SUPPLEMENTARY MATERIAL

Randomized controlled trials comparing the standard of care to alternative treatments in patients with resectable locally advanced head and neck squamous cell carcinoma: a systematic literature review

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Appendix A: Study eligibility criteria

Table A1: Study eligibility criteria of the systematic literature review

Criteria	Inclusion Criteria	Exclusion criteria
Population(s)	Newly diagnosed adult (≥18 years) patients with resectable locally advanced head and neck squamous cell carcinoma (regardless of HPV/p16 status)	• Patients not considered for primary surgery based on investigator decisions • Previously treated patients (recurrent cases) • Patients with distant metastasis • Patients exclusively comprised of patients with nasopharyngeal carcinoma, nasal cavity, paranasal sinus, salivary gland or thyroid cancer
Interventions	Surgery[a] in combination with at least one of the following: • Adjuvant therapy (RT and/or systemic treatments) • Neoadjuvant therapy (RT and/or systemic treatments)	• Interventions that do not involve planned surgery[a] at the time of randomization • Palliative RT
Comparisons	• Any treatment meeting the interventions criteria above • Surgery alone	No restrictions
Outcomes	Efficacy: • Overall survival • Event-free survival • Progression-free survival • Disease-free survival • Recurrence-free survival • Distant metastasis-free survival • Overall response rate (for neoadjuvant treatment) • Pathological complete response • Major pathological response • Pathological downstaging response Safety: • Treatment emergent adverse events • Treatment related adverse events • Grade 3-4 treatment emergent/treatment related adverse events • Serious adverse events • Discontinuations due to adverse events • Dose interruptions/dose delays • Treatment-related mortality HRQoL: • Generic instrument scores (e.g., EORTC-QLQ-C30, EQ-5D, FACT-G, SF-36, SF-12) • Disease-specific instrument scores (e.g., EORTC QLQ-H&N35, FACT-H&N) • Health-state utilities	--
Time	No time restriction	--

Criteria	Inclusion Criteria	Exclusion criteria
Study design	Phase II and III randomized controlled trials	• Phase 0 or 1 clinical trials (including dose-finding, dose-escalation, and dose-expansion trials) • Non-randomized clinical trials • Observational studies • Case studies/reports/series • Animal/in vitro studies • Pharmacokinetic or pharmacodynamic studies • Editorials, commentaries, letters, narrative reviews
Other	Language: English language only	--

[a] Surgical resection was only of interest if performed with definitive/curative intent.

EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC-QLQ-H&N35, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck 35; EQ-5D, EuroQoL-five dimensions; FACT-G, Functional Assessment of Cancer Therapy – General; FACT-H&N, Functional Assessment of Cancer Therapy – Head and Neck; HRQoL, health-related quality of life; RT, radiotherapy; SF, Short Form.

Appendix B: Search strategies

Table B1: Search strategy for Embase (Embase 1974 to November 25, 2025); Search executed on December 1, 2025

