	Neoadj atezo 840 mg Q2W × 11 + chemo → adj atezo 1200 mg Q3W × 11 (*n* = 165)	Neoadj chemo (*n* = 168)	TNBC stage II–III	**IMPassion031** (NCT03197935), phase III, co-primary endpoints: pCR in ITT and in PD-L1+	No improvement in EFS	Improved pCR	Not approved (2025)	Not approved (2025)
TNBC	Neoadj	aPD-L1	Neoadj atezo 1200 mg Q3W for 52 weeks + chemo (*n* = 773)	Neoadj chemo (*n* = 777)	TNBC cT2-3N0/N+ or cT1cN+	**NSABP-B59/GeparDouze** (NCT03281954), phase III, EFS	No improvement in EFS and OS	Improved pCR	Not approved (2025)	Not approved (2025)
TNBC	Neoadj	aPD-L1	Neoadj atezo 1200 mg Q3W × 8 + chemo (*n* = 138)	Neoadj chemo (*n* = 142)	TNBC cT1-2cN1-3, cT3-4N0-3, cTanyN2-3	**NeoadjTRIP MICHELANGELO** (NCT002620280), phase III, EFS	No improvement in EFS	No improvement in pCR	Not approved (2025)	Not approved (2025)

(*Continued*)

Table 3. *(Continued)*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
TNBC	Neoadj	aPD-L1	Neoadj durva 1500 mg Q4W × 2 + chemo (*n* = 88)	Neoadj chemo (*n* = 86)	TNBC cT1b-T4	**GeparNuevo** (NCT02685059), phase II, pCR	Improved DFS, DDFS, and OS	No improvement in pCR	Not approved (2025)	Not approved (2025)
Endometrial cancer	Adj	aPD-1	Adj Pembro 200 mg Q3w × 12 + chemo ± RT (*n* = 545)	Adj Placebo + chemo ± RT (*n* = 550)	High-risk endometrial cancer	**ENGOT-en11/GOG-3053/KEYNOTE-B21** (NCT04634877), phase III, DFS and OS	No DFS benefit in total study population (HR 1.02). DFS benefit in dMMR population (HR 0.31)	NA	Not approved (2025)	Not approved (2025)
Endometrial cancer	Neoadj	aPD-1	Neoadj Pembro 200 mg Q3w × 2 (*n* = 10)	No control arm	dMMR endometrial cancer of any grade	NCT04262089, phase I, pathologic response	DFS 20 months	pRR 50%	Not approved (2025)	Not approved (2025)
Cervical cancer	Neoadj	aPD-1	Neoadj camrelizumab 200 mg Q3w × 2 + chemo (*n* = 85)	No control arm	Cervical cancer IB3, IIA2, or IIB/IIIC1r with a tumor diameter ≥4 cm (FIGO 2018)	**NACI** (NCT04516616), phase II, ORR	NA	pCR = 38%	Not approved (2025)	Not approved (2025)
Ovarian cancer (HGSC)	Neoadj	aPD-1	Neoadj Pembro 200 mg Q3w × 4 + chemo (*n* = 61)	Neoadj chemo (*n* = 30)	HGSC stage IIIC/IV for whom upfront complete resection was unachievable	**NeoPembrOV** (NCT03275506), phase II, CRR	Improved OS	NA	Not approved (2025)	Not approved (2025)

Note: FDA and EMA approval status is indicated for each regimen.

Abbreviations: Adj, adjuvant; aPD-1, PD-1 inhibitor; aPD-L1, PD-L1 inhibitor; atezo, atezolizumab; Ave, avelumab; CR, complete response; DDFS, distant disease-free survival; DFS, disease-free survival; dMMR, mismatch repair-deficient; durva, durvalumab; EFS, event-free survival; EMA, European Medicines Agency; FDA, Food and Drug Administration; ITT, intention to treat; NA, not applicable; MPR, major pathologic response (≤10% residual viable tumor after treatment); neoadj, neoadjuvant; OS, overall survival; pCR, pathologic complete response (no residual cancer in the tumor sample); PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PR, partial response; pRR, pathologic response rate; RT, radiotherapy; TNBC, triple-negative breast cancer.

Table 4. *Summary of phase II/III clinical trials evaluating neoadjuvant and/or adjuvant PD-1, PD-L1, and CTLA-4 inhibitors in urological cancers.*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
Renal cell carcinoma (RCC)	Adj	aPD-1	Adj pembro 200 mg Q3W × 17 ($n = 496$)	Adj placebo ($n = 498$)	ccRCC. pT2 grade 4 or sarcomatoid; or pT3-T4; or pN1; or M1 NED	**KEYNOTE-564** (NCT03142334), phase III, DFS	Improved DFS, improved OS	NA	2021	2022
RCC	Adj	aPD-1 + aCTLA-4	Adj nivo 240 mg Q2W × 12 + ipi 1 mg/kg Q6W × 4 ($n = 405$)	Adj placebo ($n = 411$)	ccRCC. pT2a, grade 3/4 (N0M0); or pT2b-T4, any grade (N0M0); or pT, any grade (N1M0)	**CheckMate 914** Part A (NCT03138512), phase III, DFS	No DFS benefit	NA	Not approved (2025)	Not approved (2025)
RCC	Adj	aPD-1 + aCTLA-4	Adj nivo 240 mg Q2W × 12 + placebo ($n = 411$); or Adj nivo 240 mg Q2W × 12 + ipi 1 mg/kg Q6W × 4 ($n = 206$)	Adj placebo ($n = 208$)	ccRCC. pT2a, grade 3/4 (N0M0); or pT2b-T4, any grade (N0M0); or pT, any grade (N1M0)	**CheckMate 914** Part B (NCT03138512), phase III, DFS	No DFS benefit, no OS benefit	NA	Not approved (2025)	Not approved (2025)
RCC	Adj	aPD-L1	Adj atezo 1200 mg Q3W × 16 ($n = 390$)	Adj Placebo ($n = 388$)	ccRCC or sarcomatoid histology. pT2, grade 4 (N0M0); or pT3a, grade 3/4 (N0M0); pT3b/c-T4, any grade (N0M0); or TxN+, any grade or pT3-T4; or pN1; or M1 NED	**ImMotion010** (NCT03024996), phase III, DFS	No DFS benefit, no OS benefit	NA	Not approved (2025)	Not approved (2025)
RCC	Adj	aPD-L1 + aCTLA-4	Adj durvalumab 1500 mg Q4W × 13 + tremelimumab 75 mg Q4W × 2 ($n = 225$)	Active monitoring ($n = 340$)	High or intermediate risk according to Leibovich score; or M1 NED (fully resected synchronous ipsilateral adrenal or soft tissue met)	**RAMPART** Arm C versus A (NCT03288532), phase III	Improved DFS, OS is awaited	NA	Not approved (2025)	Not approved (2025)

(*Continued*)

