What's on the horizon to tackle unmet needs in recurrent/metastatic SCCHN?

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Unmet treatment needs for patients with recurrent/metastatic SCCHN

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What is the current standard of care for patients with R/M SCCHN?

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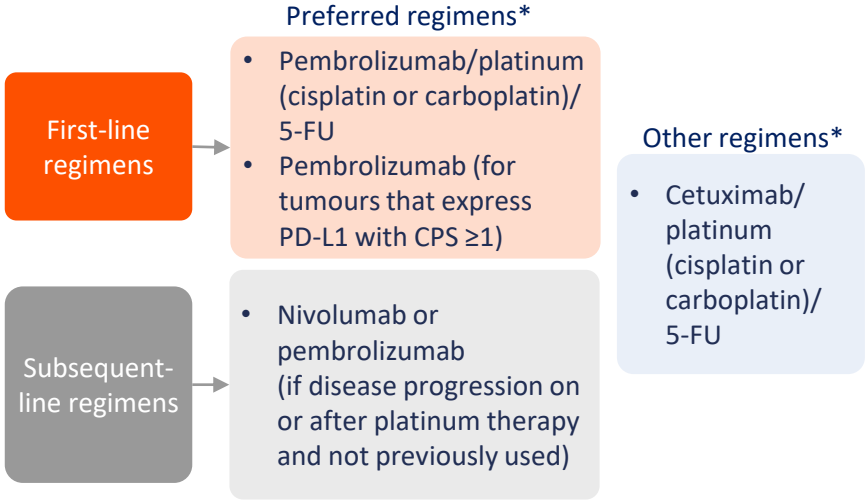
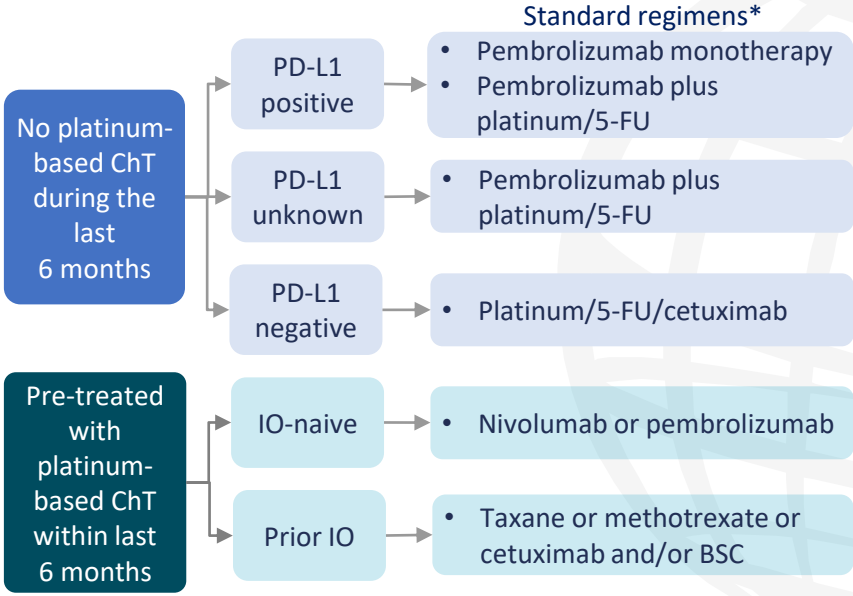
Current SOC for patients with R/M SCCHN

NCCN guidelines[1]



The choice of systemic therapy should be individualized based on patient characteristics (e.g. PS, goals of therapy)

EHNS–ESMO–ESTRO guidelines and Pan-Asian adaptation[2,3]



*Guidelines include alternative treatment options.

5-FU, 5-fluorouracil; BSC, best supportive care; ChT, chemotherapy; CPS, combined positive score; EHNS, European Head and Neck Society; ESMO, European Society for Medical Oncology; ESTRO, European SocieTy for Radiotherapy and Oncology; IO, immunotherapy; NCCN, National Comprehensive Cancer Network; PD-L1, programmed death-ligand 1; PS, performance status; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck; SOC, standard of care.

1. NCCN. Head and neck cancers. V2.2024. Available at: www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf (accessed January 2024);
2. Machiels J-P, et al. *Ann Oncol.* 2020;31:1462–75; 3. Keam B, et al. *ESMO Open.* 2021;6:100309.

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What are the key considerations for selecting a therapeutic strategy for individual patients with R/M SCCHN?

Factors to consider when making treatment decisions

Disease pathology[1]

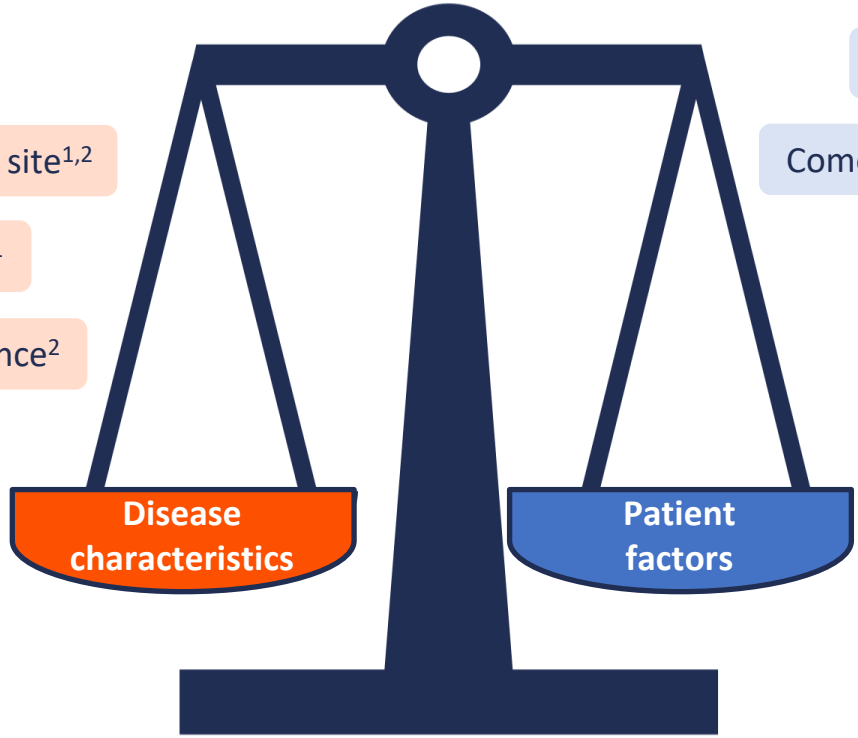
Tumour burden[2,3]

Tumour site[1,2]

Disease aggressiveness[1]

Platinum sensitivity/resistance[2]

PD-L1 expression[2,3]



Age[1]

Functional status[2]

Comorbidities[1,3]

Patient wishes[2]

Symptom burden[2,3]

Treatment history[2]

Contraindication to 5-FU[3]

5-FU, 5-fluorouracil; PD-L1, programmed death-ligand 1.

