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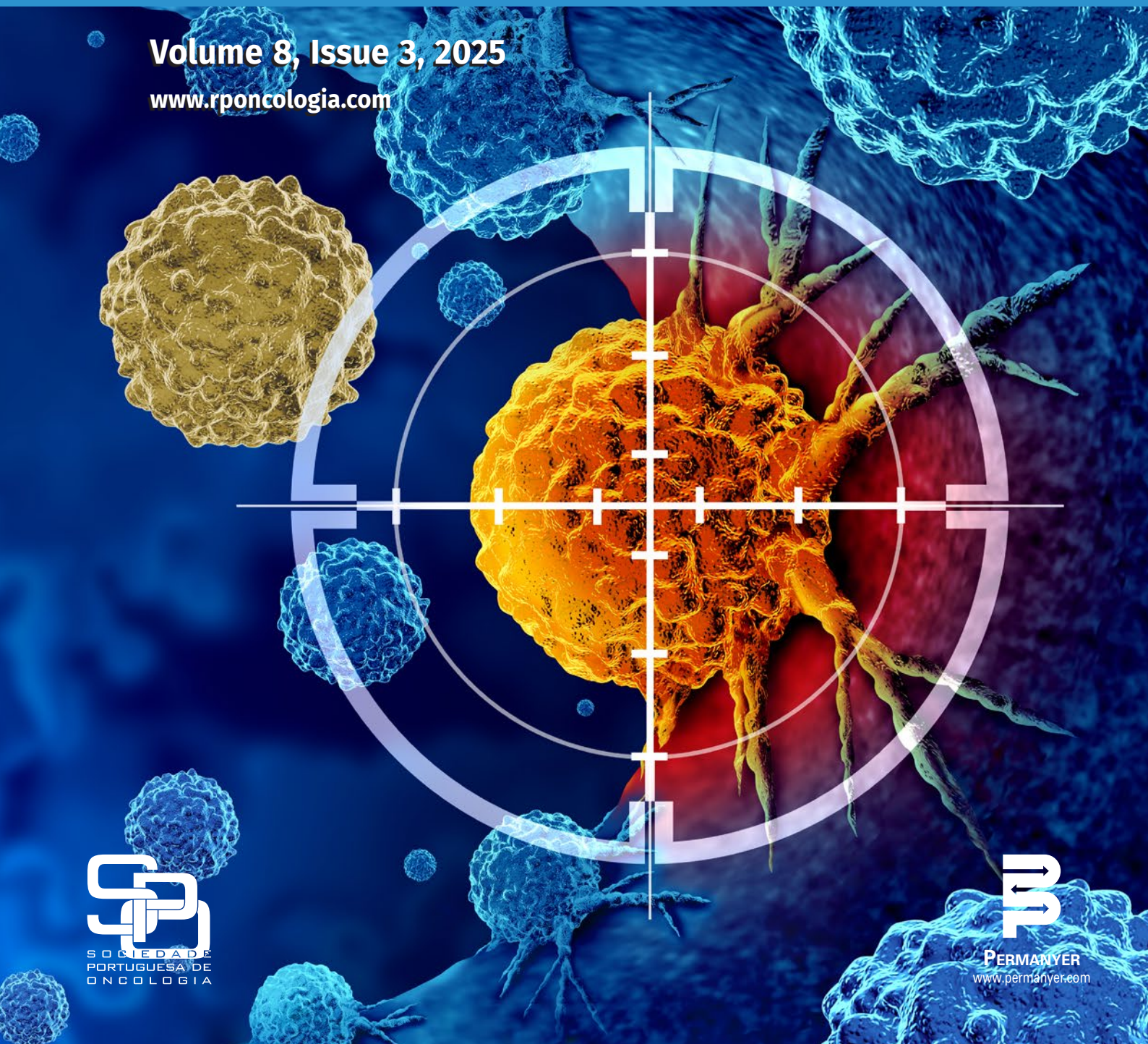
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Highlights from the 2025 American Society of Clinical Oncology Annual meeting: head-and-neck cancers



Inês Leão

Unidade Local de Saúde de Santa Maria, Santa Maria, Portugal

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents a heterogenous group of diseases, and remains a major global health challenge, with survival rates for locally advanced disease showing limited improvement despite multimodal therapy strategies. The American Society of Clinical Oncology (ASCO) Annual Meeting is a premier global forum for presenting cutting-edge oncology research and clinical trials that shape future standards of care. The 2025 meeting highlighted pivotal phase III studies poised to redefine treatment paradigms in head and neck oncology. NIVOPOSTOP (GORTEC 2018-01) evaluated adjuvant nivolumab in resected high-risk HNSCC, while KEYNOTE-689 established the benefit of perioperative pembrolizumab. Updated results from KEYNOTE-412 assessed pembrolizumab combined with definitive chemoradiation in unresectable disease. Furthermore, the DIAMOND trial introduced a cisplatin-sparing immunotherapy regimen for nasopharyngeal carcinoma (NPC), aiming to maintain efficacy while reducing toxicity.

This review critically examines the latest phase III evidence supporting immune checkpoint inhibition in curative settings for HNSCC and emerging de-escalation approaches in NPC.

HNSCC

The integration of immune checkpoint inhibitors into the management of HNSCC is well established in the recurrent/metastatic setting. In first line, for tumors with programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥ 1, this approach is supported by the results of the KEYNOTE-048 trial, which led to the approval of pembrolizumab based on improved overall survival[1-4]. Nivolumab has also been approved for platinum-resistant disease following the results of the CHECKMATE-141 trial[5]. However, translating these benefits to earlier-stage disease has been challenging. Several phase III trials have failed to demonstrate statistically significant improvements in their primary endpoints, tempering the initial optimism surrounding immunotherapy in the curative setting[6-8].

The integration of immunotherapy in curative-intent settings is supported by the immunomodulatory effects of radiotherapy (RT), which promotes immunogenic cell death and the release of damage-associated molecular patterns, modulation of the tumor microenvironment, enhancing antigen presentation and dendritic cells activation and maturation[9]. In some cases, RT may induce systemic antitumor effects (abscopal responses)[9].

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However, RT also triggers immunosuppressive mechanisms, including PD-L1 upregulation, Treg expansion, lymphopenia, and impaired immune priming due to lymph node irradiation[9]. These opposing effects highlight both the promise and complexity of combining RT with immune checkpoint blockade in curative settings.

Resectable HNSCC

In resectable HNSCC, the standard adjuvant treatment–RT with or without cisplatin–has remained unchanged for over two decades[4,10]. This approach is based on a pooled analysis of two pivotal phase III trials (EORTC 22931 and RTOG 9501), which identified extracapsular extension (ECE) and positive margins as key pathological risk factors warranting the addition of high-dose cisplatin (100 mg/m^2 every 3 weeks) to RT[11].

Nivopostop trial (Gortec 2018-01)[12]

Phase III trial that enrolled 680 patients with resected, high-risk locally advanced HNSCC, randomizing them to receive either standard adjuvant chemo RT (CRT) or CRT combined with nivolumab. Eligible patients had high-risk features, including ECE, positive/close margins, ≥ 4 involved lymph nodes (without ECE), or multiple perineural invasions. With median follow-up of 30.3 months, the trial met its primary endpoint, showing improved 3-year disease-free survival (63.1% vs. 52.5%, hazard ratio [HR] 0.76), driven mainly by reduced locoregional recurrence. Distant metastasis rates were similar between arms. Treatment compliance was high. Acute toxicity was comparable, though the nivolumab arm had a modest increase in grade 4 toxicities (mainly renal disorder and dysphagia) without increased mortality. Overall survival data remain immature but suggest a numerical benefit with nivolumab.

Keynote-689[13]

This phase III trial investigated perioperative pembrolizumab in 714 patients with resectable, locally advanced HNSCC. Patients were randomized to standard of care (SOC) surgery followed by risk-adapted adjuvant RT ± high-dose cisplatin, or an experimental arm receiving two cycles of neoadjuvant pembrolizumab, surgery, then three cycles of adjuvant pembrolizumab with RT ± cisplatin (according to pathological risk-factors), followed by up to 12 maintenance pembrolizumab cycles. At a median follow-up of 38.3 months, the primary endpoint of event-free survival (EFS) was significantly improved in the pembrolizumab arm (modified EFS [mEFS] 51.8 vs. 30.4 months, HR 0.73). Subgroup analyses showed consistent benefits in PD-L1 CPS ≥ 10 (mEFS 59.7 vs. 26.9 months, HR 0.66) and CPS ≥1 (mEFS 59.7 vs. 29.6 months, HR 0.70). Major pathologic response rates with pembrolizumab were 9.4% overall and 13.7% in patients with CPS ≥ 10. Pathologic complete response rates were 3.0% and 4.3%, respectively. Distant metastasis free survival (DMFS) favored the pembrolizumab arm (metastatic DMFS [mDMFS] 51.8 vs. 35.7 months, HR 0.71), while locoregional failure rates were similar.

Discussion and clinical impact

The 2025 ASCO Annual Meeting spotlighted the evolving role of immunotherapy in resectable, locally advanced HNSCC, with pivotal data from the NIVOPOSTOP and KEYNOTE-689 trials. Despite differences in trial design, both studies were positive and demonstrated meaningful improvements in recurrence outcomes beyond standard trimodal therapy (Table 1).