Table 4. *(Continued)*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
RCC	Neoadj + Adj	aPD-1	Neoadj nivo 240 mg Q2W × 2 → Adj nivo 240 mg Q2W × 8; or neoadj nivo 480 mg Q4W × 1 → Adj nivo 480 mg Q4W × 9, $n = 404$	Observation ($n = 415$)	RCC, any histology. Clinical ≥T2 (N0M0) or Tany N+ (N0M0); (M1 ≤3 metastases later permitted)	**PROSPER EA8143** (NCT03055013), phase III, RFS	No RFS benefit, no OS benefit, terminated early due to futility	NA	Not approved (2025)	Not approved (2025)
RCC	Neoadj + Adj	aPD-1	Neoadj pembro Q3W × 4 + lenvatinib over 12 weeks → Adj pembro Q3W × 13 ($n = 17$)	No control arm	ccRCC. ≥T3Nx; TanyN+; or unresectable disease	NCT04393350, phase II, ORR	PR 17.6% (3/17) at week 12, median tumor size reduction 22%	NA	Not approved (2025)	Not approved (2025)
RCC	Neoadj	aPD-1	Neoadj, nivo Q2W × 4 ($n = 18$)	No control arm	ccRCC. Any T, any N, M0.	NCT02595918, phase II, feasibility to receive ≥3 doses and proceed with surgery	94% feasibility rate; 82% 1-year RFS	NA	Not approved (2025)	Not approved (2025)
RCC	Neoadj	aPD-L1	Neoadj ave 10 mg/kg Q2W × 6 + axitinib for 12 weeks ($n = 40$)	No control arm	ccRCC. cT1b-T2a, grade 4; cT2b-3a, grade 3–4; cT3-T4, any grade; resectable N+	NeoadjAvAx (NCT03341845), phase II, pRR	30% PR of the PT, DFS, and OS are awaited	30% pPR, 7.5% MPR	Not approved (2025)	Not approved (2025)
RCC	Neoadj	aPD-1	Neoadj nivo 240 mg Q2W × 3 + sitravatinib ($n = 25$)	No control arm	ccRCC. cT2-T3b (N0M0)	NCT 03680521, phase II, ORR	ORR 12%	NA	Not approved (2025)	Not approved (2025)
RCC	Neoadj	aPD-1	Neoadj toripalimab 240 mg Q3W × 4+ axitinib ($n = 29$)	No control arm	ccRCC. IVC tumor thrombus (cT3b/c, C0/1, M0/1)	**NeoadjTAX**, phase II, down-staging rate of tumor thrombus (TT) level	44% had reduction in TT level; 96% had reduction in TT length	NA	Not approved (2025)	Not approved (2025)

(*Continued*)

Table 4. *(Continued)*

Cancer type	Treatment type	Antibody	Experimental arm (*n*)	Control arm (*n*)	Patient selection	Study, phase, endpoint	Survival outcomes	Pathological response	FDA approval	EMA Approval
Urothelial cancer (UC)*	Adj	aPD-1	Adj nivo 240 mg Q2W for up to 1 year ($n = 353$)	Placebo ($n = 356$)	UC pT3, pT4a, or pN+, R0; or ypT2 to ypT4a or ypN+, R0	**CheckMate 274** (NCT02632409), phase III, DFS	Improved DFS in both ITT and PD-L1+, mature OS outcome is awaited	NA	2021	2022 for PD-L1+
UC	Adj	aPD-1	Adj pembro 200 mg Q3W for up to 1 year ($n = 354$)	Observation ($n = 348$)	UC pT3 or higher, pN+, or microscopic positive surgical margins; or ypT2 or higher, ypN+, or microscopic positive surgical margins	**AMBASSADOR** (NCT03244384), phase III, DFS and OS	Improved DFS, not mature OS	NA	Not approved (2025)	Not approved (2025)
UC	Adj	aPD-L1	Adj atezo1680 mg Q4W for up to 1 year in the ctDNA-positive cohort ($n = 167$)	Placebo ($n = 83$)	UC pT3 or higher, pN+, or microscopic positive surgical margins; or ypT2 or higher, ypN+	**IMvigor011** (NCT04660344), phase III, DFS and OS	Improved DFS and OS	NA	Not approved (2025)	Not approved (2025)
UC	Neoadj	aPD-L1	Neoadj durva Q3W × 4 + chemo → Adj durva 1500 mg Q4W × 8 ($n = 533$)	Neoadj chemo → observation ($n = 530$)	Cisplatin-eligible patients with MIBC; T2, T3, or T4a, N0 or N1, and M0 (AJCC Manual 16)	**NIAGARA** (NCT03732677), phase III, pCR and EFS	Improved both EFS and OS	No difference in pCR	Approved (2025)	Approved (2025)
UC	Neoadj	aPD1	Neoadj EV 1.25 mg/kg d1/d8 + pembro 200 mg d1×3 → RC + PLND → adj 6 cycles EV + 14 cycles pembro ($n = 170$)	PC + PLND only ($n = 174$)	T2-T4aN0M0 or T1-T4aN1M0 MIBC, ineligible for or declining cisplatin	**KEYNOTE-905/EV-303** (NCT03924895), phase III, EFS, OS, pCR	Improved EFS, OS, and pCR (pT0pN0)	pCR 57.1% vs. 8.6%	Not approved (2025)	Not approved (2025)

Note: FDA and EMA approval status is indicated for each regimen.

Abbreviations: aCTLA-4, CTLA-4 inhibitor; Adj, adjuvant; aPD-1, PD-1 inhibitor; aPD-L1, PD-L1 inhibitor; atezo, atezolizumab; Ave, avelumab; ccRCC, clear cell renal cell carcinoma; DFS, disease-free survival; Durva, durvalumab; EFS, event-free survival; EMA, European Medicines Agency; EV, enfortumab vedotin; FDA, Food and Drug Administration; Ipi, ipilimumab; ITT, intention to treat; NA, not applicable; M1 NED, metastatic (M1) but no evidence of disease after surgery; MIBC, muscle invasive bladder cancer; MPR, major pathologic response (≤10% residual viable tumor after treatment); neoadj, neoadjuvant; nivo, nivolumab; OS, overall survival; pCR, pathologic complete response (no residual cancer in the tumor sample); PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PLND, pelvic lymph node dissection; PR, partial response; pRR, pathologic response rate; RC, radical cystectomy; RCC, renal cell carcinoma; RFS, relapse-free survival; UC, urothelial cancer.

*The selected studies for UC were phase III trials with positive outcomes.

Melanoma

Despite therapeutic advances, melanoma continues to cause significant morbidity and mortality worldwide, with the global death count estimated to approach 100,000 annually by 2040 [8]. The introduction of ICIs has revolutionized treatment, first in the metastatic setting and subsequently in earlier disease stages. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved several ICIs for metastatic melanoma, including ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)) in 2011, pembrolizumab and nivolumab (both anti-programmed cell death protein 1 (PD-1)) in 2014 by FDA and 2015 by EMA, and nivolumab + ipilimumab in 2015 by FDA and 2016 by EMA [9].

Adjuvant treatment

The standard management for resectable stage II and stage III melanoma was historically surgery followed by observation. This paradigm shifted after multiple clinical trials from 2015 onwards indicated survival benefits of adjuvant immunotherapy [10–15] (Table 1).

For stage III melanoma, the EORTC-1807 trial showed ipilimumab improved recurrence-free survival (RFS) compared to placebo (26.1 vs. 17.1 months median) [11]. Further, there was an OS benefit for ipilimumab (60% vs. 51.3% at 7 years) [16]. However, 52% of the patients discontinued treatment due to irAEs. Although adjuvant ipilimumab was approved by the FDA in 2015, EMA has not approved it. In the CheckMate 238 trial, adjuvant nivolumab improved RFS compared to ipilimumab (50% vs. 39% at 5 years) in patients with resected stage IIIB/C and IV melanoma [17]. In the pivotal KEYNOTE-054-trial comparing adjuvant pembrolizumab to placebo in over 1000 patients with stage III melanoma, an improvement in RFS (50% vs. 36%) and distant metastasis-free survival (54% vs. 42%) was reported in the 7-year update [18]. OS outcomes are still pending. Adjuvant nivolumab was approved by the FDA in 2017 and by EMA in 2018, and adjuvant pembrolizumab was approved by the FDA in 2019 and by EMA in 2018.

Although adjuvant ICI treatment is widespread internationally, no trial comparing adjuvant anti-PD-1 to placebo in stage III melanoma has demonstrated an OS benefit. In 2023, an observational study by Helgadottir et al. found no improvement in OS at 2 years of follow-up [19].

KEYNOTE-716 compared pembrolizumab with placebo in stage IIB/C, demonstrating improved RFS at 20.9 months (85.2% vs. 76.5%) [15]. CheckMate-76K found improved RFS at 12 months (89% vs. 79.4%) [10]. Data on OS are awaited from both trials. Although pembrolizumab was approved by the FDA in 2021 and by EMA in 2022, and nivolumab by the FDA and EMA in 2023, adoption of adjuvant ICI treatment for stage IIB/C patients has varied internationally due to the absent mature OS data.