No.	Terms	Hits
1	exp head cancer/	139,238
2	exp neck cancer/	204,101
3	exp larynx cancer/	28,021
4	exp mouth cancer/	64,155
5	exp pharynx cancer/	71,578
6	exp hypopharynx cancer/	8,327
7	exp oropharynx cancer/	30,510
8	exp larynx tumor/	40,749
9	exp larynx carcinoma/	14,090
10	((mouth or gingival or lip* or palat* or tongue or Laryn* or pharyn* or hypopharyn* or oropharyn* or tonsil* or throat or otorhinolaryngologic or oral) adj6 (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC)).mp.	259,815
11	(head adj3 neck adj6 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan* or SCC)).mp.	155,034
12	(H&N adj6 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan* or SCC)).mp.	3,677
13	(HNSCC or HN SCC or SCCHN or SCC HN or HNSC or HNC or OP SCC or OPSCC).mp.	39,556
14	or/1-13	561,207
15	(advanc* or (stage* adj2 3*) or (stage* adj2 iii*) or (stage* adj2 iv*) or (stage* adj2 4*) or operable or resectable or resected or T3* or T4* or N2* or N3*).mp.	2,987,133
16	14 and 15	100,495
17	Clinical Trial/	1,661,944
18	Randomized Controlled Trial/	1,122,935
19	controlled clinical trial/	460,848
20	multicenter study/	526,337
21	Phase 3 clinical trial/	117,223
22	Phase 4 clinical trial/	16,537
23	exp RANDOMIZATION/	102,074
24	Single Blind Procedure/	84,149
25	Double Blind Procedure/	313,694
26	Crossover Procedure/	106,168
27	PLACEBO/	509,128
28	randomi?ed controlled trial$.tw.	448,741
29	rct.tw.	78,006
30	(random$ adj2 allocat$).tw.	71,688
31	single blind$.tw.	46,017
32	double blind$.tw.	329,843
33	((treble or triple) adj blind$).tw.	3,352

No.	Terms	Hits
34	placebo$.tw.	472,286
35	Prospective Study/	1,019,749
36	or/17-35	3,876,859
37	Case Study/	112,273
38	case report.tw.	641,469
39	abstract report/ or letter/	1,409,394
40	Conference proceeding.pt.	0
41	Conference abstract.pt.	5,728,810
42	Editorial.pt.	853,630
43	Letter.pt.	1,387,265
44	Note.pt.	1,026,136
45	or/37-44	9,640,704
46	36 not 45	2,913,464
47	16 and 46	14,319
48	limit 47 to english language	13,759

Table B2: Search strategy for MEDLINE (Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to November 26, 2025); Search executed on November 26, 2025); Search executed on December 1, 2025

No.	Terms	Hits
1	exp "Head and Neck Neoplasms"/	378,673
2	exp Laryngeal Neoplasms/	30,070
3	exp Mouth Neoplasms/	82,288
4	exp Pharyngeal Neoplasms/	41,554
5	exp Hypopharyngeal Neoplasms/	3,747
6	exp Oropharyngeal Neoplasms/	10,929
7	((mouth or gingival or lip* or palat* or tongue or Laryn* or pharyn* or hypopharyn* or oropharyn* or tonsil* or throat or otorhinolaryngologic or oral) adj6 (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC)).mp.	205,068
8	(head adj3 neck adj6 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan* or SCC)).mp.	108,003
9	(H&N adj6 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan* or SCC)).mp.	1,575
10	(HNSCC or HN SCC or SCCHN or SCC HN or HNSC or HNC or OP SCC or OPSCC).mp.	25,021
11	or/1-10	489,446
12	(advanc* or (stage* adj2 3*) or (stage* adj2 iii*) or (stage* adj2 iv*) or (stage* adj2 4*) or operable or resectable or resected or T3* or T4* or N2* or N3*).mp.	1,962,687
13	11 and 12	65,688
14	Randomized Controlled Trials as Topic/	188,993
15	randomized controlled trial/	651,171
16	Random Allocation/	109,017
17	Double Blind Method/	187,063
18	Single Blind Method/	35,835
19	clinical trial/	538,038
20	clinical trial, phase i.pt.	28,376
21	clinical trial, phase ii.pt.	44,989
22	clinical trial, phase iii.pt.	25,821
23	clinical trial, phase iv.pt.	2,894
24	controlled clinical trial.pt.	95,765
25	randomized controlled trial.pt.	651,171
26	multicenter study.pt.	384,831
27	clinical trial.pt.	538,038
28	exp Clinical Trials as topic/	416,487
29	or/14-28	1,706,681
30	(clinical adj trial$).tw.	579,897
31	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	219,274
32	PLACEBOS/	36,166
33	placebo$.tw.	272,936
34	randomly allocated.tw.	42,682
35	(allocated adj2 random$).tw.	46,780
36	or/30-35	913,230
37	29 or 36	2,133,943
38	case report.tw.	483,464