In KEYNOTE-689, neoadjuvant pembrolizumab may raise concerns about pre-operative disease progression (12.4% vs. 1.2%) and surgical timing. Although surgery and adjuvant therapy completion rates were comparable, the longer neoadjuvant interval may pose risks for rapidly growing tumors. NIVOPOSTOP, in contrast, focused only on adjuvant nivolumab post-CRT, showing reduced locoregional recurrence, possibly favoring tumors with aggressive local behavior. Biomarker analyses revealed limited pathologic responses in PD-L1-negative tumors, casting doubt on the predictive value of CPS < 1 in the early-stage setting, although this group is underrepresented in KYENOTE-689 (3.8%) and NIVOPOSTOP (3.5%). Notably, pembrolizumab reduced the proportion of patients with high-risk pathology (11.9% lower in the pembrolizumab group) and subsequent adjuvant cisplatin use (11.6% fewer patients receiving adjuvant cisplatin), hinting at possible risk de-escalation benefits, though the long-term impact remains unproven. Overall, these findings support integrating immunotherapy into curative-intent strategies as new SOC, though optimal timing, patient selection, and long-term efficacy continue to warrant investigation.

Table 1. Trial characteristics

Trial	Combination	Treatment	Eligibility criteria	Risk population	Efficacy results
NIVOPOSTOP[12] (n = 680) Primary endpoint: DFS	Adjuvant	Nivolumab 1 cycle Nivolumab 3/3 w 3 cycles + cisplatin + RT 66 Gy Nivolumab 4/4 w 6 cycles	Larynx/hypopharynx/ oropharynx/oral cavity with: Complete ressection pStage III or IVA (II if HPV + oropharynx + T3/T4 + ≥ 20 UMA) High-risk pathological features of relapse Extracapsular extension Positive margins (R1 or close margins ≤ M1 mm) ≥ 4 positive cervical nodal involvements (without ECE) Multiple peri-neural invasion	High pathological risk. Intermedial pathological risk (10.5%)	ITT 3-year DFS 63.1% versus 52.5% (HR 0.76) PD-L1 CPS not strongly correlated with DFS, but most patients CPS > 1 (82%) Decrease the locoregional recurrence (39% vs. 61%, HR 0.63) Similar distant recurrence
Keynote-689[13] (n = 714) Primary endpoint: EFS	Neoadjuvant + adjuvant	Pembrolizumab 2 cycles Surgery High risk: Pembrolizumab 3/3 w 3 cycles + cisplatin + RT 66 Gy//Low risk:_ Pembrolizumab 3/3 w 3 cycles + RT 66 Gy Pembrolizumab 3/3 w 12 cycles	Ressectable locally advanced Larynx/hypopharynx/oral cavity III/IVA Oropharyngeal p16 - III/ IVA Oropharyngeal p16 + T4 N0-2	High and intermedial clinical risk	mEFS ITT - 51.8 versus 30.4 m (HR 0.73) PD-L1 CPS ≥ 10 (65% of the ITT) – 59.7 versus 26.9 m (HR 0.66) PD-L1 CPS ≥ 1 (96% of the ITT) – 59.7 versus 29.6 m (HR 0.70) Decrease the distant recurrence (35.7 vs. 51.8 months, HR 0.71) Similar locoregional recurrence.

CPS: combined positive score; DFS: disease free survival; ECE: extracapsular extension; EFS: event-free survival; HR: hazard ratio; ITT: intention to treat population; n: number; RT: radiotherapy; w: week, mEFS: modified event-free survival; PD-L1: programmed death-ligand 1.

Unresectable HNSCC

For the past two decades, definitive CRT with high-dose cisplatin has remained the SOC for patients with unresectable, locally advanced HNSCC[4,10,14]. Despite its curative intent, long-term outcomes remain suboptimal: up to 50% of patients experience locoregional recurrence, approximately 30% develop distant metastases, and 5-year overall survival hovers around 60%. These figures underscore the urgent need for novel strategies to improve durable disease control and survival in this population.

Keynote-412[15]

Phase III trial evaluating the addition of pembrolizumab to definitive CRT in 804 patients with locally advanced, high-risk, unresectable HNSCC. Patients received pembrolizumab, starting one cycle before CRT, continuing during CRT, and up to 14 maintenance cycles post-CRT, or placebo. Initial 4-year analysis showed no significant benefit[8]. However, updated data with 74.4 months median follow-up revealed a significant improvement in EFS (mEFS 71.8 vs. 49.8 months, HR 0.79). The primary benefit was in DMFS (mDMFS NR vs. 64.3 months, HR 0.80). Median OS was not reached (NR) in either arm, with curve separation after year 3 (60-month OS 64.4% vs. 59.8%). Subgroup analyses showed greater benefit in PD-L1 positive tumors: for CPS ≥ 1, mEFS 70.9 versus 48.3 months (HR 0.80), mOS NR versus NR (HR 0.84); for CPS ≥ 20, mEFS NR versus 65.9 months (HR 0.70), mOS NR versus NR (HR 0.73).

Discussion and clinical impact

Although early analyses were negative, the extended data suggests a clinically meaningful long-term benefit, with an absolute improvement of 7.5% in 5-year EFS, along with improved DMFS in the pembrolizumab arm, supporting a role in enhanced systemic disease

Table 2. Summary of phase III clinical trials investigating the addition of immunotherapy to locally advanced NPC treatment

Trial	Combination	Experimental arm	Eligibility criteria	Primary endpoint	Preliminary results
Beacon[19] (n = 450)	Induction + adjuvant	Tislelizumab + IC 3 cycles CCRT Tislelizumab 8 cycles	III-VA (except T3N0, or T3N1 with retropharyngeal positive lymph nodes)	CCR after induction therapy 3-year PFS	CCR 30.5% versus 16.7% (p < 0.001) ORR 93.3% versus 90.7%
Dipper[20] (n = 450)	Adjuvant	CCRT -> camrelizumab 12 cycles	III-IVA (T4N1 or T1-4N2-3)	3-year EFS	3-year EFS: 86.9% versus 77.4% (HR 0.61)
Continuum[18] (n = 425)	Full course	Sintilimab + IC 3 cycles -> Sintilimab 3 cycles + CCRT Sintilimab 6 cycles	III-IVA (except T3-4N0 or T3N1)	3-years EFS	3-year EFS: 86.1% versus 76.0% (HR 0.59) 3-year OS: 92.8% versus 92.9% (HR 0.95)

CCR: clinical complete response; CCRT: concomitant chemoradiotherapy; EFS: event free survival; HR: hazard ratio; IC: induction chemotherapy; N: number; ORR: overall response rate; PFS: progression free survival; OS: overall survival.

control. Notably, OS curves separated late, potentially due to the high proportion of human papillomavirus -positive tumors (26.5%) and stage III disease (34.5%), both associated with more favorable prognoses. The benefit was more pronounced in patients with higher PD-L1 expression, especially those with a CPS ≥ 20. These findings reinforce the relevance of PD-L1 as a potential predictive biomarker and underscore the importance of long-term follow-up to fully capture the therapeutic impact of immunotherapy in this setting.

NPC

The SOC for locally advanced NPC in Western guidelines involves induction chemotherapy with gemcitabine and cisplatin, followed by high-dose cisplatin-based concurrent CRT, but this regimen is associated with considerable toxicity[10,16,17]. In endemic regions, emerging phase III data support integrating immunotherapy into the treatment paradigm. Three recent trials in China demonstrated improved 3-year EFS (from 76% to 86% in CONTINUUM trial[18]) and increased complete response rates (from 17% to 31% in BEACON trial[19]) with the addition of immune checkpoint inhibitors, irrespective of PD-L1 expression[18-20]. This shift is biologically supported, as NPC is highly immunogenic, Epstein-Barr virus (EBV)-associated, and shows high PD-L1 expression. De-escalation strategies are also under investigation. The phase II PLATINUM trial evaluated nivolumab with gemcitabine–cisplatin induction followed by RT without concurrent cisplatin, yielding 88.5% 3-year failure-free survival (FFS) with reduced grade 3-4 toxicities, highlighting a potential safer alternative[21].

DIAMOND[22]

A phase III trial investigating a cisplatin-free strategy in locally advanced NPC, randomizing 532 patients to receive toripalimab plus induction chemotherapy (gemcitabine/cisplatin) followed by RT alone (experimental arm) or standard induction chemotherapy followed by concurrent high-dose cisplatin-based CRT (SOC arm). Toripalimab was given for 17 cycles in both arms. The trial had two co-primary endpoints: FFS (FFS; tested for non-inferiority) and the incidence of any-grade vomiting (tested for superiority). At a median follow-up of 36 months, 3-year FFS was 88.3% in the experimental arm versus 87.6% in the SOC arm, meeting the non-inferiority criterion. Vomiting of any grade was significantly lower in the experimental arm (25.6% vs. 69.0%). Grade 3-4 adverse events (AEs) (52.3% vs. 63.6%) and immune-related AEs (5.0% vs. 8.4%) were also reduced. Patient-reported quality of life was better across multiple domains, supporting this cisplatin-free approach as a less toxic alternative without compromising efficacy.

Discussion and clinical impact

NPC is rare in Europe, with only 4,500 cases annually, representing 3.7% of global incidence, compared to over 80% of cases occurring in Asia[23]. Most phase III trials, including DIAMOND, focus on endemic populations. NPC in non-endemic regions shows greater biological heterogeneity and worse prognosis[24], raising questions about applying DIAMOND's cisplatin-free immunotherapy results to Western patients. Despite this, most tumors in Europe are EBV-positive

and exhibit high PD-L1 expression along with prominent lymphocytic infiltration, supporting the use of immunotherapy[25]. DIAMOND suggests a promising, less toxic treatment approach, but longer follow-up and validation, ideally in non-endemic settings, are needed before broader European adoption.