1. Kaidar-Person O, et al. *Drug Resist Updat*. 2018;40:13–6; 2. Johnson DE, et al. *Nat Rev Dis Primers*. 2020;6:92; 3. Guigay J, et al. *Lancet Oncol*. 2021;22:463–75.

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What are some of the challenges to manage when treating patients with the EXTREME regimen?

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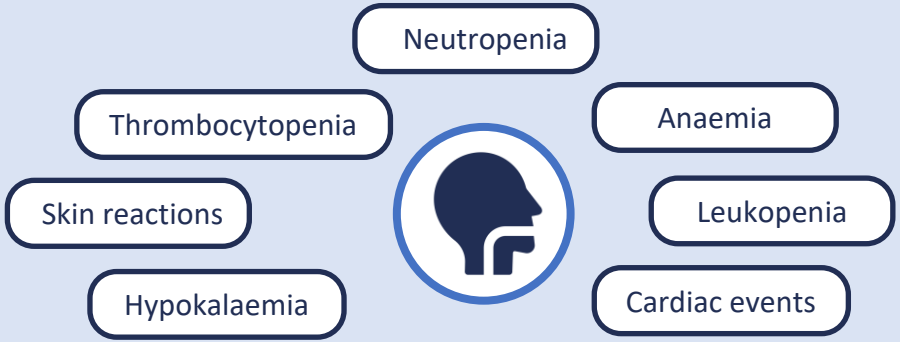
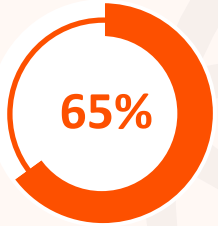
Adverse events associated with the EXTREME regimen*

Fluorouracil component of EXTREME regimen is associated with mucositis and diarrhoea[1,2]

Grade 3 or 4 adverse events with the EXTREME regimen (>5%)[3]



Real-world data[4]



of patients receiving the EXTREME regimen reported that they are "some-what", "quite a bit" or "very much" bothered by side effects of treatment

*Cetuximab + platinum + 5-FU.
5-FU, 5-fluorouracil.
1. Lo EKK, et al. *Curr Opin Toxicol.* 2023;36:100423; 2. Brown TJ, Gupta A. *JCO Oncol Pract.* 2020;16:103–9; 3. Vermorken JB, et al. *N Engl Med.* 2008;359:1116–27; 4. Singh P, et al. *BMC Cancer.* 2021;21:854.

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What role do currently approved immunotherapies play in improving outcomes in patients with R/M SCCHN?

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Long-term outcomes with ICIs for R/M SCCHN

Study	KEYNOTE-048[1]		CheckMate 141[2]
Study agents	Pembrolizumab vs EXTREME regimen*	Pembrolizumab + ChT vs EXTREME regimen*	Nivolumab vs investigator's choice
Key efficacy results	**PD-L1 CPS ≥20** • Median OS: 14.9 mos vs 10.8 mos • ORR: 23.3% vs 36.1% **PD-L1 CPS ≥1** • Median OS: 12.3 mos vs 10.4 mos • ORR: 19.1% vs 34.9% **Total population** • Median OS: 11.5 mos vs 10.7 mos • ORR: 16.9% vs 36.0%	**PD-L1 CPS ≥20** • Median OS: 14.7 mos vs 11.1 mos • ORR: 43.7% vs 38.2% **PD-L1 CPS ≥1** • Median OS: 13.6 mos vs 10.6 mos • ORR: 37.2% vs 35.7% **Total population** • Median OS: 13.0 mos vs 10.7 mos • ORR: 36.3% vs 36.3%	• 24-month OS: 20.4% vs 3.8% • 24-month PFS: 14.8% vs 0% • ORR: 20.0% vs 11.5% • Median DoR: NR with nivolumab
Summary	With a 4-year follow-up, 1L pembrolizumab alone and pembrolizumab + ChT continued to demonstrate survival benefit compared with cetuximab ChT in R/M SCCHN		With a 2-year follow-up, an OS benefit with nivolumab was maintained compared with investigator's choice

Direct comparisons between trials should not be made due to differences in trial design.
*Cetuximab + platinum + 5-FU.
5-FU, 5-fluorouracil; 1L, first-line; ChT, chemotherapy; CPS, combined positive score; DoR, duration of response; ICI, immune checkpoint inhibitor; mo, month; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck.
1. Harrington KJ, et al. *J Clin Oncol.* 2023;41:790–802; 2. Gillison ML, et al. *Oncologist.* 2022;27:e194–8.

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Which patients with R/M SCCHN will benefit from treatment with immunotherapy with or without chemotherapy versus chemotherapy alone?