No.	Terms	Hits
39	letter/	1,317,613
40	historical article/	375,984
41	or/38-40	2,155,392
42	37 not 41	2,088,028
43	13 and 42	10,291
44	limit 43 to english language	9,664

Table B3: Search strategy for CENTRAL (EBM Reviews - Cochrane Central Register of Controlled Trials - October 2025); Search executed on December 1, 2025

No.	Terms	Hits
1	exp "Head and Neck Neoplasms"/	9,754
2	exp Laryngeal Neoplasms/	459
3	exp Mouth Neoplasms/	982
4	exp Pharyngeal Neoplasms/	1,395
5	exp Hypopharyngeal Neoplasms/	102
6	exp Oropharyngeal Neoplasms/	388
7	((mouth or gingival or lip* or palat* or tongue or Laryn* or pharyn* or hypopharyn* or oropharyn* or tonsil* or throat or otorhinolaryngologic or oral) adj6 (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC)).mp.	10,241
8	(head adj3 neck adj6 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan* or SCC)).mp.	10,027
9	(H&N adj6 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan* or SCC)).mp.	290
10	(HNSCC or HN SCC or SCCHN or SCC HN or HNSC or HNC or OP SCC or OPSCC).mp.	2,780
11	or/1-10	22,543
12	(advanc* or (stage* adj2 3*) or (stage* adj2 iii*) or (stage* adj2 iv*) or (stage* adj2 4*) or operable or resectable or resected or T3* or T4* or N2* or N3*).mp.	200,294
13	11 and 12	7,852
14	limit 13 to english language	7,461

Table B4: Search strategy for the Northern Light database (Northern Light Life Sciences Conference Abstracts 2010 – 2025 Week 47); Search executed: December 1, 2025

No.	Terms	Hits
1	exp "Head and Neck Neoplasms"/	39,882
2	exp Laryngeal Neoplasms/	1,356
3	exp Mouth Neoplasms/	4,159
4	exp Pharyngeal Neoplasms/	3,750
5	exp Hypopharyngeal Neoplasms/	357
6	exp Oropharyngeal Neoplasms/	2,435
7	((mouth or gingival or lip* or palat* or tongue or Laryn* or pharyn* or hypopharyn* or oropharyn* or tonsil* or throat or otorhinolaryngologic or oral or paranasal or maxillary sinus or ethmoid sinus) adj6 (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC)).mp.	19,949
8	(head adj3 neck adj6 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan* or SCC)).mp.	20,418
9	(H&N adj6 (cancer* or carcinoma* or neoplas* or tumo?r* or malignan* or SCC)).mp.	548
10	(HNSCC or HN SCC or SCCHN or SCC HN or HNSC or HNC or OP SCC or OPSCC).mp.	7,452
11	or/1-10	56,373
12	(advanc* or (stage* adj2 3*) or (stage* adj2 iii*) or (stage* adj2 iv*) or (stage* adj2 4*) or operable or resect* or T3* or T4* or N2* or N3*).mp.	250,776
13	11 and 12	8,439
14	American Association for Cancer Research.cf.	80,047
15	American Society of Clinical Oncology.cf.	92,658
16	American Society for Radiation Oncology.cf.	35,608
17	European Society for Medical Oncology.cf.	27,885
18	or/14-17	236,198
19	13 and 18	3,172
20	limit 19 to yr="2022-current"	943

The recent iterations of the conferences listed below were searched:

- American Association for Cancer Research (AACR)
- American Society of Clinical Oncology (ASCO)
- American Society for Radiation Oncology (ASTRO)
- European Society for Medical Oncology (ESMO)
- American Head and Neck Society (AHNS)
- Canadian Society of Otolaryngology – Head and Neck Surgery (CSOHNS)
- European Congress on Innovative Approaches in Head and Neck Oncology (ECHNO)
- European Society for Radiation Oncology (ESTRO)
- International Congress on Innovative Approaches in Head and Neck Oncology (ICHNO)
- Multidisciplinary Head and Neck Cancers Symposium (MHNCS)