Conclusion

The 2025 ASCO Annual Meeting marked a pivotal moment in head and neck oncology, reinforcing the expanding role of immunotherapy in curative-intent treatment. Phase III data support the integration of immune checkpoint inhibitors in resectable HNSCC–and potentially in unresectable cases–with sustained benefits. In NPC, immunotherapy-based de-escalation strategies show promise in preserving efficacy while minimizing treatment-related toxicity. Collectively, these findings reflect a move toward more personalized and less toxic curative approaches, highlighting the need for continued research and thoughtful clinical implementation.

References

1. Harrington KJ, Burtness B, Greil R, Soulieres D, Tahara M, De Castro G Jr., et al. Pembrolizumab with or without chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma: updated results of the phase III KEYNOTE-048 study. J Clin Oncol. 2022;41:790-801.
2. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, De Castro G Jr., et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019;394:1915-28.
3. Burtness B, Rischin D, Greil R, Soulieres D, Tahara M, De Castro G Jr., et al. Pembrolizumab alone or with chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma in KEYNOTE-048: subgroup analysis by programmed death ligand-1 combined positive score. J Clin Oncol. 2022;40:2321-32.
4. Machiels JP, Rene Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V, et al. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:1462-75.
5. Ferris RL, Blumenschein G Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016;375:1856-67.
6. Mell LK, Torres-Saavedra PA, Wong SJ, Kish JA, Chang SS, Jordan RC, et al. Radiotherapy with cetuximab or durvalumab for locoregionally advanced head and neck cancer in patients with a contraindication to cisplatin (NRG-HN004): an open-label, multicentre, parallel-group, randomised, phase 2/3 trial. Lancet Oncol. 2024;25:1576-88.
7. Tao Y, Auperin A, Sun X, Sire C, Martin L, Coutte A, et al. Avelumab-cetuximab-radiotherapy versus standards of care in locally advanced squamous-cell carcinoma of the head and neck: the safety phase of a randomised phase III trial GORTEC 2017-01 (REACH). Eur J Cancer. 2020;141:21-9.
8. Machiels JP, Tao Y, Licitra L, Burtness B, Tahara M, Rischin D, et al. Pembrolizumab plus concurrent chemoradiotherapy versus placebo plus concurrent chemoradiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (KEYNOTE-412): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2024;25:572-87.
9. Sharon S, Daher-Ghanem N, Zaid D, Gough MJ, Kravchenko-Balasha N. The immunogenic radiation and new players in immunotherapy and targeted therapy for head and neck cancer. Front Oral Health. 2023;4:1180869.
10. Head and neck cancer. NCCN clinical practice guidelines in oncology. 2025.
11. Bernier J, Cooper JS, Pajak TF, Van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27:843-50.
12. Bourhis J, Auperin A, Borel C, Lefebvre G, Racadot S, Geoffrois L, et al. NIVOPOSTOP (GORTEC 2018-01): a phase III randomized trial of adjuvant nivolumab added to radio-chemotherapy in patients with resected head and neck squamous cell carcinoma at high risk of relapse. J Clin Oncol. 2025;43:LBA2.
13. Adkins D, Haddad RI, Tao Y, Tourneau CL, Lee NY, Sindhu K, et al. Neoadjuvant and adjuvant pembrolizumab plus standard of care (SOC) in resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC): exploratory efficacy analyses of the phase 3 KEYNOTE-689 study. J Clin Oncol. 2025;43:6012.
14. Lacas B, Carmel A, Landais C, Wong SJ, Licitra L, Tobias JS, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC group. Radiother Oncol. 2021;156:281-93.
15. Tao Y, Siu LL, Licitra LF, Burtness B, Tahara M, Rischin D, et al. Long-term results of the randomized, phase 3 KEYNOTE-412 trial of pembrolizumab (pembro) or placebo (pbo) plus concurrent chemoradiotherapy (CRT) for unresected, locally advanced head and neck squamous cell carcinoma (LA HNSCC). J Clin Oncol. 2025;43:6013.
16. Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, et al. Nasopharyngeal carcinoma: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up(dagger). Ann Oncol. 2021;32:452-65.
17. Zhang Y, Chen L, Hu GQ, Zhang N, Zhu XD, Yang KY, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. N Engl J Med. 2019;381:1124-35.
18. Liu X, Zhang Y, Yang KY, Zhang N, Jin F, Zou GR, et al. Induction-concurrent chemoradiotherapy with or without sintilimab in patients with locoregionally advanced nasopharyngeal carcinoma in China (CONTINUUM): a multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial. Lancet. 2024;403:2720-31.
19. Mai HQ, Liu SL, Chen QY, Tang LQ, Jin F, Guo L, et al. Tislelizumab versus placebo combined with induction chemotherapy followed by concurrent chemoradiotherapy and adjuvant tislelizumab or placebo for locoregionally advanced nasopharyngeal carcinoma: interim analysis of a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial. J Clin Oncol. 2024;42:6001.
20. Liang YL, Liu X, Shen LF, Hu GY, Zou GR, Zhang N, et al. Adjuvant PD-1 blockade with camrelizumab for nasopharyngeal carcinoma: the DIPPER randomized clinical trial. JAMA. 2025;333:1589-98.
21. Xu C, Zhou GQ, Li WF, Hu DS, Chen XZ, Lin SJ, et al. Nivolumab combined with induction chemotherapy and radiotherapy in nasopharyngeal carcinoma: a multicenter phase 2 PLATINUM trial. Cancer Cell. 2025;43:925-36.e4.
22. Ma J, Sun Y, Xu C, Shen L, Jin F, Yang K, et al. PD-1 blockade with toripalimab incorporated into induction chemotherapy and radiotherapy with or without concurrent cisplatin in locoregionally advanced nasopharyngeal carcinoma (DIAMOND): a multicenter, non-inferiority, phase 3, randomized controlled trial. J Clin Oncol. 2025;43:LBA6003.
23. Cancer Today - Nasopharyngeal Carcinoma. GLOBOCAN. 2022.
24. Bossi P, Trama A, Bernasconi A, Grisanti S, Mohamad I, Galiana IL, et al. Nasopharyngeal cancer in non-endemic areas: impact of treatment intensity within a large retrospective multicentre cohort. Eur J Cancer. 2021;159:194-204.
25. Minichsdorfer C, Oberndorfer F, Krall C, Kornek G, Mullauer L, Wagner C, et al. PD-L1 expression on tumor cells is associated with a poor outcome in a cohort of caucasian nasopharyngeal carcinoma patients. Front Oncol. 2019;9:1334.

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Molecularly targeted agents and tumor biology



Ana Rodrigues

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Regarding the area of "Developmental Therapeutics Molecularly Targeted Agents and Tumor Biology," the presentations selected were:

- Abstract 3002 – Phase I study of iza-bren (BL-B01D1), an epidermal growth factor receptor × human epidermal growth factor receptor 3 (EGFR × HER3) bispecific antibody-drug conjugate (ADC), in patients (pts) with locally advanced or metastatic small cell lung cancer (SCLC).
- Abstract 3004 – Efficacy and safety of the Delta-like ligand 3 (DLL3)/CD3 T-cell engager obrixtamig in pts with extrapulmonary neuroendocrine carcinomas (epNEC) with high or low DLL3 expression – Results from an ongoing phase I trial.
- Abstract 2501 – First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA-encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in pts with CLDN6-positive advanced solid tumors.

Iza-bren (BL-B01D1) is a first-in-class ADC composed of an EGFR × HER3 bispecific antibody conjugated to a topo-I inhibitor payload (Ed-04). Unlike existing ADCs, which typically target general tumor antigens, iza-bren specifically targets EGFR and HER3 pathways, both of which are implicated in the aggressive biology of SCLC. This phase 1 study (3002) included 58 pts with locally advanced or metastatic SCLC who had progressed on prior systemic therapies, with a median follow-up of 16.4 months. In the overall population, the confirmed overall response rate (ORR) was 44.8%, median progression-free survival (PFS) was 4.0 months, and median overall survival (OS) was 12.0 months. A promising efficacy was seen in 20 of the 52 patients treated at 2.5 mg/kg, who had progressed after only one prior line of PD(L)-1 and platinum-based chemotherapy. In this subgroup, the confirmed ORR was 75.0%, the median duration of response (DOR) was 5.6 months, the median PFS was 6.9 months, and the median OS was 15.1 months. Regarding the safely profile, the most frequent treatment related adverse events (TRAE) (all grades) were anemia (84.5%), leukopenia (74.1%), thrombocytopenia (72.4%), and neutropenia (70.7%); the most frequent non-hematologic TRAEs were asthenia (41.4%), hypoalbuminemia (39.7%), stomatitis (34.5%), nausea (31.0%), and vomiting (31.0%); the discontinuation rate was 12.1% and no interstitial lung disease was observed. These results position iza-bren as a promising novel therapeutic option for SCLC, a disease that has seen limited advancements in treatment over the decades. A phase III study comparing iza-bren to topotecan as a second-line treatment in SCLC patients who received one prior line of PD(L)-1 and platinum-based chemotherapy is currently underway (NCT06500026) in China. However, considering the results presented at the American Society of Clinical Oncology regarding tarlatamab as a second-line treatment (DeLLphi304), questions may arise about the selected control arm for that trial[1].