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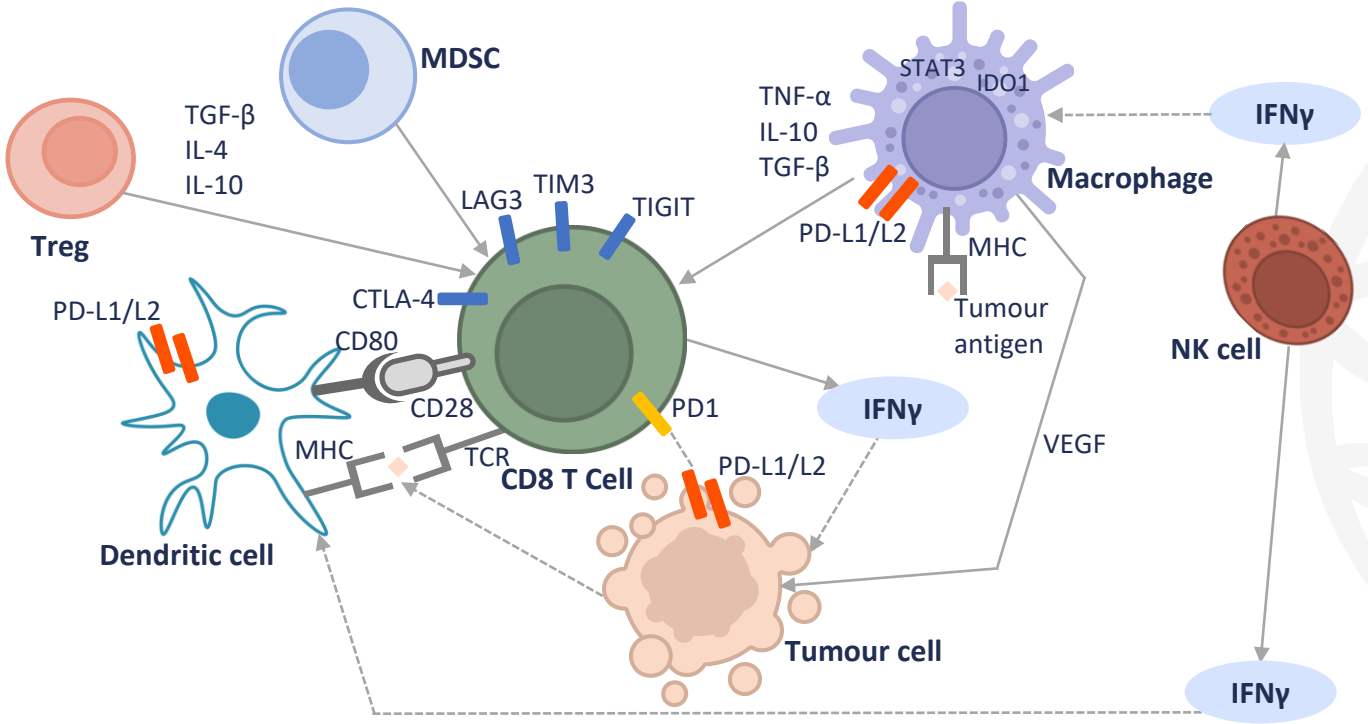
Tumour microenvironment of SCCHN



CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein 4; IDO1, indoleamine 2,3-dioxygenase-1; IFNγ, interferon gamma; IL, interleukin; LAG3, lymphocyte activation gene 3; MDSC, myeloid-derived suppressor cells; MHC, major histocompatibility complex; NK, natural killer; PD1, programmed cell death 1; PD-L1/L2, programmed death-ligand 1/2; SCCHN, squamous cell carcinoma of the head and neck; STAT3, signal transducer and activator of transcription 3; TCR, T-cell receptor; TGF-β, transforming growth factor beta; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains; TIM3, T-cell immunoglobulin mucin-3; TNF-α, tumour necrosis factor alpha; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

Chen SMY, et al. *Mol Carcinog.* 2020;59:766–74.

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Future treatment directions: Immunotherapy-based strategies

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What is the rationale for additional immunotherapy-based treatment options for R/M SCCHN?

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Outcomes with approved ICIs for R/M SCCHN

	First-line setting	Second-line setting	
Study	**KEYNOTE 048[1]**	**KEYNOTE 040[2]**	**CheckMate 141[3]**
Treatment	**Pembrolizumab** vs **Pembrolizumab + platinum + 5-FU** vs EXTREME regimen*	**Pembrolizumab** vs Methotrexate, docetaxel or cetuximab	**Nivolumab** vs Methotrexate, docetaxel or cetuximab
Key efficacy results	**PD-L1 CPS ≥20** • mOS: **14.9** vs 10.7 mos / **14.7** vs 11.0 mos • mPFS: **3.4** vs 5.0 mos / **5.8** vs 5.2 mos • ORR: **23%** vs 36% **PD-L1 CPS ≥1** • mOS: **12.3** vs 10.3 mos / **13.6** vs 10.4 mos • mPFS: **3.2** vs 5.0 mos / **5.0** vs 5.0 mos • ORR: **19%** vs 35% **Total population** • mOS: **11.6** vs 10.7 mos / **13.0** vs 10.7 mos • mPFS: **2.3** vs 5.2 / **4.9** vs 5.1 mos • ORR: **17%** vs 36%	**Intention-to-treat** • mOS: **8.4** vs 6.9 mos **Total population** • mPFS: **2.1** vs 2.3 mos	**Total population** • mOS: **7.5** vs 5.1 mos • mPFS: **2.0** vs 2.3 mos • ORR: **13.3%** vs 5.8%

Direct comparisons between trials should not be made due to differences in trial design.
*Cetuximab + platinum + 5-FU.
5-FU, 5-fluorouracil; CPS, combined positive score; ICI, immune checkpoint inhibitor; m, median; mos, months; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck.
1. Burtness B, et al. *Lancet*. 2019;394:1915–28; 2. Cohen EEW, et al. *Lancet*. 2019;393:156–67; 3. Ferris RL, et al. *N Engl J Med*. 2016;375:1856–67.

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What immunotherapy-based strategies are currently under investigation for R/M SCCHN?

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Key immunotherapeutic approaches in development

Clinical development landscape in patients with R/M SCCHN

Investigational ICI combinations

ICI + ChT	ICI + cetuximab[3]
Durvalumab + carboplatin + paclitaxel[1]	Pembrolizumab + cetuximab
Pembrolizumab + carboplatin + paclitaxel[2]	Avelumab + cetuximab
	Nivolumab + cetuximab
	Durvalumab + cetuximab

Novel immunotherapeutic strategies

ICI + CTLA-4[4]	ICI + TKI	ICI + LAG3	Triplet therapies	ICI + ADC	ICI + bispecific antibody
Durvalumab + tremelimumab	Pembrolizumab + lenvatinib[4]	Pembrolizumab + eftilagimod alpha[3]	Durvalumab + cetuximab + monalizumab[3]	Pembrolizumab + enfortumab vedotin[9]	Pembrolizumab + petosemtamab[11]
Nivolumab + ipilimumab	Pembrolizumab + anlotinib[4]	Retifanlimab + INCAGN02385/ INCAGN023906[6]	Avelumab + palbociclib + cetuximab[7]	Pembrolizumab + SGN-B6A[10]	Pembrolizumab + BCA101[12]
	Pembrolizumab + afatinib[4]		Dostarlimab + belrestotug + GSK609760[8]		
	Atezolizumab + cabozantinib[5]				

Other therapies: Cytokine modulators, T-cell therapy, vaccines and oncolytic viruses[3,4]

ADC, antibody–drug conjugate; ChT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ICI, immune checkpoint inhibitor; LAG3, lymphocyte activation gene 3; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck; TKI, tyrosine kinase inhibitor.