Appendix C: Other trials included in the broader systematic literature review

Table C1: Trials included in the broader systematic literature review that were not described in this report

Trial	Title	Reason for exclusion
Awwad et al., 2002[1]	Accelerated hyperfractionation (ahf) compared to conventional fractionation (cf) in the postoperative radiotherapy of locally advanced head and neck cancer: Influence of proliferation	Published before 2004
Clinical trial registry record for the Morpheus-Head & Neck Cancer trial (NCT05459129)[2]	A Study Evaluating Efficacy and Safety of Multiple Treatment Combinations in Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck (Morpheus-Head and Neck Cancer)	Did not compare experimental arm to SoC; only 6 patients were recruited per arm as trial was terminated early
Dou et al., 2024 (IMPORT) (NCT04523883)[3]	Survival outcomes of concurrent radiotherapy and toripalimab versus radiotherapy alone for elderly patients with postoperative head and neck squamous cell carcinoma unfit for cisplat	Did not report outcomes of interest
Endicott et al., 1987[4]	Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the head and neck contracts program	Published before 2004
Ferris et al., 2022 (ECOG-ACRIN (E3311)) (NCT01898494)[5]	Phase ii randomized trial of transoral surgery and low-dose intensity modulated radiation therapy in resectable p16+ locally advanced oropharynx cancer: An ecog-acrin cancer research group trial (e3311)	Evaluated surgery + RT in both randomized arms
Harari et al., 2014 (RTOG 0234) (NCT00084318)[6]	Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234	Did not report outcomes of interest
Kiyota et al., 2022 (JCOG1008) (jRCTs031180135)[7]	Weekly cisplatin plus radiation for postoperative head and neck cancer (jcog1008): A multicenter, noninferiority, phase ii/iii randomized controlled trial	Evaluated surgery + RT + cisplatin in both arms
Kokal et al., 1988[8]	Postoperative Radiation as Adjuvant Treatment for Carcinoma of the Oral Cavity, larynx, and Pharynx: Preliminary Report of a Prospective Randomized Trial	Published before 2004
Lam et al., 2001[9]	Prospective randomized study of post-operative chemotherapy with levamisole and uft for head and neck carcinoma	Published before 2004
Laramore et al., 1992 (INTERGROUP STUDY 0034)[10]	Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: Report on intergroup study 0034	Published before 2004