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Moving on to obrixtamig (BI 764532), a DLL3/CD3 immunoglobulin G-like T-cell engager. The phase I dose-escalation trial NCT04429087 evaluated the efficacy of obrixtamig in patients with pulmonary and epNEC DLL3-positive (DLL3+), who did not respond to standard treatments. Abstract 3004 specifically highlights the results for epNEC DLL3+ (60 patients), further divided based on DLL3 expression levels into high (30 patients) versus low (30 patients), using a threshold of and ≥ 50% tumor cells stained with an investigational antibody for DLL3 (SP347, Roche Diagnostics). Gastroenteropancreatic NETs were the most common NECs included (45%), followed by genitourinary NECs (30%) and NECs from other or unknown primary sites (25%). The average age was 69 years in the DLL3-high group compared to 61 years in the DLL3-low group. A higher proportion of patients in the DLL3-low group had undergone more than two previous lines of treatment (50% versus 30%). Patients with epNEC DLL3-high demonstrated better outcomes in ORR, disease control rate (DCR), and DOR compared to those with DLL3-low expression, regardless of the primary tumor site's origin. For the DLL3-high group, the ORR was 40%, DCR was 67%, and the average DOR was 7.9 months. In contrast, the DLL3-low group showed an ORR of 3%, a DCR of 27%, and an average DOR of 2.8 months. Most TRAEs were mild-to-moderate across both groups, with cytokine release syndrome (CRS), pyrexia, dysgeusia, and asthenia being the most frequently observed side effects[2].

These promising findings highlight obrixtamig's potential for further exploration in this context. A Phase II trial (DAREON-5) is currently underway to evaluate obrixtamig in patients with relapsed or refractory DLL3-high epNEC[2].

Finally, BNT142 is a prodrug in the form of an mRNA encapsulated in a lipidic nanoparticle. The final drug, RiboMab02.1, is an anti-CLDN6/CD3 bispecific antibody. Claudin 6 is an oncofetal tight junction protein silenced in normal adult tissues, but aberrantly activated in some tumors such as testicular, ovarian, and non-SCLC (NSCLC), making it an excellent target. Abstract 2501 presents the results of 65 patients with CLDN6+ metastatic or unresectable solid tumors, including ovarian cancer, germ cell tumors, non-squamous NSCLC, and other rare cancers, who had undergone all available standard therapies and were enrolled in the trial. The median age was 57 years, with the majority being female (75%) and presenting an Eastern Cooperative Oncology Group performance status of 1 (60%). Most patients were heavily pre-treated, with 66.2% having received at least four lines of prior therapy (median of five lines, range of 1-14). Ovarian cancer was the most common cancer (67.7%), predominantly platinum-resistant ovarian cancer (77.3%), followed by germ cell tumors (18.5%) and NSCLC (7.7%). BNT142-01 presented encouraging preliminary anti-tumor activity in heavily pre-treated cancer patients, with most of the responses in ovarian cancer, particularly in platinum-resistant cancer. In ovarian cancer, seven partial responses and a DCR of 76.2% were observed. Regarding the exploratory analysis of CLDN6 expression levels and RECIST 1.1 response, no correlation was found. Most TRAEs were mild-to-moderate (63%), and the most common were CRS (22%) and aspartate or alanine aminotransferase increased[3].

BNT142 stands as the first clinical proof-of-concept for an mRNA-encoded bispecific T-cell engager antibody produced *in vivo*, demonstrating some activity, particularly in platinum-resistant ovarian cancer.

In summary, Iza-bren and obrixtamig emerge as promising therapies for diseases with poor prognoses and unmet treatment needs. Meanwhile, BNT142 paves the way for mRNA-encoded drugs in cancer therapy, extending beyond anti-cancer vaccines.

References

1. Yunpeng Yang, Li Zhang, Yuxiang Ma, Yuanyuan Zhao, Wenfeng Fang, Hongyun Zhao, et al. Phase I study of iza-bren (BL-B01D1), an EGFR x HER3 bispecific antibody-drug conjugate (ADC), in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with driver genomic alterations (GA) outside of classic EGFR mutations. Journal of Clinical Oncology 2025, Volume 43, Number 16_suppl. https://doi.org/10.1200/JCO.2025.43.16_suppl.3001
2. Capdevila J, Gambardella V, Kuboki Y, Alese O.B., Morgensztern D, Sayehli C, et al. Efficacy and Safety of the Dll3/Cd3 T-Cell Engager Obrixtamig in PTS with Extrapulmonary Neuroendocrine Carcinomas (Epnec) with High or Low Dll3 Expression - Results from an Ongoing Phase I Trial. Journal of Clinical Oncology 2025 Volume 43, Number 16_suppl https://doi.org/10.1200/JCO.2025.43.16_suppl.3004
3. Yap TA, Hernando-Calvo A, Calvo E, Moreno V, Marquez R, Papadopoulos KP, et al. First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in patients (pts) with CLDN6-positive advanced solid tumors. J Clin Oncol. 2025;43(16_suppl). https://doi.org/10.1200/JCO.2025.43.16_suppl.2501

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Highlights from the 2025 ASCO annual meeting: central nervous system



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Stereotactic radiation versus hippocampal avoidance whole brain radiation in patients with 5-20 brain metastases: A multicenter, phase 3 randomized trial

Prior trials have demonstrated that stereotactic radiosurgery (SRS)/stereotactic radiotherapy (SRT) yields better outcomes than traditional whole brain radiotherapy (WBRT) in patients with 1-4 brain metastases, and that hippocampal avoidance WBRT (HA-WBRT) is superior to traditional WBRT. Despite that, trials for more than 4 brain metastases are lacking, and there are no head-to-head comparisons between stereotactic radiation and HA-WBRT.

In a clinical science symposium, Dr Ayal Aizer presented the results of a multicenter, phase 3 trial that compared stereotactic radiation versus HA-WBRT in patients with 5-20 brain metastases. The primary endpoint was symptom severity and interference in daily activities, which was accessed by an *MD Anderson symptom inventory brain tumor questionnaire*, at baseline and after 6 months. Other outcomes were performance status, ability to complete activities of daily living, neurocognitive function, recurrence, and salvage therapy, among others. Between april 2017 and may 2024, 196 patients were enrolled, with a median number of brain metastases of 14, mainly from non-small cell lung cancer (47%) or breast cancer (20%). This study demonstrated that SRS/SRT reduces symptom severity and interference with daily function compared to HA-WBRT, without compromising survival. Patients experienced less symptoms such as pain, nausea, sleep, memory, speech, and humor disorders. Similarly, the ability to work and self-care was less impaired. Performance status, ability to complete daily activities, and many neurocognitive domains were also spared by SRS/SRT as opposed to HA-WBRT. Thus, the authors propose that SRS/SRT should represent the radiotherapeutic standard of care for most patients with 5-20 brain metastases.

Initial report of memory avoidance WBRT (MA-WBRT) to treat brain metastases: A prospective phase 2 trial

Still within the scope of brain radiotherapy (RT), a prospective phase 2 trial was presented as a poster and compared HA-WBRT plus memantine with "memory avoidance" WBRT. This approach is based on the knowledge that there are other structures, beyond the hippocampus, with important roles in memory and cognition, including the corpus callosum, fornix, amygdala, hypothalamus, and pituitary. They have a low propensity for harboring brain metastases and can be safely spared in an RT plan without increasing the risk of relapse and, hopefully, with less cognitive decline. Patients with more than 15 brain metastases were randomized to either MA-WBRT (30 Gy in 10 fractions) plus memantine (with or without neuropsychological evaluation and intervention). Cognition was measured by multiple tests evaluating verbal learning and memory, verbal fluency, and executive function. Results were compared with a historical control of the phase 3 NRG

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CCOO1 trial, conducted in 2020, which validated the standard of treatment with HA-WBRT plus memantine for patients with brain metastases. The cognitive decline rates of 17.2% and 48.3% at 3 and 6 months for patients receiving MA-WBRT compared very favorably to 3 and 6-month cognitive decline rates of 50% and 60% that were seen on NRG CC001 with HA-WBRT. In addition, MA-WBRT does not appear to significantly increase the risk of intracranial failure. These promising preliminary results must be fully evaluated in a randomized phase 3 trial.

Final clinical and molecular analysis of the EORTC randomized phase 3 intergroup CATNON trial on concurrent and adjuvant temozolomide (TMZ) in anaplastic glioma without 1p/19q codeletion: NCT00626990

This year, the final clinical and molecular analysis of the CATNON trial, which studied the role of concurrent and adjuvant TMZ in anaplastic glioma without 1p/19q codeletion, was presented at ASCO. This trial, with a unique 2^2 factorial design, randomized 751 adult patients with newly diagnosed non-codeleted anaplastic glioma to either: 59.4 Gy RT alone; RT with concurrent TMZ; RT and 12 cycles of adjuvant TMZ, or RT with both concurrent and 12 cycles of adjuvant TMZ. In 660 patients, IDH status could be determined: isocitrate dehydrogenase (IDH) was mutant (mt) in 444 tumors and wild type (wt) in 216 tumors.

After a median follow-up of 10.9 years, the benefit from adjuvant TMZ on overall survival (OS) in patients with IDH-mut tumors was clear. Still, no benefit of concurrent TMZ was observed regardless of IDH mutation status. The benefit of adjuvant TMZ was limited to patients with anaplastic glioma IDH-mut, of which 45% were still alive, with a median OS of 12.5 years. In exploratory analysis, molecular factors of known prognostic significance, such as high-copy number amplification of PDGFR and CDK4, homozygous deletion of the CDKN2A/B locus, or total copy number alterations, were not predictive of benefit from TMZ. In summary, the standard of post-operative care in patients with high-grade IDHmt astrocytoma should be RT followed by 12 cycles of adjuvant TMZ.