1. Fayette J, et al. *J Clin Oncol.* 2023;41(Suppl. 16):Abstr 6003; 2. Dzienis MR, et al. *Ann Oncol.* 2022;33(Suppl. 7):S839–40; 3. Wise-Draper TM, et al. *Am Soc Clin Oncol Educ Book.* 2022;42:1–14; 4. Parmar K, et al. *Cancer Treat Res Commun.* 2022;33:100649; 5. Rottey S, et al. *J Immunother Cancer.* 2022;10(Suppl. 2):A597; 6. Cohen EEW, et al. *J Clin Oncol.* 2023;41(Suppl. 16):TPS6104; 7. Dennis MJ, et al. *Oral Oncol.* 2022;135:106219; 8. ClinicalTrials.gov. NCT06062420 Available at: https://clinicaltrials.gov/study/NCT06062420 (accessed January 2024); 9; ClinicalTrials.gov. NCT04225117 Available at: https://clinicaltrials.gov/study/NCT04225117 (accessed January 2024); 10. ClinicalTrials.gov. NCT04389632 Available at: https://clinicaltrials.gov/study/NCT04389632 (accessed January 2024); 11. Cohen EEW, et al. Presented at: AACR Annual Meeting 2023, Orlando, FL, USA. 14–19 April 2023. Abstr. CT012; 12. Hanna GJ, et al. *Ann of Oncol.* 2023;34(Suppl. 2):S582–3.

What are the latest clinical trial data for investigational immunotherapy-based combinations with chemotherapy or cetuximab for patients with R/M SCCHN?

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Latest data for ICIs plus ChT for R/M SCCHN

Combination	Durvalumab + carboplatin + paclitaxel[1]	Pembrolizumab + carboplatin + paclitaxel[2]
Study	Phase II FRAIL-IMMUNE	Phase IV KEYNOTE-B10
Setting	**First-line** treatment in frail patients with R/M SCCHN not amenable to cisplatin-based ChT N=64	**First-line** treatment of patients with previously untreated R/M SCCHN N=92
Key efficacy results	• **mOS: 18 months** • **24-month OS: 45%** • **mPFS: 7.0 months** • **ORR: 71%** • **mDoR: 5.9 months**	• **mOS: 12.1 months** n=82 • **12-month OS: 58%** • **mPFS: 5.6 months** • **ORR: 43%** • **mDoR: 5.5 months**
Key safety results	• **Grade ≥3 AEs: 20.3%**	• **Grade ≥3 AEs: 71%**

Ongoing trials

Phase II NCT04282109 (NIVOTAX)[3]
- 1L nivolumab + paclitaxel in patients with R/M SCCHN ineligible for cisplatin-based ChT

Phase II NCT04858269[3]
- 1L pembrolizumab + carboplatin + paclitaxel in patients with R/M SCCHN unable to take 5-FU

Phase II NCT06052839[3]
- Pulsed-dosed carboplatin + paclitaxel + pembrolizumab in 1L R/M SCCHN

The combination of PD-1/PD-L1 inhibitors plus carboplatin and paclitaxel demonstrated anti-tumour activity and tolerable toxicity profiles in patients with R/M SCCHN[1,2]

Direct comparisons between trials should not be made due to differences in trial design.

5-FU, fluorouracil; AE, adverse event; ChT, chemotherapy; DoR, duration of response; ICI, immune checkpoint inhibitor; m, median; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck.

1. Fayette J, et al. *J Clin Oncol.* 2023;41(Suppl. 16):Abstr 6003; 2. Dzienis MR, et al. *Ann Oncol.* 2022;33(Suppl. 7):S839–40; 3. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/; clinical trials searchable by NCT number (accessed January 2024).

Latest data for ICIs plus cetuximab for R/M SCCHN

Combination	Pembrolizumab + cetuximab[1]	Avelumab + cetuximab[2]	Nivolumab + cetuximab[3]	Durvalumab + cetuximab[4]
Study	Phase II NCT03082534	Phase II NCT03494322	Phase I/II NCT03370276	Phase II NCT03370276
Setting	Platinum-resistant or platinum-ineligible patients with R/M SCCHN N=33	Patients with R/M SCCHN, no previous treatment with cetuximab N=16	Second-line and beyond treatment of patients with R/M SCCHN N=45	Patients with R/M SCCHN N=35
Key efficacy results	• ORR: 45%	• ORR: 50% n=10 • CR: 20% • PR: 30%	• 12-month OS: 44% • 12-month PFS: 19%	• mPFS: 5.8 months • mOS: 9.6 months • ORR: 39% (13/33) • mDoR: 8.6 months
Key safety results	• Serious TRAEs: 15%	• Grade 3 AEs: four patients	• Grade 4 TRAE: one patient	• 16 grade 3 TRAEs

Multiple studies have demonstrated consistent and promising results with PD-1/PD-L1 inhibitors plus cetuximab[5]

Direct comparisons between trials should not be made due to differences in trial design.
AE, adverse event; DoR, duration of response; CR, complete response; ICI, immune checkpoint inhibitor; m, median; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck; TRAE, treatment-related AE.

1. Sacco AG, et al. *Lancet Oncol.* 2021;22:883–92; 2. Forster M, et al. *Ann Oncol.* 2020;31(Suppl. 4):S665; 3. Chung CH, et al. *Cancers (Basel).* 2021;13:1180; 4. Gulati S, et al. *Clin Cancer Res.* 2023;29:1906–15; 5. Wise-Draper TM, et al. *Am Soc Clin Oncol Educ Book.* 2022;42:1–14.

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What can we learn from the latest data on novel immunotherapy-based strategies for patients with R/M SCCHN?