Trial	Title	Reason for exclusion
Liu et al., 2025 (NCT06444009)[11]	Neoadjuvant immunotherapy in combination with chemotherapy in resectable locally advanced head and neck squamous cell carcinoma: A randomized, open label, phase ii clinical trial	Recruitment incomplete (≤6 patients recruited in each arm so far)
Licitra et al., 2003[12]	Primary chemotherapy in resectable oral cavity squamous cell cancer: A randomized controlled trial	Published before 2004
Luginbuhl et al., 2022 (NCT03238365)[13]	Tadalafil enhances immune signatures in response to neoadjuvant nivolumab in resectable head and neck squamous cell carcinoma	Did not compare experimental arm to SoC; did not report pathological response with neoadjuvant Tx
Maipang et al., 1995[14]	Combination Chemotherapy as Induction Therapy for Advanced Resectable Head and Neck Cancer	Published before 2004
Marret et al., 2023 (GEP11 PREDICTOR) (NCT01415674)[15]	Randomized phase ii study of preoperative afatinib in untreated head and neck cancers: Predictive and pharmacodynamic biomarkers of activity	Did not compare experimental arm to SoC; did not report pathological response with neoadjuvant Tx
Mohr et al., 1994 (DOSAK)[16]	Preoperative radiochemotherapy and radical surgery in comparison with radical surgery alone	Published before 2004
Paccagnella et al., 1994[17]	Phase III Trial of Initial Chemotherapy in Stage III or IV Head and Neck Cancers: a Study by the Gruppo di Studio sui Tumori della Testa e del Collo	Published before 2004
Rao et al., 1991[18]	Perioperative Chemotherapy in Oral Cancer	Published before 2004
Rentschler et al., 1987[19]	Adjuvant Methotrexate Escalated To Toxicity for Resectable Stage III and IV Squamous Head and Neck Carcinomas--A Prospective, Randomized Study	Published before 2004
Sanguineti et al., 2005[20]	Accelerated versus conventional fractionated postoperative radiotherapy for advanced head and neck cancer: Results of a multicenter phase iii study	Evaluated surgery + RT in both arms
Sarma et al., 2023[21]	Comparison of Post-Operative Complications in Oral Cancer Treated with and without Neoadjuvant Chemotherapy	Did not compare experimental arm to SoC; did not report pathological response with neoadjuvant Tx
Smid et al., 2003[22]	Postoperative concomitant irradiation and chemotherapy with mitomycin c and bleomycin for advanced head-and-neck carcinoma	Published before 2004
Szabo et al., 1999[23]	Intra-Arterial Preoperative Cytostatic Treatment versus Preoperative Irradiation	Published before 2004
Terz et al., 1981[24]	Preoperative irradiation for head and neck cancer: Results of a prospective study	Published before 2004

Trial	Title	Reason for exclusion
Toohill et al., 1987[25]	Cisplatin and Fluorouracil as Neoadjuvant Therapy in Head and Neck Cancer	Published before 2004
Tupchong et al., 1991 (RTOG 73-03)[26]	Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: Long-term follow-up of rtog study 73-03	Published before 2004
Valavaara et al., 1992[27]	Interferon Combined with Irradiation in the Treatment of Operable Head and Neck Carcinoma; A pilot study	Published before 2004
Vandenbrouck et al., 1977[28]	Results of a randomized clinical trial of preoperative irradiation versus postoperative in treatment of tumors of the hypopharynx	Published before 2004
Wennerberg et al., 2022 (ARTSCAN 2) (ISRCTN0060841)[29]	Results from a prospective, randomised study on (accelerated) preoperative versus (conventional) postoperative radiotherapy in treatment of patients with resectable squamous cell carcinoma of the oral cavity - the artscan 2 study	No systemic intervention was evaluated in the experimental arm (RT followed by surgery).
Yi et al., 2017 (ChiCTR-TRC-114004322)[30]	Phase III randomized trial of preoperative concurrent chemoradiotherapy versus preoperative radiotherapy for patients with locally advanced head and neck squamous cell carcinoma	Did not compare experimental arm to SoC; pathological response was not defined and was not reported in the overall randomized patients
Zhang et al., 1998[31]	Supraglottic carcinoma: Does preoperative radiotherapy reduce the incidence of cervical metastasis?	Published before 2004

Appendix D: Risk of bias assessment

Figure D1: Quality of the included trials assessed per Cochrane Risk of Bias tool Version 2

This figure was created using the Risk-of-bias VISualization (robvis) application[32].

D1: Bias arising from the randomization process

D2: Bias due to deviations from intended interventions

D3: Bias due to missing outcome data

D4: Bias in measurement of the outcome

D5: Bias in selection of the reported result

Some concerns Low risk

Appendix E: Treatment-related adverse events

Table E1: Treatment-related adverse events in trials comparing survival outcomes with alternative regimens versus standard of care