Neoadjuvant treatment

Several trials have investigated neoadjuvant immunotherapy in resectable stage III/IV melanoma (Table 1). In the PRADO trial published in 2022, patients with stage IIIB–D melanoma received two doses of neoadjuvant nivolumab 3 mg/kg and ipilimumab 1 mg/kg [20]. Patients achieving MPR (with 10% or less viable tumor in the resected metastatic node) did not undergo further surgical treatment or adjuvant therapy. Patients with a partial response (10%–50% remaining viable tumor) underwent therapeutic lymph node dissection (TLND), and patients with no response (>50% remaining viable tumor) underwent TLND and adjuvant nivolumab treatment [20]. The PRADO trial was the first example of a response-driven approach to decide adjuvant treatment necessity. The SWOG S1801 trial compared three cycles of neoadjuvant pembrolizumab followed by adjuvant pembrolizumab with adjuvant pembrolizumab only and found improved event-free survival (EFS) in the neoadjuvant group (68% vs. 55% at 3 years) [21]. The NADINA study compared neoadjuvant nivolumab + ipilimumab with standard adjuvant nivolumab in patients with stage III melanoma. Patients in the neoadjuvant group achieving MPR received no adjuvant treatment. The estimated 24-month EFS was 77.3% in the neoadjuvant group compared to 55.7% in the adjuvant group. For patients achieving MPR, the estimated 12-month EFS was 95%. Data on OS are pending [5]. Immune-related AEs of grade ≥3 occurred in 29.7% of patients in the neoadjuvant group. Neoadjuvant ICI lacks FDA and EMA approval but is increasingly used in some countries based on emerging trial data [22].

Despite high pathologic response rates, disease recurrence occurs in a small subset of patients with initial pathologic response, possibly due to declining therapy-induced immune responses rather than acquired resistance [23].

Conclusions

Both adjuvant and neoadjuvant ICI treatments have been implemented in stage II–III melanoma. Although anti-PD1-treatment is commonly used as adjuvant treatment primarily in stage III melanoma, the OS benefit remains uncertain. As ICI treatment carries risk of severe adverse events and significant cost to healthcare systems, a thorough evaluation is paramount.

Regarding neoadjuvant treatment, studies indicate an OS benefit, but final results are pending. Pathological response appears to be a strong prognostic marker. No head-to-head comparison of combination anti-CTLA-4 + anti-PD-1-treatment versus single anti-PD-1-treatment exists, but this is being assessed in the SWE-NEO trial (NCT06794775). Future studies will clarify whether the increased risk of irAE from combination treatment is justified by superior survival outcomes.

Lung cancer

NSCLC is the most common type of lung cancer and a major cause of cancer-related death worldwide. Recent years have seen a significant shift toward curative-intent applications of ICIs in early stage disease. Perioperative strategies—incorporating ICIs before and/or after surgery—aim to reduce recurrence rates and improve long-term survival. Multiple studies have now demonstrated a clinical benefit of ICIs in the resectable setting, resulting in expanding FDA and EMA approvals from 2022 onward (Table 2).

Adjuvant treatment

The PEARLS/KEYNOTE-091 trial evaluated adjuvant pembrolizumab versus placebo in patients with completely resected stage IB–IIIA NSCLC, demonstrating improved disease-free survival (DFS) in the overall population [24]. Pembrolizumab was granted FDA and EMA approvals for adjuvant treatment in 2023.

The IMpower010 trial compared adjuvant atezolizumab versus best supportive care (BSC) [25]. DFS improved with adjuvant atezolizumab compared to BSC in all patient groups, particularly stage II–IIIA tumors expressing programmed death-ligand 1 (PD-L1) $\geq$1%. The greatest benefit was seen in PD-L1 $\geq$50% tumors. These data led to the FDA approval in 2021 for stage II–IIIA with PD-L1 $\geq$1% and EMA approval in 2022 for stage II–IIIA PD-L1 $\geq$50%. An updated analysis showed a statistically significant OS improvement with atezolizumab in stage II–IIIA PD-L1 $\geq$50%.

Neoadjuvant treatment

Early studies such as NADIM [26] and NADIM II [27] demonstrated that neoadjuvant chemoimmunotherapy in resectable stage IIIA NSCLC is feasible. The CheckMate 816 trial showed that nivolumab plus chemotherapy significantly improved OS, EFS, and pCR compared to chemotherapy alone [6, 28], leading to FDA approval in 2022 and EMA approval in 2023 for resectable stage IB–IIIA NSCLC.

KEYNOTE-671 tested perioperative pembrolizumab, showing improved EFS, higher pCR, higher MPR rates, and improved OS [29, 30]. FDA approval was granted in 2023, and EMA authorization in 2024. The AEGEAN trial demonstrated superior EFS and pCR with perioperative durvalumab plus chemotherapy versus chemotherapy alone [31], supporting FDA approval in 2023 and EMA approval in 2025.

In CheckMate 77T, resectable stage IIA–IIIB NSCLC patients received neoadjuvant nivolumab ± chemotherapy, followed by surgery and adjuvant nivolumab or placebo for 1 year [32]. At 18 months, EFS was 70.2% in the nivolumab group and 50.0% in the chemotherapy group, leading to an FDA approval in 2024 and an EMA approval in 2025 for tumors with PD-L1 $\geq$1%. The NEOTORCH and RATIONALE-315 trials similarly showed improved EFS, higher pCR rates [33, 34].

The NeoadjSTAR phase II trial showed neoadjuvant nivolumab + chemotherapy achieved substantially higher pCR (75%) and MPR (93%) compared to nivolumab + ipilimumab (pCR 17%, MPR 33%) [35].

LCMC3, a single-arm phase II study of neoadjuvant atezolizumab monotherapy, reported a 20% MPR and a 3-year OS of 80% [36].

Conclusions

Perioperative immunotherapy is becoming a cornerstone in the treatment of resectable NSCLC. Multiple phase III trials support the use of ICIs in the neoadjuvant, adjuvant, or perioperative setting, with consistent improvements in EFS and pathological response. Early OS improvements have been reported in some trials. Biomarker-driven personalization—including PD-L1 expression, ctDNA, and pathological response—holds promise for better patient selection. Key challenges remain in integrating these regimens into routine care, managing immune-related toxicities, and addressing economic implications.

Triple-negative breast cancer

Several lines of evidence highlight the prognostic value of the immune infiltrate in breast cancer [37, 38], its association with chemosensitivity [39, 40], and the potential clinical utility for chemotherapy de-escalation for early stage, lymphocyte-rich TNBC [41]. The clinically and molecularly heterogeneous group of TNBC carries poor prognosis and exhibits the highest counts of tumor-infiltrating lymphocytes (TIL), thus setting up both the unmet need and the biologic rationale for the clinical use of ICIs. Accordingly, some [42, 43] but not all [44, 45] randomized trials demonstrated an OS benefit with the addition of immunotherapy to first-line chemotherapy for patients with metastatic PD-L1-positive TNBC. Despite rapid regulatory approvals (and, in the case of atezolizumab, subsequent voluntary withdrawal of approval by the FDA but not by the EMA), unresolved issues remain related to the optimal method of assessment and cut-off of PD-L1 expression [46], its spatiotemporal heterogeneity [47], and the appropriate chemotherapy backbone.

Adjuvant treatment

In contrast with the metastatic and neoadjuvant settings, ICIs are not approved following primary resection of TNBC (Table 3). Two randomized trials have investigated the addition of postoperative atezolizumab [48] or durvalumab [49] to standard adjuvant chemotherapy, without improving the primary endpoint of DFS. In the latter trial, durvalumab improved the secondary endpoint of OS, as well as DFS among patients who had been treated with neoadjuvant chemotherapy and had residual invasive cancer [49]. The clinical relevance of this finding is unclear, considering the availability of other options at the post-neoadjuvant setting [50, 51] and the ongoing trials that evaluate Trop2-targeting antibody–drug conjugates, with or without immunotherapy [52].