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PD-1/PD-L1 inhibitors in combination with CTLA-4 inhibitors

Patients with R/M SCCHN

	Durvalumab (D) ± tremelimumab (T)		Nivolumab (N) + ipilimumab (I)[3]	
Study	**EAGLE**[1] Phase III	**KESTREL**[2] Phase III	**CheckMate 714**[3] Phase II	**CheckMate 651**[4] Phase III
Treatment	**Second-line** durvalumab (n=240) or durvalumab + tremelimumab (n=247) vs single-agent SoC (n=249)	**First-line** durvalumab (n=204) or durvalumab + tremelimumab (n=413) vs EXTREME* (n=206)	**First-line** nivolumab + ipilimumab (PR n=159; PE n=123) vs nivolumab + placebo (PR n=82; PE n=61)	**First-line** nivolumab + ipilimumab (n=472) vs EXTREME* (n=475)
Key efficacy results	**mOS** • **D: 7.6 months** • **D + T: 6.5 months** • **SoC: 8.3 months**	**mOS** • **D: 9.9 months** • **D + T: 10.7 months** • **EXTREME: 10.3 months**	**ORR (PR)** • **N + I: 13.2%** • **N: 18.3%** **ORR (PE)** • **N + I: 20.3%** • **N: 29.5%**	**mOS** • **N + I: 13.9 months** • **EXTREME: 13.5 months**

Multiple studies did not meet their primary end point (OS/ORR) when assessing the efficacy of CTLA-4 inhibition in combination with anti-PD-1/PD-L1 monoclonal antibodies compared to SoC regimens.[1–4]

Direct comparisons between trials should not be made due to differences in trial design.

*Cetuximab + platinum + 5-FU.

5-FU, 5-fluorouracil; CTLA-4, cytotoxic T-lymphocyte associated protein 4; m, median; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PE, platinum eligible; PR, platinum refractory; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck; SoC, standard of care.

1. Ferris RL, et al. *Ann Oncol.* 2020;31:942–50; 2. Psyrri A, et al. *Ann Oncol.* 2023;34:262–74; 3. Harrington KJ, et al. *JAMA Oncol.* 2023;9:779–89;
4. Haddad RI, et al. *J Clin Oncol.* 2022;41:2166–80.

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LAG3 inhibitor or TKIs in combination with ICIs

Patients with R/M SCCHN

	LAG3 inhibitor	TKI			
Combination	**Eftilagimod alpha + pembrolizumab**[1]	**Cabozantinib + atezolizumab**[2]	**Anlotinb + pembrolizumab**[3]	**Afatinib + pembrolizumab**[4]	**Lenvatinib + pembrolizumab**[5]
Study	**TACTI-002** Phase II	**COSMIC-021** Phase Ib	**NCT04999800** Phase II	**ALPHA study** Phase II	**LEAP-010** **Phase III**
Treatment	**Second-line** eftilagimod alpha + pembrolizumab (n=37)	**Second- or third-line** cabozantinib + atezolizumab (N=30)	**First-line** Anlotinb + pembrolizumab (N=15)	**Second-line** Afatinib + pembrolizumab (n=29)	**First-line** **Lenvatinib + pembrolizumab** (n=256) or placebo + pembrolizumab (n=255)
Key efficacy results	• **ORR: 30%** • **mPFS: 2.1 months** • **mOS: 8.7 months**	• **ORR: 17%** • **mPFS: 2.9 months** • **mOS: 9.2 months**	• **ORR: 46.7%** • **mPFS: NR** • **mOS: NR**	• **mPFS: 4.1 months** • **mOS: 8.9 months**	• **ORR: 46.1% vs 25.4%*** • **mPFS: 6.2 vs 2.8 months*** • **mOS: 15.0 vs 17.9 months***
Key safety results	**Most common AEs:** Hypothyroidism (21%) Asthenia (21%) Cough (18%)	**Most common TRAEs:** Fatigue (30%) Stomatitis (30%) Hypertension (27%)	**Most common TRAEs:** Hypertension (25%)	**Most common TRAEs:** Skin rash (75.9%) Diarrhoea (58.9%) Paronychia (44.8%)	**Grade ≥3 TRAEs (IA2):** 61.4% vs 17.8%

Direct comparisons between trials should not be made due to differences in trial design.

*Per the prespecified analysis plan, ORR and PFS are reported from the first interim analysis (IA1) and OS and DOR are reported from second interim analysis (IA2). Data cutoff dates were July 6, 2022 for IA1 and May 30, 2023 for IA2.

AE, adverse event; IA2, interim analysis 2; ICI, immune checkpoint inhibitor; LAG3, lymphocyte activation gene 3; m, median; NR, not reached. ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck; TKI, tyrosine kinase inhibitor; TRAE, treatment-related AE.

1. Doger de Spéville BD, et al. *J Clin Oncol.* 2023;41(Suppl. 16):6029; 2. Rottey S, et al. *J Immunother Cancer.* 2022;10(Suppl. 2): A597;
3. Gui L, et al. *Ann Oncol.* 2022;33(Suppl. 9):S1524; 4. Kao HF, et al. *Clin Cancer Res.* 2022;128:1560–71; 5. Licitra L, et al. Presented at: Multidisciplinary Head and Neck Cancers Symposium 2024, Phoenix, AZ, USA. 29 February–2 March 2024. Abstr.

Other novel combinations including ICIs

Patients with R/M SCCHN

	Triplet combinations		Bispecific antibody
Combination	**Durvalumab + monalizumab + cetuximab[1]**	**Avelumab + palbociclib + cetuximab[2]**	**BCA101 + pembrolizumab[3]**
Study	**NCT02643550** Phase II	**NCT03498378** Phase I	**NCT04429542[4]** Phase I
Setting	**First line** n=40	**First line** N=12	**First line** N=33
Key efficacy results	**ORR: 33%** **mPFS: 6.9 months** **12-month OS: 59%**	**ORR: 41.7%** **mPFS: 6.5 months** **mOS: NR** **DCR: 75%**	**ORR: 48%** n=31 • **ORR (HPV-): 65% (13/20)** • **ORR (CPS 1–19): 50% (5/10)** **mPFS (HPV-): NR**
Key safety results	**Grade 3 or 4 TRAEs: 48%**	**Any grade TRAEs: 100%** **Grade ≥3 TRAEs: 75%**	**Grade ≥3 TRAEs: 27%**

Direct comparisons between trials should not be made due to differences in trial design.

CPS, combined positive score; DCR, disease control rate; HPV, human papillomavirus ; ICI, immune checkpoint inhibitor; m, median; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/M SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck; TRAE, treatment-related adverse event.

1. Colevas DA, et al. *Ann Oncol.* 2021;32(Suppl. 7):S1432; 2. Dennis MJ, et al. *Oral Oncol.* 2022;135:106219; 3. Hanna GJ, et al. *Ann of Oncol.* 2023;34:S582–S583;
4. ClinicalTrials.gov. NCT04429542. Available at: https://clinicaltrials.gov/NCT04429542 (accessed January 2024).