Trial	Treatment arms [a]	N	Any-grade TRAE	Grade 3-4 TRAE	Comments
Trials evaluating perioperative treatments					
He et al., 2025 (CAMORAL)	**Camrelizumab** + **nab-paclitaxel** + **carboplatin** + surgery + RT + **camrelizumab** ± cisplatin	63	--	--	--
	Surgery + RT ± cisplatin	62	--	--	--
Uppaluri et al., 2025 (KEYNOTE-689)	**Pembrolizumab** + surgery + **pembrolizumab** + RT ± cisplatin	361	81.4	43.5	--
	Surgery + RT ± cisplatin	315	81.9	42.5	--
Trials evaluating neoadjuvant treatments					
Chaukar et al., 2022	**Docetaxel + cisplatin + 5-FU** + surgery + RT ± cisplatin	34	--	--	--
	Surgery + RT ± cisplatin	34	--	--	--
Talor et al., 2022 (IT-MATTERS)	**Leukocyte interleukin + cyclophosphamide + indomethacin + zinc** + surgery + RT ± cisplatin	383	17	--	--
	Leukocyte interleukin + surgery + RT ± cisplatin	129	19.4	--	--
	Surgery + RT ± cisplatin	367	0	--	--
Zhong et al., 2013	**Docetaxel** + **cisplatin** + **5-FU** + surgery + RT	128	--	--	--
	Surgery + RT	128	--	--	--
Zhong et al., 2022 (EAGLE)	**Cetuximab + docetaxel + cisplatin** + surgery + RT	134	--	42	--
	Surgery + RT	136	--	44.9	--
Trials evaluating adjuvant treatments					
Bernier et al., 2004 (EORTC 22931)	Surgery + RT + **cisplatin**	167	--	--	--
	Surgery + RT	167	--	--	--
Bourhis et al., 2025 (NIVOPOST-OP)	Surgery + RT + cisplatin + **nivolumab**	312	96.5	72.4	First safety period (until 100 days after the last treatment of lead-in and concomitant phases)
	Surgery + RT + cisplatin	306	99.3	67.3	

Trial	Treatment arms [a]	N	Any-grade TRAE	Grade 3-4 TRAE	Comments
	Surgery + RT + cisplatin + **nivolumab**	256	60.2	11.3	Second safety period (from 101 days up to 9 months after the last treatment of lead-in and concomitant phases)
	Surgery + RT + cisplatin	265	30.9	4.9	
	Surgery + RT + cisplatin + **nivolumab**	234	33.3	4.3	Third safety period (from 9 months after the last treatment of lead-in and concomitant phases)
	Surgery + RT + cisplatin	235	30.6	3.4	
Cooper et al., 2004 (RTOG 9501)	Surgery + RT + **cisplatin**	206	--	--	--
	Surgery + RT	210	--	--	--
Dietz et al., 2025 (ADRISK)	Surgery + RT + cisplatin + **pembrolizumab**	102	--	--	--
	Surgery + RT + cisplatin	102	--	--	--
Haddad et al., 2025 (IMvoke010)	Surgery ± RT + **atezolizumab**	79	--	--	--
	Surgery ± RT	77	--	--	--
Harrington et al., 2015 (EGF102988)	Surgery + **lapatinib** + RT + cisplatin + maintenance **lapatinib**	349	65.3	--	--
	Surgery + RT + cisplatin	336	60.7	--	--
Iyer et al., 2025 (IHN01)	Surgery + RT + cisplatin + **nimotuzumab**	208	--	--	--
	Surgery + RT + cisplatin	214	--	--	--
Jiang et al., 2024	Surgery + RT + **docetaxel**	110	100	--	100% of patients were reported to have experienced treatment-related dermatitis
	Surgery + RT + cisplatin	112	100	--	100% of patients were reported to have experienced treatment-related dermatitis
Laskar et al., 2023	Surgery + RT(5fr/wk) + **cisplatin**	300	--	--	--
	Surgery + RT(6fr/wk)	301	--	--	--
	Surgery + RT(5fr/wk)	299	--	--	--
Ma et al., 2025 (MC1675)	Surgery + RT + **docetaxel**	130	--	--	--
	Surgery + RT + cisplatin	64	--	--	--
	Surgery + RT + **cetuximab**	276	--	70.3	--