Neoadjuvant treatment

The practice-defining trial at the neoadjuvant setting is KEYNOTE-522, which enrolled patients with TNBC with an indication for preoperative treatment (cT2-4N0-2 or cT1cN1-2) [53]. Patients were randomized 2:1 to neoadjuvant paclitaxel/carboplatin followed by anthracycline/cyclophosphamide, with or without pembrolizumab. Following surgery, pembrolizumab or placebo was continued as monotherapy for nine more cycles. The co-primary endpoint of pCR was reported at the first interim analysis ($n = 602$), with an improvement in pCR rates by 13.6% (64.8% vs. 51.2%, $p = 0.00055$) [53]. Notably, at the fourth interim analysis on the entire intention-to-treat population ($N = 1174$), the difference in pCR rates was only 7.4% (63% vs. 55.6%), not formally tested based on the statistical hierarchy. At the latest follow-up (median 75.1 months) [54], the addition of pembrolizumab improved both OS (hazard ratio [HR] = 0.66, 95% CI 0.50–0.87; 5-year rates 86.6% vs. 81.7%) and the co-primary endpoint of EFS (HR = 0.63, 95% CI 0.49–0.81; 5-year rates 81.3% vs. 72.3%). Toxicity was manageable with no new safety flags. Based on these results, pembrolizumab was approved for the treatment of non-metastatic TNBC by FDA in 2021 and EMA in 2022 (Table 3).

Conclusions

Several questions remain unanswered. No predictive biomarkers have been identified. In KEYNOTE-522, pembrolizumab efficacy was not limited to PD-L1-positive patients, possibly due to the spatial heterogeneity of the immune infiltrate not captured by diagnostic biopsy [56]. Tumor mutational burden, immune- and non-immune-related gene signatures, homologous recombination deficiency, and molecular subtypes all failed to predict benefit from pembrolizumab [57]. Whether adjuvant pembrolizumab contributes to improved outcomes is unclear. Patients in the pembrolizumab arm had better survival across all residual cancer burden classes, including patients with pCR [4]. However, this is not a randomized comparison, as randomization occurred before neoadjuvant therapy, not at surgery. In addition, indirect evidence—including lack of efficacy of adjuvant ICI after primary surgery for TNBC [48], improved

OS with neoadjuvant only ICI [58], and a network meta-analysis showing no effect of adjuvant ICI following pCR [59]—suggests that adjuvant pembrolizumab is unnecessary. The OptimICE-PCR (NCT05812807) trial will address this issue. Several trials with a similar design to KEYNOTE-522 have evaluated atezolizumab, but none have shown improvement in time-to-failure outcomes [60–62]. Whether this is caused by small differences in the study populations or a true difference in drug efficacy is not known. Finally, the optimal chemotherapy backbone for pembrolizumab is debated. Dose-dense treatment is feasible [55], was associated with numerically improved pCR rates in a retrospective analysis [63], and is supported by multiple randomized trials at the adjuvant setting [64, 65]. Omission of anthracyclines did not compromise pCR rates in the phase II single-arm NeoPACT trial [66] and is being investigated in the phase III SCARLET trial (NCT05929768).

Esophageal and gastroesophageal junction cancer

Esophageal and GEJ cancer is the 11th most common cancer worldwide with around 500,000 new cases annually. In 2020, nivolumab gained FDA and EMA approval in the second-line setting for advanced, recurrent, or metastatic squamous cell carcinoma based on the ATTRACTION-3 trial [67]. In 2021, pembrolizumab and nivolumab in combination with fluoropyridine and platinum-based chemotherapy gained FDA and EMA approval for HER2-negative advanced or metastatic disease based on KEYNOTE-590 [68] and CheckMate 649 [69]. For HER2-positive metastatic or advanced GEJ cancer, pembrolizumab in combination with trastuzumab and chemotherapy gained FDA and EMA approval in 2021 and 2023, respectively, based on KEYNOTE-811 [70].

Neoadjuvant and adjuvant treatment

In 2021, FDA and EMA approved nivolumab as adjuvant therapy for resected esophageal or GEJ cancer following neoadjuvant chemotherapy based on CheckMate-577 [71]. At 24.4 months median follow-up, median DFS was 22.4 months with nivolumab versus 11 months with placebo (HR 0.69). Grade 3–4 irAEs were observed in 13% versus 6% in the placebo group. The treatment became standard practice in Sweden (Table 2). Five-year data showed OS rates of 46% with nivolumab versus 41% with placebo [72].

In 2022, the phase II study GERCOR NEONPIGA examined neoadjuvant and adjuvant ipilimumab and nivolumab for locally advanced gastric and GEJ adenocarcinoma (T2-4, Nx, M0) with MSI high status [73]. At 14.9 months median follow-up, 17 of the 29 patients who underwent surgery (58.6%) had pCR. Grade 3–4 irAEs were observed in six patients (19%). In patients who underwent surgery, no recurrence was observed during follow-up. The phase III MATTERHORN trial showed that perioperative durvalumab plus FLOT (vs. placebo plus FLOT) improved 2-year EFS (67.4% vs. 58.5%), OS (75.7% vs. 70.4%), and pCR (19.2% vs. 7.2%) without increased toxicity, leading to an ongoing FDA priority review [74].

Conclusions

Immunotherapy for esophageal/GEJ cancer in neoadjuvant/adjuvant settings is emerging with great promise. Further biomarkers like PD-L1 are needed to identify treatment responders. Neoadjuvant settings warrant particular focus due to greater tumor antigen availability, though CheckMate 577 showed an adjuvant benefit.

Renal cell carcinoma

Since their introduction—beginning with nivolumab in second line in 2015 and later followed by ipilimumab–nivolumab combination in first line in 2018—ICIs have profoundly changed the therapeutic landscape of clear cell RCC (ccRCC) in the metastatic setting, improving OS. Recent data indicate that ICI may be of value also in non-clear cell metastatic RCC [75].

Adjuvant treatment

Based on the improvements in survival in metastatic RCC, it was hypothesized that ICIs would be of benefit to patients with localized RCC and an increased risk of recurrence. Five phase III trials have been conducted—four adjuvant and one perioperative—with conflicting results (Table 4) [76]. Two adjuvant trials were positive. KEYNOTE-564 evaluated 1 year of pembrolizumab versus placebo in 994 patients with ccRCC with intermediate-high or high-risk features. The primary endpoint was DFS with an HR of 0.72 (CI 0.59–0.87) in favor of pembrolizumab, translating into a 4-year DFS rate of 65% versus 57%. Extended follow-up showed an OS benefit with pembrolizumab with an HR of 0.62 (CI 0.44–0.87). In absolute terms, 4-year OS was 91% versus

86%. Toxicity was manageable without novel safety signals. Based on the DFS benefit, adjuvant pembrolizumab was approved by FDA in 2021 and by EMA in 2022.

The phase III RAMPART trial found that adjuvant durvalumab plus tremelimumab significantly improved DFS versus active monitoring in resected RCC (HR 0.65), with benefit confined to Leibovich high-risk patients [77].

In contrast, three trials with ICI reported negative results for both DFS and OS. CheckMate 914 evaluated adjuvant ipilimumab–nivolumab and nivolumab monotherapy for patients with surgically resected stage II/III ccRCC with high risk of recurrence, with HR of 0.92 (CI 0.71–1.19) and 0.87 (CI 0.62–1.21), respectively, compared to placebo [78, 79]. IMmotion010 tested adjuvant atezolizumab versus placebo, without demonstrating a DFS benefit, HR 0.93 (95% CI 0.75–1.15) [80]. Following regulatory approval of adjuvant pembrolizumab based on DFS benefit in KEYNOTE-564, implementation in clinical practice varied considerably across treatment centers. Prior to the reporting of an OS benefit, concerns among treating physicians were frequent—particularly given the negative findings with nivolumab ± ipilimumab and atezolizumab—leading to discrepancies in real-world implementation of adjuvant pembrolizumab. The demonstrated OS benefit, however, strengthens the indication. The European Association of Urology (EAU) has issued a strong recommendation to offer adjuvant pembrolizumab to RCC patients with an increased risk of recurrence as defined in the KEYNOTE-564. Notably, the EAU urges clinicians to discuss both the risk of overtreatment and the conflicting data from the other adjuvant ICI trials with the patient prior to a joint decision [76].