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How do you think emerging immunotherapy-based regimens may impact the treatment landscape for R/M SCCHN in the future?

Predictive biomarkers to support treatment decisions in R/M SCCHN

Molecular biomarkers support the diagnosis of SCCHN, monitoring disease progression and predicting response to treatment[1]

Current predictive markers[2,3]

- **PD-L1** 1< CPS ≥1
- **HPV status and/or P16**

Investigational predictive markers[2]

- **Oral microbiome**
- **CTC/ctDNA**
- **Genetic signature (TMB/MSI)**

Biomarkers for most likely IO response[4]

		IO responder	IO non-responder
Tumour-related factors	IFN-γ	High	Low
	PD-L1	High	Low
	TMB	High	Low
Tumour micro-environment	Gene expression	Inflamed	Non-inflamed
	Immune landscape	↑ CD3, CD8, FOXP3, T-cell clonality, M1 macrophages, TLS	↑ MDSCs, M2 macrophages, N2 neutrophils
Patient factors	HPV	Positive	Negative
	Microbiome	e.g. *Akkermansia muciniphila*	e.g. *Bacteriodales*

↑, increased; +, positive; -, negative; CD, cluster of differentiation; CPS, combined positive score; CTC, circulating tumour cells; ctDNA, circulating tumour DNA; HPV, human papillomavirus; IFN-γ, interferon gamma; IO, immunotherapy; MDSC, myeloid-derived suppressor cells; MSI, microsatellite instability; PD-L1, programmed death-ligand 1; R/M, recurrent or metastatic; SCCHN, squamous cell carcinoma of the head and neck; TMB, tumour mutational burden; TLS, tertiary lymphoid structures.

1. Veigas F, et al. *Cancers.* 2021;13:1018; 2. Wang H-C, et al. *Int J Mol Sci.* 2020;21:7621; 3. De Keukeleire SJ, et al. *Cancers*. 2021;13:1714;
4. Gavrielatou N, et al. *Cancer Treat Rev*. 2020;84:101977.

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Future treatment directions: Targeted therapies

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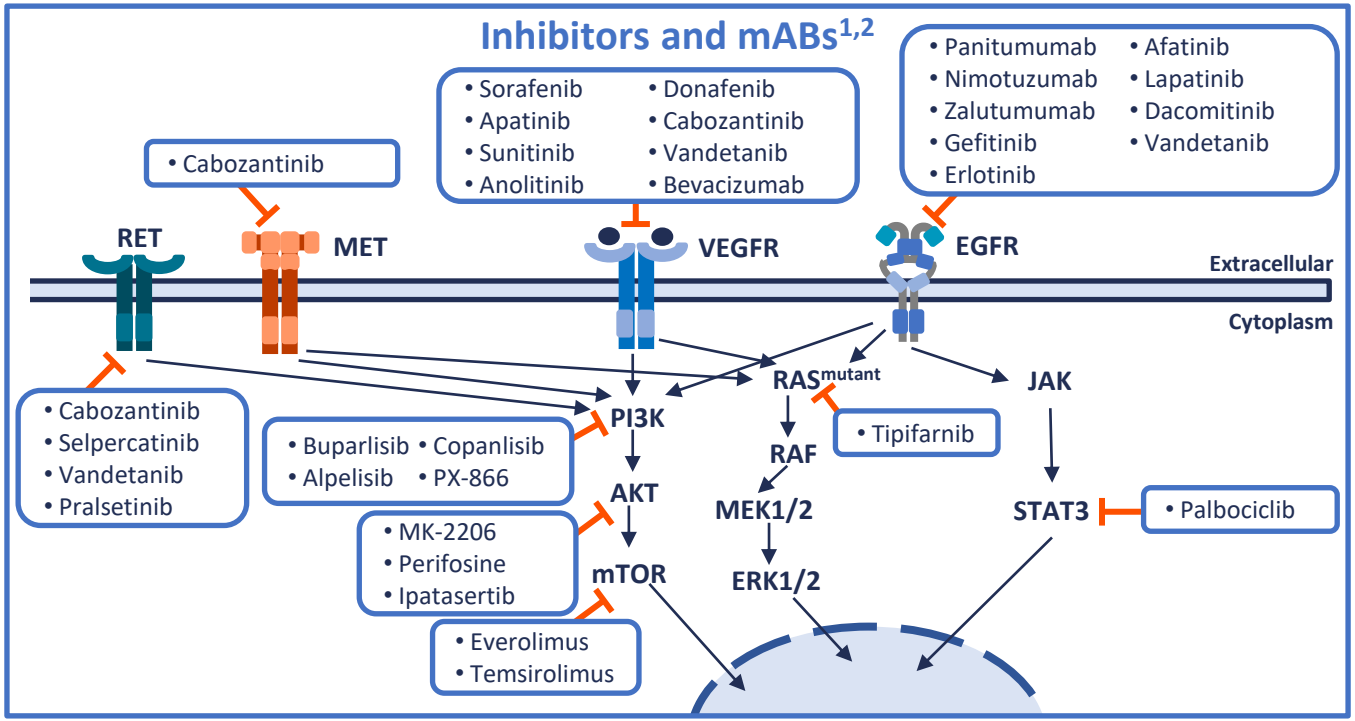
What is the rationale for developing additional targeted therapies for R/M SCCHN and what novel targeted treatments are currently under investigation?

Targeted treatments in development for R/M SCCHN



Antibody–drug conjugates

Key components:[3]

ADC	Target
Tistotumab vedotin[4]	Tissue factor
Enfortumab vedotin[5]	Nectin-4
MRG003[6]	EGFR
Disitamab vedotin[7,8]	HER2
SGN-B6A[9]	Integrin beta-6
Ozurifatamab vedotin[10]	ROR2

ADC, antibody–drug conjugate; AKT, serine/threonine-specific protein kinase; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1/2; HER2, human epidermal growth factor receptor 2; JAK, Janus-activated kinase; mAB, monoclonal antibody; MEK, mitogen-activated extracellular signal-regulated kinase MET, mesenchymal–epithelial transition factor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerating fibrosarcoma; RAS, rat sarcoma; RET, rearranged during transfection; R/M SCCHN, recurrent/metastatic squamous cell carcinoma of the head and neck; ROR2, receptor tyrosine kinase-like orphan receptor 2; STAT3, signal transducer and activator of transcription 3; VEGFR, vascular endothelial growth factor receptor.