Risk of intracranial hemorrhage with direct oral anticoagulants (DOACs) versus low molecular weight heparin (LMWH) in patients with cancer-associated thrombosis and brain metastases

Finally, some notes on a very important work for clinical practice.

Cancer-associated thrombosis is a major complication in cancer patients, significantly increasing morbidity and mortality. There is also an increased risk of bleeding in patients with cancer on anticoagulants compared with those without cancer, and patients with brain metastases, particularly those with high-risk primary tumors, have an increased risk of intracranial hemorrhage. However, only a minority of patients with brain metastases are included across landmark trials.

This retrospective study enrolled over 8400 patients with solid tumors, mainly with lung (51.9%) and breast (16.2%) cancer, who developed a thromboembolic event within 6 months of brain metastases diagnosis. Therapeutic approaches were compared between DOACs, such as apixaban, rivaroxaban, edoxaban, and LMWH, regarding intracranial hemorrhage incidence, bleeding events, intensive care unit (ICU) admissions, and all-cause mortality. DOACs were associated with a statistically significant lower risk of intracranial hemorrhage incidence (hazard ratio: 0.855, 95% confidence interval: 0.731-0.999, $p = 0.049$), supporting their role as a viable and well-tolerated alternative. In addition, significantly lower rates of ICU admission (16.7% vs. 20.3%; $p = 0.001$) and all-cause mortality at 12 months (42.4% vs. 48.9%; $p = 0.001$) were observed in the DOAC group, indicating that they also have a favorable profile and can be safely used, without significant differences by cancer type.

In general, all these studies highlight the path that is being traced in oncology, toward more individualized and patient-centered strategies.

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BREAST CANCER

Breast cancer panel: summary of 5 key studies



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At the Best of ASCO 2025 meeting hosted by the Portuguese Society of Oncology, five studies were presented in the Breast Cancer panel, all considered relevant to present clinical practice. One focused on early-stage breast cancer (NeoCARHP), while the remaining studies addressed advanced breast cancer (aBC), including two on luminal human epidermal growth factor receptor (HER2)-negative subtypes (inavolisib [INAVO]120 and SERENA-6), one on triple negative breast cancer (ASCENT-04/KEYNOTE-D19), and one on HER2-positive disease (DESTINY-Breast09).

Below is a summary of each of these studies:

De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP): a multicenter, open-label, randomized, phase 3 trial

Phase III non-inferiority trial, which aimed to evaluate the efficacy and safety of de-escalating treatment in HER2-positive early breast cancer. The study compared taxane (docetaxel, paclitaxel, or nab-paclitaxel) given every 3 weeks for six cycles, trastuzumab, and pertuzumab (THP), with or without carboplatin, in the neoadjuvant setting. A total of 774 previously untreated patients with stage II-III tumors (77% being stage II) were included. The primary endpoint, pathological complete response (pCR), met the non-inferiority criteria, with a difference of only 1.8% between arms: 64.1% in the arm without carboplatin and 65.9% in the arm with carboplatin. When stratified by hormone receptor (HR) status, the difference in pCR was just 0.4% in HR-negative tumors (77.8 and 78.2% with and without carboplatin, respectively) and 3% in HR-positive tumors (58.8 vs. 55.8%, with and without carboplatin, respectively). The group treated with carboplatin had a higher number of partial and complete responses (364 vs. 351). The rate of adverse events (AEs) was also higher in the carboplatin group, especially hematologic toxicity, with twice as many cases of febrile neutropenia. The overall AE profile was also more common with carboplatin. Despite demonstrating that THP without carboplatin is non-inferior in terms of pCR, this study has limitations, including the use of taxanes every 3 weeks (less effective than weekly paclitaxel) and the fact that only about one-quarter of patients had stage III tumors. Therefore, further follow-up (FUP) is needed for more robust evidence supporting this de-escalation strategy in stage III disease.

INAVO120: phase III trial final overall survival (OS) analysis of first-line (1L) INAVO/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with *PIK3CA*-mutated, HR-positive (HR+), HER2-negative (HER2–), endocrine-resistant aBC

The INAVO120 trial evaluated the use of INAVO or PBO, in combination with PALBO and FULV, as 1L

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treatment for advanced, endocrine-resistant breast cancer with *PIK3CA* mutations. Patients with fasting glucose above 126 mg/dL or HbA1c above 6% were excluded. The trial included 325 patients and the primary endpoint, progression-free survival (PFS), had been previously reported, showing a median of 15 months in the INAVO arm versus 7.3 months in the PBO arm (hazard ratio 0.43; 95% confidence interval [CI] 0.32-0.59; p < 0.0001), with a median FUP of 21 months. At ASCO 2025, final OS results were presented: 34 months in the INAVO group versus 27 months in the PBO group (hazard ratio 0.67; 95% CI 0.48-0.94; p = 0.0190), with a median FUP of 34.2 months. Updated PFS was 17.2 months in the triplet group versus 7.3 months in the PBO group (hazard ratio 0.42; 95% CI = 0.32-0.55). The objective response rate and duration of response were significantly higher with the INAVO combination (62.7 vs. 28%; 95% CI 24.5-44.8; p < 0.0001; duration of 19.2 vs. 11.1 months, respectively). INAVO also delayed the time to chemotherapy by approximately 2 years (35.6 vs. 12.6 months; hazard ratio 0.43; 95% CI = 0.30-0.60). Grade 3-4 AEs occurred in 90.7% of patients in the INAVO arm and 84.7% in the PBO arm, with more treatment discontinuations (6.8 vs. 0.6%) and more grade 5 AEs (6 vs. 2) in the INAVO group. Common toxicities of INAVO included hyperglycemia, stomatitis, and dry eye. Notably, few control-arm patients received PI3K inhibitors after progression, which may have impacted OS results. Other limitations include the exclusive use of PALBO rather than other CDK4/6 inhibitors, such as ribociclib or abemaciclib, and the low proportion of patients who had received adjuvant CDK4/6 inhibitors, which may limit the study's applicability to present clinical practice.

Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the treatment of emergent ESR1 mutations during 1L endocrine-based therapy (ET) and ahead of disease progression in patients (pts) with HR+/HER2–aBC: phase 3, double-blind ctDNA-guided SERENA-6 trial

The SERENA-6 trial investigated whether switching from an aromatase inhibitor to camizestrant upon the emergence of ESR1 mutations (detected in circulating tumor DNA) and before progression of disease, would improve PFS in patients with HR-positive HER2-negative metastatic breast cancer receiving 1L endocrine therapy plus CDK4/6 inhibitors. A total of 315 patients were randomized. All were on a combination of aromatase inhibitor and CDK4/6 inhibitor for at least 6 months, with over 70% on PALBO—a choice that may not reflect present clinical practice. Median PFS was 16 months in the camizestrant arm versus 9.2 months in the aromatase inhibitor arm (hazard ratio 0.44; 95% CI 0.31-0.60; p < 0.00001), with this benefit observed across nearly all subgroups. Camizestrant also significantly extended time to quality-of-life deterioration (23 vs. 6.4 months; hazard ratio 0.53; 95% CI 0.33-0.82, p < 0.001). Notably 10% more patients in the experimental arm received chemotherapy after disease progression (45.6 vs. 22.9%) when compared to the control arm. Camizestrant was associated with more grade ≥ 3 AEs (60 vs. 46%), but not with higher rates of treatment discontinuation (1.3 vs. 1.9%). A typical side effect of camizestrant, photopsia, did not impact daily activities and it didn't impair vision or eye structure. Since cross-over was not permitted in the trial, it remains unclear whether switching therapy upon ESR1 mutation detection leads to better outcomes than switching only at disease progression (i.e., using camizestrant as a second-line therapy).

Sacituzumab govitecan (SG) + pembrolizumab (pembro) versus chemotherapy (chemo) + pembro in previously untreated PD-L1-positive advanced triple-negative breast cancer (TNBC): primary results from the randomized phase 3 ASCENT-04/KEYNOTE-D19 study

The *ASCENT-04/KEYNOTE-D19* study was a phase III trial evaluating SG plus pembrolizumab versus chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine with carboplatin) plus pembrolizumab in 1L treatment of PD-L1-positive (CPS ≥ 10; 22C3 assay) advanced TNBC. Patients needed to have completed prior curative treatment at least 6 months earlier, and prior use of anti-PD-(L)1 agents was allowed. Of the 443 randomized patients, most had visceral disease, 34% in each arm had *de novo* metastatic disease, and 48% had a disease-free interval of over 12 months; 18% had recurrence within 6-12 months. Only 20 patients had previously received an anti-PD-(L)1 therapy. With a median FUP of 14 months, the primary endpoint of PFS was 11.2 months in the SG + pembrolizumab arm versus 7.8 months in the chemotherapy + pembrolizumab arm (hazard ratio 0.65; 95% CI 0.51-0.84; p = 0.0009), with benefits observed across nearly all subgroups. OS data remain immature. Notably, 81% of

patients in the control arm who received further treatment after discontinuation were treated with SG. The duration of response was substantially longer in the SG+pembrolizumab arm (16.5 vs. 9.2 months). Diarrhea, nausea, and vomiting were more frequent with SG + pembrolizumab, but the incidence of grade ≥ 3 AEs was similar between arms. The combination of SG and pembrolizumab did not lead to more treatment discontinuations or dose reductions compared to chemotherapy with pembrolizumab.

Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) versus taxane + trastuzumab + pertuzumab (THP) for 1L treatment of patients (pts) with HER2+ advanced/metastatic breast cancer (a/mBC): interim results from DESTINY-Breast09:

Finally, the DESTINY-Breast09 trial evaluated trastuzumab deruxtecan (T-DXd) with pertuzumab versus taxane plus trastuzumab and pertuzumab (THP) as 1L treatment for HER2-positive advanced or metastatic breast cancer. A total of 1157 patients were randomized. Eligible participants had to have completed curative-intent treatment at least 6 months prior, and one prior line of hormone therapy for metastatic disease was allowed. Although the study had three arms (T-DXd with PBO, T-DXd with pertuzumab, and THP), only the latter two were presented in this analysis. T-DXd was administered until disease progression, while the taxane was given for at least six cycles. In the event of T-DXd discontinuation due to AEs, patients could receive trastuzumab (with pertuzumab or with PBO) depending on their original assignment. Endocrine therapy was permitted in HR-positive tumors after six T-DXd cycles or upon taxane discontinuation, but it was used in only 13.5% of patients in the T-DXd arm and 38.3% in the THP arm. Anti-HER2 therapy usage in early disease was relatively low: 56.6% had received trastuzumab, 14.3% pertuzumab, and 1.8% T-DM1. With a median FUP of 29.2 months, PFS was significantly improved in the T-DXd plus pertuzumab arm (40.7 vs. 26.9 months; hazard ratio 0.56; 95% CI 0.44-0.71; $p < 0.00001$), with benefit observed across nearly all subgroups. The rate of complete responses nearly doubled (15.1 vs. 8.5%), and the median duration of response exceeded 3 years. In the control arm, 10% later received T-DXd and 12% received T-DM1. Second PFS2 showed a hazard ratio of 0.60. OS data are still immature. Grade 3-4 AE rates were similar between arms and T-DXd-related pneumonitis occurred in 12% of patients, mostly grade 1-2, with two grade 5 events.

Clinicians are left with unanswered questions regarding optimal treatment duration, sequencing, and patient selection, as it remains unclear who truly benefits from this strategy versus those who may have durable responses to the present standard of care without the added potential toxicities of T-DXd.

References

1. Gao HF, Li W, Wu Z, Dong J, Cao Y, Zhao Y, et al. De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP): a multicentre, open-label, randomised, phase 3 trial. J Clin Oncol. 2025;43:LBA500.
2. Turner NC, Im SA, Saura C, Juric D, Loi S, Jin Y, et al. INAVO120: phase III trial final overall survival (OS) analysis of first-line inavolisib (INAVO)/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV) in patients (pts) with PIK3CA-mutated, hormone receptor-positive (HR+), HER2-negative (HER2-), endocrine-resistant advanced breast cancer (aBC). J Clin Oncol. 2025;43:1003.
3. Turner NC, Mayer EL, Park YH, Janni W, Ma CX, Fox S, et al. Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the treatment of emergent ESR1 mutations during first-line (1L) endocrine-based therapy (ET) and ahead of disease progression in patients (pts) with HR+/HER2- advanced breast cancer (ABC): phase 3, double-blind ctDNA-guided SERENA-6 trial. J Clin Oncol. 2025;43:LBA4.
4. Tolaney SM, De Azambuja E, Kalinsky K, Loi S, Kim SB, Yam C, et al. Sacituzumab govitecan (SG) + pembrolizumab (pembro) vs chemotherapy (chemo) + pembro in previously untreated PD-L1-positive advanced triple-negative breast cancer (TNBC): primary results from the randomized phase 3 ASCENT-04/KEYNOTE-D19 study. J Clin Oncol. 2025;43:LBA109.
5. Tolaney SM, Zhang Q, Barroso-Sousa R, Park YH, Rimawi MF, Manich CS, et al. Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for first-line (1L) treatment of patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) advanced/metastatic breast cancer (a/mBC): interim results from DESTINY-breast09. J Clin Oncol. 2025;43:LBA1008.

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SKIN CANCER

Best of ASCO 2025 narrative review article – Skin cancer



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DREAMseq: A phase III trial of treatment sequences in BRAFV600-mutant (m) metastatic melanoma (MM) – Final clinical results

BRAF is one of the most commonly mutated oncogenes in melanoma[1]. Patients with BRAF-mutant MM can be treated either with targeted therapy (TT) or with combined immunotherapy (IO)[2-4] such as nivolumab and ipilimumab[5] both of which have demonstrated significant clinical benefit. However, the optimal sequencing of these treatments has remained unclear, with limited data available to guide clinical decision-making.

The DREAMseq, led by ECOG-ACRIN Cancer Research Group, was a phase 3, two-arm, two-step, open-label, randomized study. The trial enrolled treatment-naive patients with BRAFV600-mutant MM, who were stratified by ECOG performance status (PS) and lactate dehydrogenase (LDH) levels, and then randomized to arm A (combination nivolumab/ipilimumab) or arm B (dabrafenib/trametinib) in Step 1, and at disease progression, if eligible, they were enrolled in Step 2 receiving the alternate therapy, dabrafenib/trametinib (Arm C) or nivolumab/ipilimumab (Arm D).

The primary endpoint was 2-year overall survival (OS), with secondary endpoints including 3-year OS, overall response rate (ORR), response duration, progression-free survival (PFS), crossover feasibility, and safety.

The primary analysis–first presented at the 2023 ASCO inaugural virtual plenary session and published in JCO[6]–demonstrated a significantly higher 2-year OS for patients receiving IO first (72% vs. 52%; p = 0.01). The benefit of starting with IO was consistent across all clinical subgroups, leading to more durable and ongoing responses (88 vs. 48% still in response). TT showed similar efficacy in both first- and second-line settings, while IO showed reduced efficacy when used in second-line. The PFS and OS curves crossed at 6 and 19 months, respectively, reflecting a biphasic treatment effect. Notably, early deaths occurred more frequently in the IO-first group, typically among patients with poor prognosis who never received second-line TT. Adverse events (AEs) profiles differed between arms, but the rates of grade ≥ 3 were similar.

Updated results presented by Dr. Michael B. Atkins at ASCO 2025 (data cutoff: July 2024; median follow-up: 58 months) confirmed–and further reinforced–the survival advantage of initiating treatment with IO in patients with treatment-naive BRAFV600-mutant MM. Five-year OS was 63.3% in the IO-first arm compared to 33.3% in patients who received TT as first-line treatment. Similarly, 5-year PFS was significantly higher in the IO-first group (39.4%) versus the TT-first group (12.8%), with $p < 0.01$. These long-term benefits were consistent across all patient subgroups.

Notably, although the ORR was nearly identical between arms–51.5% with IO versus 51.1% with TT–the durability of response was markedly superior in the IO-first group. At 5 years, 76.4% of responders in the IO arm remained in response, compared to just 23.9% in the TT-first arm. Radiographic response durability also differed significantly. Among patients who received TT first, 41.2% of partial responses (PR) observed at 12 weeks were not confirmed at 24 weeks, compared to only 16.9% in the IO-first group. Investigators

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suggested that this apparent discrepancy in ORR may partly reflect differences in imaging intervals: the DREAMseq trial used longer scan intervals compared to earlier TT registration trials. If imaging had been performed at 8 and 16 weeks, as in earlier studies, the TT-first arm may have shown higher ORRs.

Patients in the IO-first group were also significantly less likely to develop central nervous system (CNS) metastases. At 2 years, 86.8% of patients in the IO arm remained free of CNS metastases, compared to 62.1% in the TT-first group. At 4 years, these rates were 76% and 62.1%, respectively.

These data are practice-changing and provide strong support for initiating treatment with IO in the majority of patients with treatment-naive BRAFV600-mutant MM.

Ongoing biomarker studies on blood and tumor samples aim to identify patients who might benefit from a short upfront course of TT; patients likely to progress early on fist-line IO and requiring earlier switch to TT; and patients who fail both modalities and may require alternative strategies.

A randomized phase 2 trial of encorafenib + binimetinib + nivolumab versus ipilimumab + nivolumab in BRAFV600-mutant melanoma brain metastases: SWOG S2000 (NCT04511013)

The SWOG S2000 trial marks a significant advancement in the treatment of patients with BRAFV600-mutant melanoma and brain metastases (MBM). This randomized phase 2 study is the first of its kind to prospectively compare a triplet regimen of TT and IO with the current standard of dual immune checkpoint blockade in this high-risk population.

Patients with MBM, particularly those harboring BRAFV600 mutations, face a poor prognosis, with median survival < 12 months despite recent therapeutic advances[7,8]. Immune checkpoint inhibitors (ICI)–notably, the combination of nivolumab and ipilimumab–have shown durable intracranial responses in MBM, particularly in asymptomatic patients with limited corticosteroid requirements[9,10]. Separately, TT involving BRAF and MEK inhibitors has demonstrated rapid tumor responses, including intracranial activity, though durability has been a challenge[11-13].

Despite the efficacy of both IO and TT in MBM, the optimal sequencing or combination therapy remains unclear, especially in patients with symptomatic disease or active CNS involvement[14,15]. The SWOG S2000 trial was therefore designed to directly compare these two strategies–triplet IO/TT versus dual IO–in a randomized, prospective study, aiming to address a critical gap in the management of BRAFV600-mutant MBM.