Neoadjuvant treatment

The PROSPER trial assessed perioperative nivolumab with phase III design [81]. A short neoadjuvant phase was administered, followed by additional adjuvant nivolumab, compared to placebo. The primary endpoint (RFS) was not met with an HR of 0.94 (95% CI 0.74–1.21). Median OS was not reached in either arm with no OS signal, HR 1.28 (95% CI 0.84–1.95). Additionally, phase II trials have assessed feasibility and responses of resectable RCC to neoadjuvant treatment with nivolumab, either alone [82] or in combination with axitinib, lenvatinib, or sitravatinib with objective responses seen in 12%–30% [83–85]. One phase II study with the PD-1-inhibitor torapalimab in combination with axitinib as neoadjuvant approach for patients with RCC with inferior vena cava involvement reported a 44% downstaging in tumor thrombus level [86].

Conclusion

Adjuvant pembrolizumab confers an OS advantage and should be considered in patients with localized ccRCC with defined risk factors. Furthermore, the recently reported positive DFS results for durvalumab in combination with a short course of tremelimumab deserve attention. Conflicting data exists with negative findings for other ICI in the adjuvant space, which should be discussed with patients, as should the possibility of overtreatment and the risk of immune-mediated severe or long-term toxicity. No randomized data so far exist to support neoadjuvant ICI in RCC, but results from ongoing studies are awaited. Apart from sarcomatoid features, which are associated with increased benefit from ICI, no predictive factor has so far been implemented in RCC. Liquid biomarkers are not yet used in clinical routine, but early attempts show interesting preliminary data with ctDNA and Kidney Injury Molecule-1 baseline levels and dynamics [87, 88].

Urothelial cancer

ICIs entered the treatment landscape of metastatic UC (mUC) in 2016 with atezolizumab's approval for patients progressing after platinum-based chemotherapy [89]. Pembrolizumab, avelumab, and nivolumab subsequently expanded immunotherapy options [90–92]. Currently, all standard first-line regimens for eligible patients include ICIs, either in combination with antibody–drug conjugates and chemotherapy or as maintenance therapy following chemotherapy [90, 93, 94].

Adjuvant treatment

The landmark CheckMate 274 trial evaluated nivolumab versus placebo after radical surgery in high-risk UC patients (pT3, pT4a, or pN+, or with residual muscle-invasive tumors or ypN+ after neoadjuvant chemotherapy) [95]. The study demonstrated a significant DFS benefit, particularly in PD-L1 positive patients. Median DFS was 22.0 and 10.9 months with nivolumab versus

placebo (HR 0.71; 95% CI 0.58–0.86), respectively. Interim OS analysis showed a 24% reduction in risk of death in nivolumab-treated patients overall and a 44% reduction for patients with tumor PD-L1 ≥1% [96]. These data led to FDA (2021) and EMA (2022) approvals for adjuvant nivolumab (Table 4). The AMBASSADOR phase III trial assigned 702 patients to receive adjuvant pembrolizumab versus observation. Median DFS was 29.6 months with pembrolizumab and 14.2 months with observation (HR 0.73; 95% CI 0.59–0.90). Data on OS are not mature, and pembrolizumab adjuvant is not yet approved [97]. The IMvigor010 trial of adjuvant atezolizumab failed to show DFS benefit (HR 0.89), reinforcing that not all ICIs deliver consistent benefit [98]. Exploratory ctDNA analysis suggested that only patients with detectable ctDNA benefited from atezolizumab. The phase III IMvigor011 trial prospectively validated ctDNA-guided therapy, showing that ctDNA-positive patients treated with atezolizumab had significantly longer DFS (9.9 vs. 4.8 months) and OS (32.8 vs. 21.1 months) than placebo, whereas ctDNA-negative patients (2-year DFS 88%) did well with surveillance alone [99].

Neoadjuvant treatment

The NIAGARA study assigned 533 cisplatin-eligible patients with muscle-invasive bladder cancer (MIBC) to neoadjuvant durvalumab plus standard of care (SOC) with cisplatin-gemcitabine, followed by radical cystectomy and adjuvant durvalumab, or to SOC followed by radical cystectomy alone [100]. Complete pathological response was 37.3% and 27.5% in the durvalumab and control arms, respectively. Estimated 24-month EFS was 67.8% for the experimental arm and 59.8% in the control arm (HR 0.68; 95% CI 0.56 to 0.82; $p < 0.001$), and 24-month OS was 82.2% versus 75.2% (HR 0.75; 95% CI 0.59–0.93; $p < 0.001$). Cystectomy was performed in 88.0% of the patients in the durvalumab group versus 83.2% of controls [100]. These results led to FDA approval (March 2025) and EMA approval (July 2025) for this perioperative regimen (Table 4). The KEYNOTE-905/EV-303 trial showed that perioperative enfortumab vedotin plus pembrolizumab markedly improved outcomes in cisplatin-ineligible MIBC, reducing recurrence or death by 60% and achieving a pCR rate of 57% versus 9% with surgery alone [101].

Conclusions

Remaining challenges include the lack of mature OS data, overtreatment risk, irAEs, and high costs. Reliable predictive biomarkers are urgently needed, with ctDNA emerging as a promising tool to better guide treatment decisions.

Head and neck squamous cell carcinoma

HNSCC includes a large and diverse group of cancers and is the 6th most common cancer globally, accounting for approximately 5% of all cancer diagnoses [102]. The general 5-year survival is 60%–70%; however, it varies largely by stage and site [102, 103]. HNSCC accounts for approximately 450,000 deaths annually, and its incidence is increasing globally [102–104]. In the metastatic/recurrent setting, treatment options have evolved significantly with the arrival of ICIs [105–107]. This is not yet the case for adjuvant/neoadjuvant treatment, where today's SOC for resected HNSCC is two decades old, including postoperative radiotherapy ± chemotherapy with cisplatin [108].

Adjuvant treatment

Until recently, head and neck oncologists have lacked promising evidence for ICIs in early treatment stages. Several trials found no meaningful survival benefit of ICIs in the adjuvant setting [109–111] (Table 2). At ASCO 2025, a new SOC including adjuvant ICI was proposed for locally advanced HNSCC. The NIVOPOSTOP trial was a randomized phase III trial, evaluating the addition of nivolumab to SOC (postoperative radiotherapy + cisplatin) [112]. The 3-year DFS was 63.1% in the nivolumab + SOC group compared to 52.5% in the SOC group (HR 0.76 (95% CI 0.60–0.98, $p = 0.034$)). This DFS benefit was seen across all PD-L1 subgroups. The OS data are still immature.

Neoadjuvant treatment

Due to various large negative adjuvant ICI trials [109–111], the focus in HNSCC has shifted toward neoadjuvant treatment. Early neoadjuvant and perioperative trials have shown good tolerability and promising effects [113] (Table 2). At the 2025 American Association for Cancer Research meeting, the KEYNOTE-689 was presented. This is the first completed phase III randomized trial evaluating perioperative ICI (neoadjuvant and adjuvant pembrolizumab + SOC) in resectable HNSCC with positive results. The trial met its primary endpoint—EFS—at the first interim analysis with median follow-up of 38.3 months, independent of PD-L1 score (51.8 vs. 30.4 months, HR 0.73, 95%

CI 0.58–0.92, $p = 0.004$) [114]. The additional follow-up for OS is ongoing; however, a positive trend has been shown [114]. When looking at toxicity, grade ≥3 AE frequency was similar between the two groups. There are other similar trials ongoing, including IMSTAR-HN 47 (neoadjuvant + adjuvant nivolumab ± ipilimumab vs. SOC) [115].

Conclusions

NIVOPOSTOP and KEYNOTE-689 demonstrate that ICIs might play an important role in early treatment of HNSCC. Both trials show that timing and sequencing of ICIs is important, where the perioperative approach seems to be more promising than the concurrent chemoradiotherapy approaches that failed to show survival benefits [116, 117]. Following these trials, perioperative pembrolizumab for locally advanced HNSCC was approved by both FDA (June 2025) and EMA (October 2025).