Trial	Treatment arms [a]	N	Any-grade TRAE	Grade 3-4 TRAE	Comments
Machtay et al., 2025 (RTOG 0920)	Surgery + RT	282	--	39.7	--
Tobias et al., 2010 (UKHAN1)	Surgery + RT ± **methotrexate ± vincristine ± bleomycin ± 5-FU**	118	--	--	--
	Surgery + RT	135	--	--	--
Wozniak et al., 2020	Surgery + RT + **cisplatin**	54	--	--	--
	Surgery + RT	57	--	--	--

Interventions appearing before and after 'surgery' were administered in the neoadjuvant and adjuvant settings, respectively. Double-dashes indicate values that were not reported.

5-FU, fluorouracil; RT, radiotherapy; TRAE, treatment-related adverse event; wk, week.

Table E2: Treatment-related adverse events in trials reporting pathological response with neoadjuvant treatments

Trial	Treatment arms [a]	N	Any-grade TRAE	Grade 3-4 TRAE	Comments
Ferris et al., 2023	**Nivolumab + ipilimumab +** surgery	10	--	--	--
	Nivolumab + relatlimab + surgery	13	--	--	--
	Nivolumab + surgery	10	--	--	--
He et al., 2025 (CAMORAL)	**Camrelizumab** + **nab-paclitaxel** + **carboplatin** + surgery + RT + **camrelizumab** ± cisplatin	63	--	--	--
Kim et al., 2024	**Durvalumab + tremelimumab** + surgery + RT ± chemotherapy + durvalumab	24	31.1 [a]	4.4	Preoperative cases reported for the entire population
	Durvalumab + surgery + RT ± chemotherapy + durvalumab	21			
Le et al., 2022	**Docetaxel + cisplatin (carboplatin) + erlotinib** + surgery	24	96	33	Preoperative TRAEs
	Docetaxel + cisplatin (carboplatin) + surgery	28	96	36	Preoperative TRAEs
Liu et al., 2025 (NEOPBOSCC)	**Camrelizumab + docetaxel + cisplatin + 5-FU** + surgery + RT ± chemotherapy	34	--	23.5	--
	Camrelizumab + surgery + RT ± chemotherapy	34	--	5.9	--
Mastrolonardo et al., 2025	**Nivolumab + linrodostat** + surgery	31	IRAE: 35.5 Non-IRAE: 54.8	6.5	Preoperative TRAEs
	Nivolumab + surgery	30	IRAE: 26.7 Non-IRAE: 53.3	0.0	Preoperative TRAEs

Trial	Treatment arms [a]	N	Any-grade TRAE	Grade 3-4 TRAE	Comments
Uppaluri et al., 2025 (KEYNOTE-689)[b]	**Pembrolizumab** + surgery + pembrolizumab + RT ± cisplatin	363	81.4	43.5	--
Wang et al., 2025	**Toripalimab + cisplatin + nab-paclitaxel** + surgery	61	97.8	13.1	--
	Cisplatin + nab-paclitaxel + surgery	61	95.4	9.8	--
Zhong et al., 2013 [b]	**Docetaxel** + **cisplatin** + **5-FU** + surgery + RT	128	--	--	--
Zhong et al., 2022 (EAGLE) [b]	**Cetuximab + docetaxel + cisplatin** + surgery + RT	134	--	42	--

Interventions appearing before and after 'surgery' were administered in the neoadjuvant and adjuvant settings, respectively. Double-dashes indicate values that were not reported.

[a] Reported for the entire population.

[b] Only trial arms evaluating neoadjuvant treatments are presented.

5-FU, fluorouracil; IRAE, immune-related adverse event; RT, radiotherapy; TRAE, treatment-related adverse event.

References

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