SWOG S2000 was a multicenter, open-label, randomized phase 2 trial enrolling patients with histologically confirmed BRAFV600-mutant MM and measurable brain metastases, either untreated or progressing following local therapy. Eligible patients could have symptomatic disease or require steroids (dexamethasone ≤ 8 mg/day or equivalent). Participants were randomized to receive triplet therapy with encorafenib, binimetinib and nivolumab (Arm A) or nivolumab plus ipilimumab (Arm B).

The primary endpoint was 6-month PFS, with secondary endpoints including intracranial response rate (iORR), overall PFS, OS, duration of response, and safety.

A total of 37 patients were randomized in a 1:1 ratio. Baseline characteristics were generally well balanced between the two arms, including the number and size of brain metastases, presence of symptoms, and prior local CNS-directed therapies. However, the triple therapy arm included more patients with non-BRAFV600E mutations, while the IO arm had more proportion of patients with elevated LDH levels.

With a median follow-up of 18 months, the triplet therapy arm demonstrated superior efficacy across multiple clinical endpoints compared to the IO arm. At 6 months, the PFS rate was 54% in the triplet group compared to 20% in the IO group (hazard ratio [HR]: 0.47; 1-side 90% confidence interval [CI]: 0-0.82; p = 0.04). Median PFS was significantly longer with triplet therapy, reaching 6.2 months, compared to just 1.5 months in the IO arm.

Intracranial outcomes followed a similar trend. The iORR was notably higher in patients receiving triplet therapy, with 75% achieving a radiographic response, in contrast to 13% in the IO group. Median intracranial PFS was also prolonged in the triplet arm at 8.7 months versus 1.5 months in the IO group (HR: 0.39; 1-side 90% CI; 0-0.68; p = 0.01).

The triplet regimen led to earlier and more frequent responses, translating into improved control of both intracranial and extracranial disease. The ORR was 67% in the triplet therapy arm, compared to 14% in the IO arm.

Grade ≥ 3 treatment-related AEs occurred in 69% of patients in the triplet arm and 75% in the IO arm. Despite the higher incidence of dose modifications in the triplet arm (75% vs. 32%), treatment discontinuation

due to toxicity was lower (19% triplet vs. 32% IO). Most common AEs in the triplet arm were pyrexia, rash, fatigue, diarrhea, and elevated liver enzymes. Immune-related AEs predominated in the IO arm.

SWOG S2000 represents the first randomized, prospective comparison of TT combined with IO versus standard dual IO in patients with melanoma brain metastases. The results show a clear clinical advantage for triplet regimen, particularly in terms of iORR and PFS, key measures in the management of symptomatic CNS disease.

The rapid onset of response seen with BRAF and MEK inhibitors is particularly important in patients at risk of neurologic deterioration. The addition of nivolumab may contribute to more sustained disease control. These results build on prior single-arm studies and reinforce growing interest in combining IO/TT strategies in BRAF-mutant melanoma.

While OS data are still immature, the early PFS and iORR results support a potential role for triplet therapy in first-line treatment in selected patients. Further research is warranted to refine patient selection, optimize treatment sequencing, explore the addition of agents such as anti-angiogenic therapies, and evaluate the potential of intermittent dosing strategies.

In summary, this study shows that combining encorafenib, binimetinib, and nivolumab significantly improves intracranial disease control and PFS compared with nivolumab and ipilimumab in patients with symptomatic BRAFV600-mutant MBM. This triplet regimen offers a promising new option for patients with active CNS disease, particularly when rapid response is clinically necessary. Final survival data and correlative biomarker analyses are awaited.

Lifileucel in patients with advanced melanoma: 5-year outcomes of the C-144-01 study

ICIs have transformed the treatment landscape for MM offering durable responses for many patients. However, a significant proportion ultimately experiences disease progression due to either primary[16-18] or acquired resistance[18,19]. As a result, there remains a critical need for effective therapies capable of overcoming ICI resistance in this population.

Lifileucel is an autologous tumor-infiltrating lymphocyte (TIL) therapy, approved by the U.S. Food and Drug Administration for the treatment of patients with advanced melanoma who have progressed after anti-PD-1 therapy and, if BRAFV600 mutant, BRAF ± MEK TT. In the registrational phase 2 C-144-01 study, lifileucel previously demonstrated an objective response rate (ORR) of 31.4% in a treatment-refractory population[20].

At the ASCO 2025 Annual Meeting, Dr. Theresa Medina presented the final 5-year efficacy and safety results from C-144-01 trial–representing the longest prospective follow-up of TIL therapy in advanced melanoma to date.

The final analysis included 153 patients from Cohorts 2 and 4 of the C-144-01 trial. Eligible patients had unresectable or MM with prior progression on ICI and, if applicable, TT. All patients received a single infusion of lifileucel following non-myeloablative lymphodepletion (NMA-LD), and subsequent interleukin (IL)-2 administration. At the data cutoff on November 20, 2024 with a median follow-up of 57.8 months, all patients had completed the study, and 28 patients (8.3%) had reached the 5-year follow-up milestone. The median age was 56 years (range 20-79), 83% were male, and 26.8% harbored BRAF V600E/K mutations. Patients had received a median of 3 prior systemic therapies (range 1-9).

Lifileucel demonstrated durable and clinically meaningful responses with extended follow-up. The ORR was confirmed at 31.4%, including 5.9% complete responses (CR), and 25.5% PR, with 79.3% of patients experiencing a reduction in tumor burden. The median duration of response, as assessed by an Independent Review Committee, was 36.5 months (95% CI: 8.3–not reached [NR]). Notably, 15 of 45 responders (33.3%) maintained such response throughout the entire follow-up period, with the longest ongoing response lasting 58.7 months. Importantly, 16 patients initially categorized as having stable disease or PR showed deepening of responses over time, including four patients who converted from PR to CR as late as 3 years after treatment, highlighting the potential for delayed but durable responses with TIL therapy.

The median OS for the entire cohort was 13.9 months, with an estimated 5-year OS rate of 19.7%. These findings highlight the durable survival benefit attainable with a single lifileucel infusion in a heavily pretreated population with limited therapeutic alternatives.

The safety profile of lifileucel was consistent with the expected effects of NMA-LD and IL-2 administration, with AEs primarily attributable to these treatments. The incidence of AEs declined significantly after the first 2 weeks post-infusion, and no new or late-onset lifileucel-related toxicities were observed. Grade 3/4 cytopenias occurred in all patients but resolved to grade ≤ 2

in most cases within 30 days. Red blood cell and platelet transfusions were predominantly confined to the first 2 weeks following NMA-LD initiation.

In summary, the final 5-year results from the C-144-01 study confirmed the durability, safety, and long-term survival benefit of lifileucel in patients with ICI-refractory advanced melanoma. These findings represent the longest prospective dataset to date for any cellular therapy in this setting and support the role of TIL therapy as a 1-time treatment capable of inducing sustained clinical benefit in heavily pretreated patients.

Future research, including the ongoing phase 3 TILVANCE-301 trial, will further evaluate this option in earlier lines of therapy and help define its role in evolving melanoma treatment algorithms.

Phase 3 trial of adjuvant cemiplimab versus placebo for high-risk cutaneous squamous cell carcinoma (CSCC)

CSCC is one of the most common malignancies worldwide. While most cases are effectively treated with surgery and radiation, a subset of patients with high-risk features–such as nodal involvement, perineural invasion, or poor differentiation–remain at significant risk of recurrence[21]. At present, no systemic adjuvant therapies are approved for this high-risk population[22].

Cemiplimab, an anti–PD-1 antibody, is already established as a standard of care for patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or radiotherapy. In these advanced settings, cemiplimab has demonstrated an ORR of approximately 47%, with durable clinical benefit[23,24].

At the 2025 ASCO Annual Meeting, the results of the phase 3 C-POST trial were presented, providing compelling evidence that adjuvant cemiplimab may reduce recurrence and improve outcomes in patients with resected high-risk CSCC. The C-POST trial enrolled 415 patients with resected high-risk CSCC who had also completed adjuvant radiotherapy. Participants were randomized 1:1 to receive either cemiplimab (n = 209) or placebo (n = 206). Cemiplimab was administered at 350 mg intravenously every 3 weeks for 12 weeks, followed by 700 mg every 6 weeks, for a total treatment duration of up to 48 weeks.

Stratification factors included tumor location (head and neck vs. non-head and neck), geographic region (North America, Australia/New Zealand, Rest of World), high-risk classification (nodal vs. non-nodal), ECOG PS (0 vs. 1), and history of chronic lymphocytic leukemia. The primary endpoint was disease-free survival (DFS). Secondary endpoints included freedom from locoregional recurrence (FFLRR), freedom from distant recurrence (FFDR), OS, and safety. At data cutoff (October 4, 2024), the median follow-up was 24 months (range 2-64 months).

Baseline characteristics were well balanced between the two arms, including tumor location, geographic distribution, and risk classification. Cemiplimab demonstrated a statistically significant reduction in recurrence risk. DFS events occurred in 24 patients in the cemiplimab arm compared to 65 in the placebo arm (HR: 0.32; 95% CI: 0.20-0.51; $p < 0.001$). At 3 years, DFS was 83.1% with cemiplimab versus 60.4% with placebo. Median DFS was not reached in the cemiplimab group, compared to 49.4 months with placebo. The benefit was consistent across all pre-specified subgroups.