Colorectal cancer

The MMR system protects the genome. With impaired function, mutations increase significantly. The MMR system depends on four genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. If one or more of these genes are inactivated, MSI results. The condition is called dMMR if diagnosed with immunohistochemistry and MSI-H when next-generation sequencing is used. In CRC, 5%–20% of tumors are MSI-H [118], more commonly found in right-sided and early stage tumors. Although CRC tumors generally are not sensitive to immunotherapy, the dMMR subtype shows a remarkable response. The use of PD-1 antibodies alone and with CTLA-4 antibodies in palliative treatment of dMMR CRC is approved by EMA and FDA.

Adjuvant treatment

ATOMIC randomized 712 dMMR colon cancer patients to standard adjuvant mFOLFOX6 ± atezolizumab for 1 year. The primary endpoint—DFS—was significantly improved, and DFS at 3 years was 86.4% versus 76.6% [119].

Neoadjuvant treatment

The Dutch phase II non-randomized trial, NICHE-2, included 115 dMMR colon cancer patients with resectable disease [120]. Nivolumab (3 mg/kg, Days 1 + 15) and ipilimumab (1 mg/kg, Day 1) were given, and surgery was scheduled within 6 weeks. In 111 evaluable patients, MPRs were seen in 109 (98%) and clinical complete response (cCR) in 75 (68%). With a median follow-up of 26.2 (9.1–65.3) months, no disease recurrences have been seen [120].

In rectal cancer, dMMR tumors are less common, approximately only 5%. At Memorial Sloan Kettering (MSK), a single-arm phase II study included 50 patients with locally advanced dMMR rectal cancer. Dostarlimab (500 mg Q3W × 9) was given. All patients reached cCR, and after a median follow-up of 30.2 (5.8–60.8) months, RFS at 2 years was 96% (1 local regrowth, 1 lymph node). Both recurrent patients could be retreated with immunotherapy, and no patient has needed surgery at the time of writing [121] (Table 2).

Conclusions

CRC dMMR tumors are highly sensitive to immunotherapy. In rectal cancer, a cCR is a tremendous gain for the patient, given the consequences of SOC. In the MSK study, dMMR non-rectal gastrointestinal tumors showed 65% cCR, suggesting rectal cancer may be especially responsive to immunotherapy. A randomized trial in rectal cancer won't be feasible or ethical with those figures. This treatment indication should be approved rapidly.

Merkel cell carcinoma

Merkel cell carcinoma is a rare but highly aggressive neuroendocrine skin cancer with a strong propensity for early metastasis, frequently associated with Merkel cell polyomavirus (MVPyV). ICIs have significantly changed the therapeutic landscape. In the metastatic setting, three ICIs are currently approved. Avelumab, an anti-PD-L1 antibody, received FDA approval in 2017 and EMA approval in 2018 based on the JAVELIN Merkel 200 trial [122]. Pembrolizumab, an anti-PD-1 antibody, followed in 2018 (FDA), supported by the durable responses observed in the KEYNOTE-913 trial [123]. Retifanlimab, another anti-PD-1 agent, was approved by the FDA in 2023 and the EMA in 2024, based on the POD1UM-201 trial demonstrating an objective response rate of 52% and a favorable safety profile [124].

Adjuvant treatment

In the adjuvant setting, ICIs are under investigation to prevent recurrence in patients with resected disease. The ADMEC-O phase II trial with

nivolumab showed a trend toward improved DFS (84% vs. 73%) versus observation, especially in MCPyV-negative tumors, though statistical significance was not reached [125]. Two phase III studies, STAMP (pembrolizumab vs. observation) and ADAM (avelumab vs. placebo), have completed accrual. Although no ICI has yet been approved for adjuvant MCC, real-world use is expanding, particularly for high-risk patients (Table 1). Challenges include potential immune-related toxicity, long-term benefit uncertainty, and high treatment costs. National policies and reimbursement structures affect local implementation.

Neoadjuvant treatment

In the neoadjuvant setting, ICIs have shown particularly strong biological rationale and clinical impact. The CheckMate 358 study reported a 47% pCR with two doses of nivolumab pre-surgery [126]. A separate phase II trial using lenvatinib plus pembrolizumab achieved a pCR rate of 57.7%, suggesting synergy [127]. Neoadjuvant treatment may downstage tumors, improve long-term outcomes, and enable less aggressive surgery in the usually elderly MCC population. However, no neoadjuvant ICI regimen is currently approved for MCC (Table 1).

Conclusion

Perioperative ICI therapy in MCC holds substantial promise but requires further evidence. Early studies show meaningful response rates, especially in the neoadjuvant setting. Optimal treatment duration, timing, and patient selection criteria remain unclear. Biomarkers such as MCPyV status, PD-L1 expression, and TIL profiles may guide future personalization but are not yet validated [126, 127]. Larger randomized trials will be critical to assess survival benefits and identify predictive biomarkers. Immune checkpoint blockade has revolutionized MCC treatment, with three agents now approved in advanced disease. Adjuvant and neoadjuvant immunotherapy are emerging frontiers, supported by promising data but not yet SOC. Given that patients with MCC are often elderly and frail, treatment strategies with manageable toxicity and shorter duration may be especially beneficial in this population.

Cutaneous squamous cell carcinoma

cSCC is one of the most common of all cancers, with an increasing incidence, specifically in Western populations [128]. The management of locally advanced or metastatic cSCC includes treatment with anti-PD-1 (i.e., cemiplimab [129, 130], pembrolizumab [131–133], or nivolumab [134]) as well as anti-PD-L1 (i.e., cosibelimab-ipdl [135]), all of which have FDA approval, but only cemiplimab is EMA approved.

Adjuvant treatment

The phase III (C-POST) trial included 209 patients with high-risk cSCC (i.e., local or regional cSCC, after surgical resection and postoperative radiotherapy, at high risk for recurrence owing to nodal features or non-nodal features, perineural invasion, or locally recurrent tumor with ≥1 additional risk feature), receiving adjuvant cemiplimab (350 mg Q3W IV) for 12 weeks followed by cemiplimab (700 mg Q6W IV) up to 36 weeks (≤48 weeks total) or placebo [136]. The DFS was significantly improved (24 vs. 65 events; HR 0.32; 95% CI 0.20–0.51; $p < 0.001$) for cemiplimab. The 24-month DFS was 87.1% (95% CI 80.3–91.6) with cemiplimab and 64.1% (95% CI 55.9–71.1) with placebo. Cemiplimab was associated with lower locoregional recurrences (HR 0.20; 95% CI 0.09–0.40) as well as distant recurrences (HR 0.35; 95% CI 0.17–0.72).

Neoadjuvant treatment

A single-armed phase II trial included 79 patients with locally advanced stage II–IV (M0) cSCC who received up to four cycles of neoadjuvant cemiplimab (350 mg Q3W IV) followed by surgery [137]. Postoperatively, the patients could receive adjuvant cemiplimab (350 mg Q3W IV) up to 48 weeks, adjuvant radiotherapy, or observation. Overall, the 12-month EFS was 89% with a 12-month DFS of 92% and a 12-month OS of 92%. By imaging, 68% of the patients reached an OR. Pathologic complete response was found in 51% of the patients [138]. At median follow-up of 19 months, no recurrences were recorded in pCR patients.

In a single-armed phase II trial, including 20 patients with stage III–IVA cSCC in the head–neck region, with two cycles of neoadjuvant cemiplimab (350 mg Q3W IV) followed by adjuvant radiotherapy, the 12-month disease-specific survival, DFS, and OS rates were 95%, 89.5%, and 95%, with lower objective response rates by imaging (30%) than the pCR and MPR (75%) [139].

Conclusion

These data suggest excellent therapy responses to both neoadjuvant and adjuvant cemiplimab in high-risk cSCC with pCR in about 50% of the patients [140]. In October 2025, the FDA and the European Committee for Medicinal Products for Human Use approved cemiplimab-rwlc for the adjuvant treatment of adults with cSCC at high risk of recurrence after surgery and radiation based on the results from the C-POST trial [136] (Table 1).