1. Li Q, et al. *Signal Transduct Target Ther.* 2023;8:31; 2. Untch BR, et al. *Cancer Res.* 2018;78:4642–57; 3. Desai A, et al. *Lung Cancer.* 2022;163:96–106; 4. Cirauqui B, et al. *Cancer Res.* 2023;83(Suppl. 8): CT164; 5. Swiecicki P, et al. *J Clin Oncol.* 2023;41:6017; 6. Xue L, et al. *Ann Oncol.* 2023; 34(Suppl. 2):S554–93; 7. ClinicalTrials.gov. NCT06003231. Available at: https://clinicaltrials.gov/NCT06003231 (accessed January 2024). 8. Shi F, et al. *Drug Deliv.* 2022;29: 1335–44. 9. Hollebecque A, et al. *J Clin Oncol.* 2023;41:3024; 10. Ho AL, et al. *J Clin Oncol.* 2023;41:TPS6107.

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What are the latest clinical trial data for antibody-drug conjugates for patients with R/M SCCHN?

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Latest data for ADCs for R/M SCCHN

ADC	Tisotumab vedotin[1]	Enfortumab vedotin[2]	MRG003[3]	Ongoing studies[4]
Study	Phase II innovaTV 207	Phase II EV-202	Phase II[4] NCT04868162	• SGN-B6A, phase I (NCT04389632) • Disitamab vedotin, phase II (NCT06003231) • Ozuriftamab vedotin, phase II (NCT05271604)
Setting	Pts with R/M SCCHN who have received prior lines of therapy including platinum therapy (93% had received an ICI) (n=15)	Pts with la/m HNC who have previously received one platinum-based therapy (n=46)	Pts with R/M SCCHN who had progressed on at least one line of standard therapy (N=67)	
Key efficacy results	• **ORR: 40%**	• **ORR: 23.9%** • **mPFS: 3.94 months** • **mOS: 5.98 months**	• **ORR (EGFR+): 30.6%** • **ORR:* 43%** • **mPFS: 4.2 months** • **mOS: 11.3 months**	
Key safety results	**TRAEs: 13 patients** • **Asthenia (n=7)** • **PSN (n=7)** • **Vomiting (n=5)**	**TRAEs of special interest:** • **Skin reactions (45.7%)** • **Peripheral neuropathy (32.6%)** • **Hyperglycaemia (4.3%)**	**Common TRAEs:** • **Constipation (25.8%)** • **Pruritus (24.2%)** • **Anaemia (22.6%)**	

ADCs have shown promising efficacy and manageable safety profiles in various phase II trials for the treatment of R/M SCCHN

Direct comparisons between trials should not be made due to differences in trial design.
*In second- and third-line patients who had previously failed prior platinum and PD-1/PD-L1 inhibitor and who had received 2.3mg/kg dose of MRG003.
ADC, antibody–drug conjugate; ICI, immune checkpoint inhibitor; la/m HNC, locally advanced or metastatic head and neck cancer; m, median; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PSN, peripheral sensory neuropathy; pts, patients; R/M SCCHN, recurrent/metastatic squamous cell carcinoma of the head and neck; TRAE, treatment-related adverse event.

1. Cirauqui B, et al. *Cancer res*. 2023;83 (Suppl. 8):CT164; 2. Swiecicki P, et al. *J Clin Oncol.* 2023;41:6017; 3. Xue L, et al. *Ann Oncol.* 2023; 34(Suppl. 2):S554–93;
4. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/; clinical trials searchable by NCT number (accessed January 2024).

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What are the clinical trial data for EGFR and VEGF inhibition in patients with R/M SCCHN?

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Clinical trial data for EGFR inhibition in R/M SCCHN

EGFR inhibition

Cetuximab
- **The only EGFR-targeted therapy currently approved in Europe, the USA and Japan for SCCHN[1–3]**

Panitumumab
- **Phase III SPECTRUM:** Panitumumab + ChT did not improve mOS; however, mPFS was improved (5.8 vs 4.6 months) compared to the control group[4]
- **Phase II PARTNER:** Panitumumab + docetaxel/cisplatin improved mPFS compared with chemotherapy alone (6.9 vs 5.5 months)[5]

Dacomitinib
- **Phase II trials:** Dacomitinib monotherapy has demonstrated antitumor activity in patients with R/M SCCHN[6,7]

Gefitinib
- **Phase III trials:** Gefitinib monotherapy or gefitinib plus docetaxel failed to improve efficacy vs methotrexate or docetaxel plus placebo, respectively[8,9]

Afatinib
- **Phase III LUX-Head & Neck 1:** Afatinib monotherapy induced significantly prolonged PFS (2.6 vs. 1.7 months; p=0.030) vs methotrexate for R/M SCCHN[10]

Other EGFR mAbs/inhibitors of interest in SCCHN: Nimotuzumab, lapatinib and poziotinib[11]

EGFR expression and HPV status

- **Overexpression of EGFR was observed more frequently in HPV- tumours than in HPV+ tumours[12]**

- **Recent studies have shown inferior outcomes in patients with HPV+ SCCHN who received cetuximab in combination with RT or cisplatin[13]**

Only 5% of HNC patients have EGFR alterations, which may contribute to the limited effectiveness of EGFR TKIs[11]

Direct comparisons between trials should not be made due to differences in trial design.
ChT, chemotherapy; EGFR, epidermal growth factor receptor; HNC, head and neck cancer; HPV, human papillomavirus; m, median; mAb, monoclonal antibody; OS, overall survival; PFS, progression-free survival; R/M, recurrent/metastatic; RT, radiotherapy; SCCHN, squamous cell carcinoma of the head and neck; TKI, tyrosine kinase inhibitor.

1. EMA. Cetuximab SmPC. Available at: https://bit.ly/4b14A9Q (accessed January 2024); 2. FDA. Cetuximab PI. Available at: https://bit.ly/47Oulrq (accessed January 2024); 3. Szturz P, et al. *J Clin Oncol*. 2017;35:2229–31; 4. Vermorken JB, et al. *Lancet Oncol.* 2013;14:697–710; 5. Wirth LJ, et al. *Oral Oncol.* 2016:61:31–40; 6. Abdul Razak AR, et al. *Ann Oncol.* 2013;24:761–9; 7. Kim HS, et al. *Clin Cancer Res.* 2015;21:544–52; 8. Stewart JSW, et al. *J Clin Oncol.* 2009;27:1864–71; 9. Argiris A, et al. *J Clin Oncol*. 2013;31:1405–14; 10. Machiels JPH, et al. *Lancet Oncol*. 2015;16:583–94; 11. Li Q, et al. *Signal Transduct Target Ther.* 2023;8:31; 12. Chen Y, et al. *Int Immunopharmacol.* 2023:120:110329; 13. Alsahafi EN, et al. *Cancer Lett*. 2021:498:80–97.