Gynecological cancers

Endometrial cancer (EC) is the most prevalent gynecological cancer, and 15%–20% present with metastatic disease or will experience disease recurrence. Platinum-based chemotherapy is the standard treatment, and during the last years, PD-1-based therapy has introduced a new therapeutic dimension for primary advanced or recurrent EC with dMMR. In 2023, EMA and FDA granted approval of the PD-1 inhibitor dostarlimab in first-line treatment based on results of the RUBY-trial [141], and in 2024, three additional trials showed similar results and led to approval of pembrolizumab, atezolizumab, and durvalumab [142–144]. In patients with proficient MMR-proteins, improvements with PD-1/PD-L1 inhibitors are not as profound, but based on significant hazard ratios, EMA and FDA approvals were granted in late 2024.

Ovarian cancer (OC) is often diagnosed at advanced stage, and despite high response rates to platinum-based chemotherapy and the introduction of PARP inhibitors, approximately 80% of patients will experience recurrence. During the last years, multiple trials evaluating PD-L1 inhibitors in OC have shown negative results [145–148], and there are no EMA/FDA approvals. Recent KEYNOTE-B96 results showed that adding pembrolizumab to SOC improved PFS in platinum-resistant recurrent OC regardless of PD-L1 status, with an OS benefit in PD-L1-positive tumors [149].

Cervical cancer (CC) is almost exclusively related to high-risk human papillomavirus, which, through genomic integration, provides immunogenic foreign antigens that may amplify PD-L1 expression. In patients with recurrent or metastatic disease, platinum-based chemotherapy in combination with bevacizumab is the SOC, and in 2021/2022, FDA/EMA approved the addition of pembrolizumab to this combination in patients with PD-L1 combined positive score >1 [150]. Similar results were reported with atezolizumab in the BEATcc trial [151]. In 2024, extended approval of pembrolizumab was granted by EMA/FDA in combination with chemoradiotherapy in patients with locally advanced CC [152].

Adjuvant treatment

In KEYNOTE-B21, the addition of pembrolizumab to adjuvant chemotherapy in patients with EC showed no difference in DFS in the all-comer population. However, in dMMR patients, pembrolizumab significantly improved DFS [153], though there are no FDA/EMA approvals for pembrolizumab for this indication (Table 3).

Neoadjuvant treatment

In a phase I study, neoadjuvant pembrolizumab in 10 dMMR EC patients showed a pathologic response in 5/10 patients and a radiologic response in 3/10 patients, with no complete responses [154]. A phase II study has been initiated.

In a phase II study, neoadjuvant treatment with camrelizumab in combination with chemotherapy in locally advanced CC showed a 98% objective response rate, of which 19% had a complete response [155].

In another phase II study of women with advanced OC, for whom upfront complete resection was unachievable, pembrolizumab was added to standard neoadjuvant chemotherapy. Complete response rate was 74% in the pembrolizumab arm versus 70% in controls, with similar PFS but a trend toward improved OS in the pembrolizumab arm [156].

Conclusion

Adjuvant and neoadjuvant immunotherapy have not yet had any breakthrough in gynecological cancers (Table 3). Promising results with improved DFS were shown in patients with dMMR EC when adding pembrolizumab to SOC in the adjuvant setting [143]. Neoadjuvant immunotherapy is a promising approach in various cancers, but additional research is essential to further evaluate its role in gynecologic cancers.

Hepatocellular carcinoma

HCC is the third leading cause of cancer-related death worldwide [157]. More than half of patients experience recurrence after primary surgery [158]. Hence, there is an unmet need for perioperative treatment to improve long-term outcomes. Although several studies have been published and are ongoing, ICIs have not been approved in either the neoadjuvant or the adjuvant setting for HCC (Table 2).

Adjuvant treatment

The IMbrave050 trial compared adjuvant atezolizumab + bevacizumab every 3 weeks for 1 year, with active surveillance in patients with high-risk resected or ablated HCC [159]. At an interim analysis after 17.4 months of follow-up, the group treated with atezolizumab + bevacizumab had a significantly improved RFS (HR 0.72, 95% CI 0.53–0.98). An updated analysis after 35.1 months of follow-up, however, showed no difference in RFS [160]. Data on OS remain immature. Results are awaited from phase III trials of adjuvant nivolumab [161], pembrolizumab [162], and durvalumab [163].

Neoadjuvant Treatment

Several phase II trials have evaluated different neoadjuvant or perioperative ICI regimens with resectable HCC [164–167], with objective response rates ranging from 0% to 62.5%. A phase III trial evaluating neoadjuvant transarterial chemoembolization followed by camrelizumab and apatinib compared to upfront surgery in patients with resectable HCC is ongoing [168].

Conclusion

Despite high recurrence rates following curative-intent surgery for HCC, perioperative immunotherapy has not yet established clinical benefit. The loss of RFS benefit in IMbrave050 at extended follow-up emphasizes the need for mature survival data. Wide variation in neoadjuvant trial response rates (0%–62.5%) highlights HCC heterogeneity and the need for predictive biomarkers. Perioperative ICIs remain investigational in HCC, with no current role in standard practice outside clinical trials.

Discussion

The integration of ICIs into perioperative management across solid tumors marks one of the most significant shifts in modern oncology. Although early successes in the metastatic setting established proof of principle, translation of immunotherapy into earlier disease stages offers potential for cure rather than palliation. Yet the clinical evidence and regulatory landscape remain heterogeneous across tumor types.

A central theme across studies is the apparent biological advantage of neoadjuvant immunotherapy compared with purely adjuvant approaches. Delivering ICIs in the presence of an intact tumor allows for broad antigen exposure and T-cell priming, which may establish durable systemic immunity [3]. This hypothesis is supported by trials in melanoma (PRADO, SWOG S1801, NADINA) and NSCLC (CheckMate 816, AEGEAN, KEYNOTE-671, CheckMate 77T), where neoadjuvant or perioperative treatment has consistently improved EFS and pathologic response rates, with early signals suggesting long-term survival benefit [5, 6, 20, 21, 29, 31–34]. Importantly, pCR and MPR have emerged as robust surrogate endpoints correlating with relapse risk in different tumor types [4, 5].

By contrast, the adjuvant paradigm is complicated by uncertainty around overtreatment. Many patients with stage II or III disease are cured by surgery alone yet are exposed to prolonged systemic therapy with attendant risks of irAEs and substantial economic cost. In melanoma, adjuvant anti-PD-1 therapy improves RFS, but a consistent OS benefit is less clear, and real-world analyses have sometimes failed to demonstrate population-level gains [10–16, 18, 19]. The lack of predictive biomarkers exacerbates this dilemma. Emerging technologies, particularly ctDNA, may help refine risk stratification, enabling escalation in high-risk patients and de-escalation in those unlikely to benefit [7, 90].

Toxicity remains another challenge. Although perioperative ICI regimens are generally manageable, grade 3–4 irAEs occur in up to 30% of patients treated with combination protocols. Although fatal events are rare, irAEs can result in lifelong morbidity. These risks are particularly important in the adjuvant setting, where the margin for therapeutic gain is narrower [5, 20]. Cost and healthcare system impact also merit attention. ICIs are

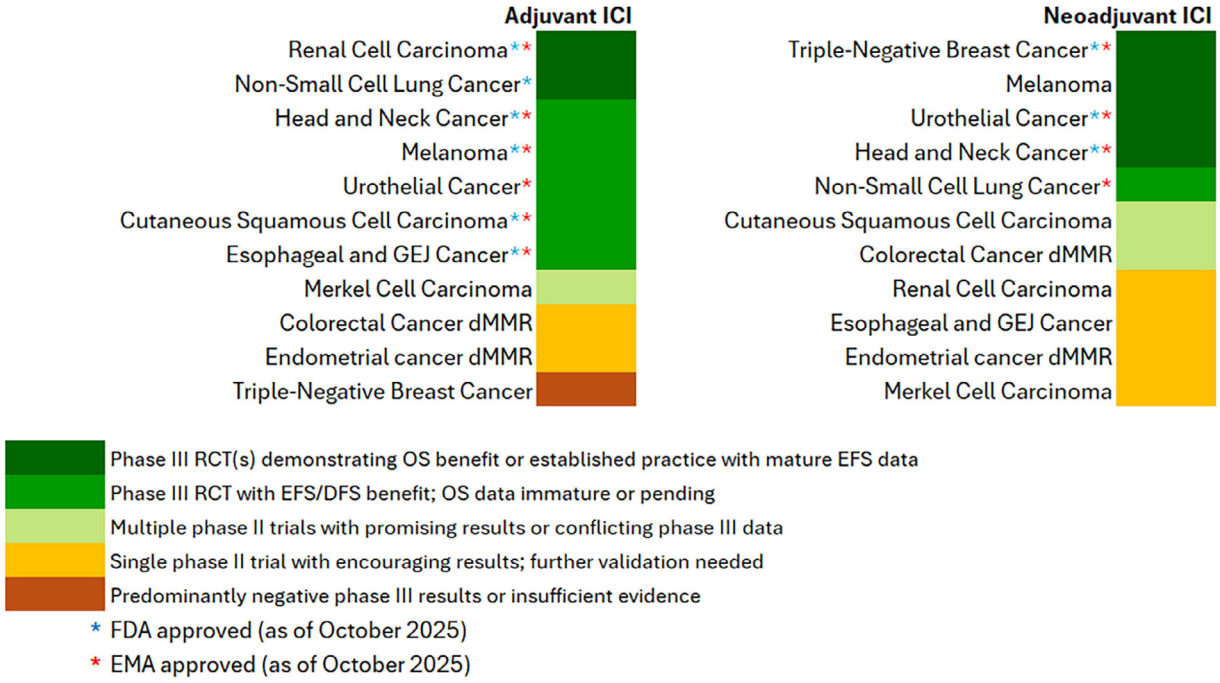

Fig. 1 *Overview of evidence of neoadjuvant and adjuvant immunotherapy across different tumor types. This figure summarizes the current state of clinical evidence and regulatory approval status for perioperative ICI therapy as of October 2025. Cancer types are stratified by level of supporting evidence using a color-coded classification system. Asterisks denote regulatory approval status. The left panel displays evidence for adjuvant ICI therapy, whereas the right panel shows evidence for neoadjuvant ICI therapy. DFS, disease-free survival; dMMR, deficient mismatch repair; EFS, event-free survival; EMA, European Medicines Agency; FDA, Food and Drug Administration; GEJ, gastroesophageal junction; ICI, immune checkpoint inhibitor; RCT, randomized controlled trial; RFS, recurrence-free survival; OS, overall survival.*

among the most expensive oncology drugs, and their use in earlier stages substantially enlarges the eligible population. Neoadjuvant strategies may be more cost-effective than adjuvant approaches, given their shorter treatment duration and potential for stronger efficacy.

Considerable heterogeneity of results across tumor types is present (Fig. 1). In melanoma, neoadjuvant and adjuvant ICI have quickly moved toward SOC, supported by positive clinical trials [5, 20, 21]. In contrast, RCC and HNSCC have produced conflicting or still maturing results [76, 78–80, 112–114], and in gynecologic cancers and HCC, evidence remains preliminary [153–156, 160, 164–167]. These discrepancies likely reflect differences in tumor immunogenicity, the role of concurrent chemotherapy or radiotherapy, and trial design.

Looking forward, several priorities emerge. First, biomarker development is imperative. In NSCLC, early ctDNA clearance during neoadjuvant therapy correlates with improved survival [26, 27] and is being prospectively tested [169]. Second, adaptive trial designs that incorporate early surrogate endpoints, molecular stratification, and response-guided therapy are likely to accelerate progress. Third, head-to-head comparisons of different perioperative regimens will help determine the optimal balance between efficacy and safety. Finally, long-term follow-up for OS, late toxicities, and quality of life is essential (Fig. 2).

In summary, perioperative immunotherapy is reshaping the curative-intent treatment of multiple solid tumors. The field has moved rapidly, with landmark trials already changing practice in melanoma, NSCLC, and TNBC. The central

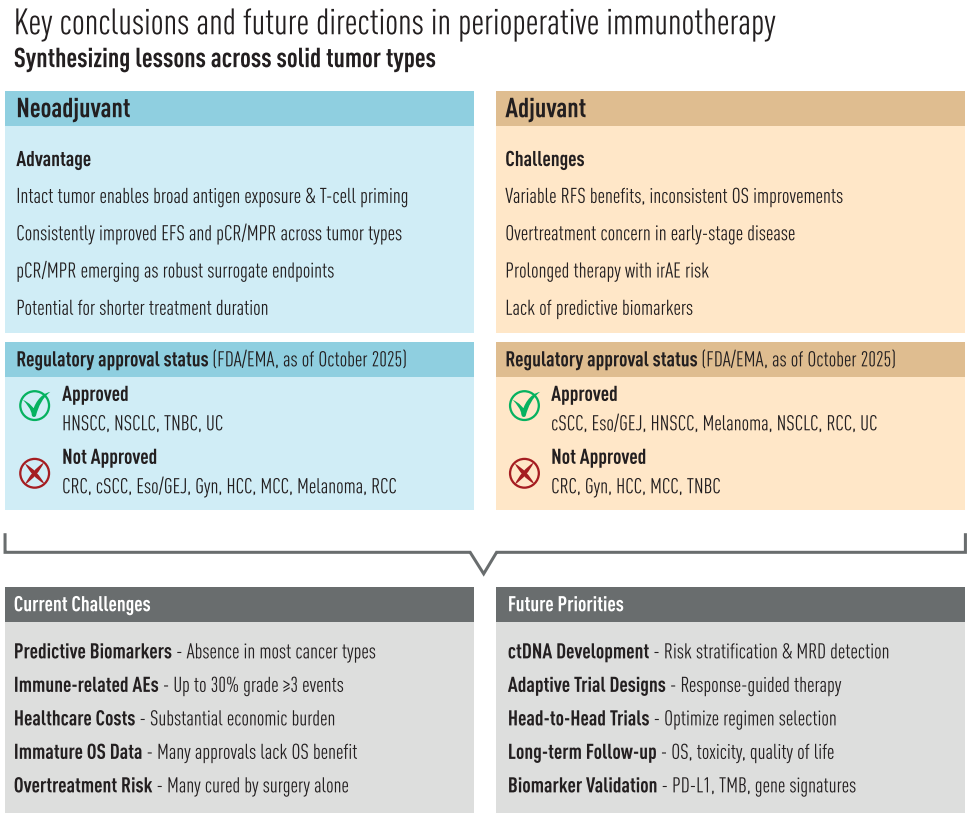

Fig. 2 *Key conclusions and future directions in perioperative immunotherapy. This figure summarizes current evidence and strategic priorities for neoadjuvant and adjuvant immunotherapy. The left panel outlines advantages of neoadjuvant therapy. The right panel presents challenges for adjuvant therapy. Regulatory approval status boxes indicate FDA/EMA-approved indications as of October 2025 across multiple cancer types. The bottom panel identifies current challenges and future priorities. CRC, colorectal cancer; cSCC, cutaneous squamous cell carcinoma; EFS, event-free survival; GEJ, gastroesophageal junction; Gyn, gynecological; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; irAE, immune-related adverse event; MCC, Merkel cell carcinoma; MPR, major pathological response; MRD, minimal residual disease; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; RCC, renal cell carcinoma; TNBC, triple-negative breast cancer; UC, urothelial carcinoma.*

challenges ahead are to refine patient selection, optimize timing and sequencing, and mitigate toxicity.

Conflict of interest statement

Alexios Matikas has received research funding (to institution) from MSD, AstraZeneca, Novartis and Veracyte. **Anders Ullén** has served in consulting or advisory roles for Astellas Pharma, Janssen-Cilag, Merck KGaA, MSD, Pierre Fabre, Pfizer, BMS, and Roche and has received research funding from Bayer, Merck KGaA, and Pierre Fabre. **Fernanda Costa Svedman** has had sponsored collaborations, including advisory board, with Astellas, Merck, MSD, Pfizer, Ipsen, BMS, and Johnson & Johnson, with all payments going exclusively to the institution. **Magnus Lindskog** has received research grants from Ipsen.

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