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Latest data for VEGF inhibition in R/M SCCHN

VEGF inhibition	Bevacizumab			
Study design	Phase II[1] Previously untreated R/M SCCHN N=40	Phase III (E1305)[2] Chemotherapy naive R/M SCCHN N=403	Phase II[3] R/M SCCHN with no more than one prior treatment N=46	Phase II[4] n=48
Treatment	Pemetrexed + bevacizumab	**Platinum doublet ChT + bevacizumab** vs platinum doublet ChT	Cetuximab + bevacizumab	Erlotinib + bevacizumab
Key efficacy results	• **mOS: 11.3 months** • **ORR: 30%**	• **mOS: 12.6** vs 11.0 months • **mPFS: 6.0** vs 4.3 months • **ORR: 35.5%** vs 24.5%	• **mOS: 7.5 months** • **mPFS: 2.8 months** • **ORR: 16%**	• **mOS: 7.1 months** • **mPFS: 4.1 months**
Key safety results	**Grade 3 to 5 bleeding events: 15%**	**Treatment-related grade 3 to 5 bleeding events: 6.7%** vs 0.5%	**Grade 3 or 4 AE: <10%**	**Most common AE of any grade:** • **Rash and diarrhoea**

The VEGF pathway is a promising therapeutic target in SCCHN; however, further studies should focus on minimizing unwanted adverse effects, especially bleeding events[5]

Direct comparisons between trials should not be made due to differences in trial design.

AE, adverse event; ChT, chemotherapy; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/M SCCHN, recurrent/metastatic squamous cell carcinoma of the head and neck; VEGF, vascular endothelial growth factor.

1. Argiris A, et al. *J Clin Oncol.* 2011;29:1140–5; 2. Argiris A, et al. *J Clin Oncol.* 2019;37:3266–74; 3. Argiris A, et al. *Ann Oncol.* 2013;24:220–5; 4. Cohen E, et al. *Lancet Oncol.* 2009;10:247–57; 5. Li Q, et al. *Signal Transduct Target Ther.* 2023;8:31.

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What are the clinical trial data for HRAS inhibitors and PI3K/AKT/mTOR pathway inhibition for patients with R/M SCCHN?

Latest data for HRAS and PI3K inhibition in R/M SCCHN

	HRAS inhibitor	PI3K inhibition	
Treatment	**Tipifarnib**[1]	**Buparlisib + cetuximab**[2]	**Buparlisib + paclitaxel** vs placebo + paclitaxel[3]
Study	Phase II NCT03719690 N=59	Phase Ib NCT01816984 (N=12)	Phase II BERIL-1 (n=158)
Key efficacy results	• **ORR: 30%** (n=50; investigator assessment) • **mOS: 7.0 months**	• **PR: 1 patient** n=10 • **SD: 4 patients**	• **ORR: 39%** vs 14% • **mOS: 10.0** vs 6.5 months
Key safety results	**Grade ≥3 TRAEs: 56%** • **Neutropenia (24%)** • **Anaemia (20%)** • **Leukopenia (14%)** • **Febrile neutropenia (7%)**	**Grade ≥3 AEs: 10 patients**	**Grade 3 or 4 AEs:** • **Hyperglycaemia (22%** vs 3%) • **Anaemia (18%** vs 12%) • **Neutropenia (17%** vs 5%) • **Fatigue (8%** vs 10%)

Other studies investigating PI3K inhibitors

- Copanlisib and PX-866 demonstrated unfavourable toxicity or no improvement in clinical outcomes when combined with cetuximab in patients with R/M SCCHN[4]
- Phase III BURAN study of buparlisib in patients with R/M SCCHN[5]

Tipifarnib showed antitumor activity for patients with mutated *HRAS* SCCHN post-IO and as later-line therapy

Clinical evaluation of PI3K inhibitors in SCCHN is mainly in early phase clinical trials[4]

Direct comparisons between trials should not be made due to differences in trial design.

AE, adverse event; HRAS, Harvey rat sarcoma viral oncogene homolog; IO, immunotherapy; m; median; ORR, objective response rate; OS, overall survival; PI3K, phosphatidylinositol 3-kinase; PR, partial response; R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease; TRAE, treatment-related AE.

1. Ho AL, et al. *Ann Oncol.* 2023;34:S1286–87; 2. Brisson RJ, et al. *Head Neck.* 2019;41:3842–49; 3. Soulieres D, et al. *J Clin Oncol.* 2016;34:6008;
4. Li Q, et al. *Signal Transduct Target Ther.* 2023;16:31; 5. ClinicalTrials.gov. NCT04338399. Available at: https://clinicaltrials.gov/study/NCT04338399 (accessed January 2024).

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How do you think novel targeted treatment options may impact the treatment landscape for R/M SCCHN in the future?

Future of targeted treatments for R/M SCCHN

Numerous targeted therapies on the horizon

- Several signalling pathways are activated in SCCHN; targeting these abnormal pathways has led to numerous agents being studied in clinical trials for patients with R/M SCCHN[1]

Personalized treatment and predictors of response

- Screening for actionable genomic variations and tailoring targeted therapy accordingly[2]
- Identifying patients with favourable outcomes via predictive biomarkers[3]

Managing adverse events

- The response to targeted therapies relies on its specific target in tumour tissue. However, off-target side effects may lead to treatment failure and severe adverse events[3]

Integrating novel targeted therapies into clinical practice

- Guidance on how to select the most appropriate treatment (e.g. monotherapy or combination strategy) for each patient and the optimal treatment sequence[4]

R/M, recurrent/metastatic; SCCHN, squamous cell carcinoma of the head and neck.

1. Wise-Draper TM, et al. *Am Soc Clin Oncol Educ Book.* 2022;42:1–14; 2. Kordbacheh F, Farah CS. *Cancers (Basel).* 2021;13:5471;
3. Li Q, et al. *Signal Transduct Target Ther.* 2023;8:31; 4. Szturz P, Vermorken JB. *Critical Issues in Head and Neck Oncology.* 2023;199–215.

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