Cemiplimab also significantly improved FFLRR (HR: 0.2; 95% CI: 0.09-0.40) and FFDR (HR: 35; 95% CI: 0.17-0.72). OS data were immature at the time of analysis, with 25 deaths reported (HR: 0.86; 95% CI: 0.39-1.90). The efficacy and safety profile of cemiplimab was consistent regardless of dosing schedule, whether administered every 3 weeks or transitioning to every 6 weeks after induction.

Toxicity was manageable at the adjuvant setting. Grade ≥ 3 AEs occurred in 24% of patients receiving cemiplimab versus 14% in the placebo group. There was one treatment-related death (due to myositis) in the cemiplimab arm. The discontinuation rate due to AEs was 10% in the cemiplimab arm compared to 1% with placebo. Immune-related AEs grade ≥ 3 occurred in 7% of patients treated with cemiplimab versus none in the placebo group. Overall, the safety profile was consistent with prior experience, with most immune-related events being manageable but requiring vigilant monitoring.

These findings represent the first positive phase 3 data supporting adjuvant IO in high-risk CSCC. With a hazard ratio of approximately 0.32 and a 3-year DFS improvement of over 20% points, cemiplimab clearly outperformed placebo. Benefits were consistent across subgroups and dosing regimens, reinforcing the robustness of the results. Although immune-related toxicities and discontinuation rate were notable, serious AEs were uncommon and generally manageable.

Adjuvant cemiplimab therefore emerges as a potential new standard of care for patients at high-risk of CSCC recurrence.

Also presented at ASCO 2025 was Keynote-630, a phase 3 trial evaluating pembrolizumab in a similar

high-risk CSCC population. Unlike C-POST, this trial did not meet its primary endpoint of recurrence-free survival (HR: 0.76, p = 0.072) and was halted early for futility. Although some subgroups showed signals of benefit, the lack of overall statistical significance limits its clinical applicability. Notably, pembrolizumab was associated with lower rates of grade ≥ 3 AEs (~8%) compared to cemiplimab (~24%), and both agents had predictable immune-related toxicity profiles. Differences in inclusion criteria and baseline characteristics may help explain the divergent outcomes between the trials.

Conclusion

The C-POST trial demonstrated that adjuvant cemiplimab significantly improves DFS and reduces both locoregional and distant recurrence in patients with resected high-risk CSCC, establishing it as a strong candidate for first-line adjuvant therapy. In contrast, Keynote-630 did not meet its primary endpoint, highlighting the need for further research into patient selection, biomarkers, and optimal treatment timing. These findings underscore the evolving role of IO in CSSC and pave the way for more individualized treatment approaches.

References

1. Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, et al. Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. J Clin Oncol. 2016;34:871-78.
2. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2018;19:1315-27.
3. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med. 2019;381:626-36.
4. Ascierto PA, McArthur GA, Dreno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAF (V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17:1248-60.
5. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol. 2022;40:127-37.
6. Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, Truong TG, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced braf-mutant melanoma: the DREAMseq trial-ECOG-ACRIN EA6134. J Clin Oncol. 2023;41:186-97.
7. Davies MA, Liu P, McIntyre S, Kim KB, Papadopoulos N, Hwu WJ, et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer. 2011;117:1687-96.
8. Georgina V Long, Victoria Atkinson, Serigne Lo, Shahneen Sandhu, Alexander D Guminski, Michael P Brown et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018 May;19(5):672-681.
9. Tawbi HA, Forsyth PA, Hodi FS, Algazi AP, Hamid O, Lao CD, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol. 2021;22:1692-704.
10. Long GV, Atkinson V, Lo SN, Guminski AD, Sandhu SK, Brown MP, et al. Ipilimumab plus nivolumab versus nivolumab alone in patients with melanoma brain metastases (ABC): 7-year follow-up of a multicentre, open-label, randomised, phase 2 study. Lancet Oncol. 2025;26:320-30.
11. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib in patients with BRAF-mutant melanoma and brain metastases: subgroup analysis of the COLUMBUS study. Eur J Cancer. 2018;104:44-52.
12. Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with $BRAF_{V600}$-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017;18:863-73.
13. Dummer R, Queirolo P, Gerard Duhard P, et al. Atezolizumab, vemurafenib, and cobimetinib in patients with melanoma with CNS metastases (TRICOTEL): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2023;24(12):e461-e471.
14. Margolin K. Treatment of brain metastases in melanoma: improving outcomes with targeted therapy and immunotherapy. Am Soc Clin Oncol Educ Book. 2019;39:e151-60.
15. Z. Eroglu, T.O. Topcu, H.M. Yu, K.A. Margolin. How I treat brain metastases of melanoma. ESMO Open 2022; 7,100598.
16. Amaral T, Seeber O, Mersi E, Sanchez S, Thomas I, Meiwes A, et al. Primary resistance to PD-1-based immunotherapy-a study in 319 patients with stage IV melanoma. Cancers (Basel). 2020;12:1027.
17. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23-34.
18. Ribas A, Hamid O, Daud A, Hodi FS, Wolchok JD, Kefford R, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. JAMA. 2016;315:1600-9.
19. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019;30:582-8.
20. Chesney J, Lewis KD, Kluger H, Hamid O, Whitman E, Thomas S, et al. Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study. J Immunother Cancer. 2022;10:e005755.
21. Chong CY, Goh MS, Porceddu SV, Rischin D, Lim AM. The current treatment landscape of cutaneous squamous cell carcinoma. Am J Clin Dermatol. 2023;24:25-40.
22. Killock D. Postoperative chemoradiotherapy versus radiotherapy for high-risk cutaneous disease. Nat Rev Clin Oncol. 2018;15:344.
23. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018;379:341-51.
24. Hughes BG, Guminski A, Bowyer S, Migden MR, Schmults CD, Khushalani NI, et al. A phase 2 open-label study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (EMPOWER-CSCC-1): final long-term analysis of groups 1, 2, and 3, and primary analysis of fixed-dose treatment group 6. J Am Acad Dermatol. 2025;92:68-77.

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Best of ASCO 2025 – Survivorship



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Introduction

For the section *Survivorship and Symptom Control* at the Sociedade Portuguesa de Oncologia (SPO) *Best of ASCO 2025 – Official Licensed Annual Meeting,* we aimed to select abstracts answering tangible questions regarding the management of frequent challenges encountered by oncologists on their daily routine. Evidence has shown that the development of optimized supportive care in oncology is tied with the improvement of patient outcomes, while the use of patient-reported outcome measures is giving interesting new insights on aspects considered as important by patients and caregivers, which previously have been under-evaluated. Present best practice in oncology recognizes the importance of a multidisciplinary approach not only in diagnosis, staging, and treatment but also in supportive care during and after treatment, as well as in survivor care with a focus on quality of life (QoL), rehabilitation, and prevention. Models of integrated care with embedded oncology clinics and early integration of palliative care have consistently shown to improve QoL and symptom control, greater patient and caregiver satisfaction with care, and less aggressive care at the end-of-life[1-8].

Methods

We considered the abstracts submitted and presented during the ASCO Conference 2025, in the category *Survivorship*, on the topics *of Symptom Science and Palliative Care* and *Quality Care/Health Services Research*.

A consensus was reached between the members of the Supportive and Palliative Care Working Group of the SPO, with background in Medical Oncology and Palliative Care, on the abstracts to present at the SPO Meeting.

Results

The following abstracts were selected:

- Abstract 508 – Efficacy and safety of elinzanetant for vasomotor symptoms (VMS) associated with endocrine therapy: Phase III OASIS-4 trial[9].
- Abstract 11003 – Randomized trial of a supportive oncology care at home intervention for patients with cancer receiving curative treatment[10].
- Abstract 12006 – A multicenter, randomized, controlled, open-label trial to determine the optimal duration of steroid therapy for mild pneumonitis associated with immune checkpoint inhibitors (ICIs)–results from the PROTECT study[11].
- Abstract 12007 – Romiplostim for chemotherapy-induced thrombocytopenia in colorectal, gastroesophageal, and pancreatic cancers: a global, phase III, randomized, placebo-controlled trial[12].

Discussion

Abstract 508

Summary

The Phase III OASIS-4 trial evaluated elinzanetant (EZN), a dual neurokinin-1 and -3 receptor antagonist, for treating VMS associated with adjuvant endocrine

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therapy (AET) in women with or at risk for hormone receptor-positive breast cancer. In the 52-week study, women receiving EZN showed significantly greater reductions in VMS frequency and severity compared to placebo, with effects noticeable by week 1 and statistically significant by weeks 4 and 12. EZN was generally well tolerated, with manageable treatment-emergent adverse events. These findings suggest EZN may improve adherence to AET, potentially enhancing breast cancer outcomes and patient QoL.

Comment

VMS are common in women under AET and may be more severe than those associated with physiological menopause. Furthermore, VMS are associated with reduced QoL and cognitive function and contribute to non-adherence to therapy. No treatment is currently approved specifically for VMS in this setting; antidepressants (namely, SSRI/SNRIs) and acupuncture are sometimes suggested. EZN has previously been shown to improve VMS, sleep disturbances, and QoL in the Phase III OASIS-1, OASIS-2, and OASIS-3 trials[13-17].

The OASIS trials provide evidence for the use of EZN to manage one of the side-effects of AET most commonly associated with an impact on QoL. Considering the growing role of endocrine therapy in different breast cancer settings, with emerging new single-agent and combination regimens, a reduction in VMS can be regarded as an important component of patient care[18].

Abstract 11003

Summary

This randomized trial evaluated a Supportive Oncology Care at Home intervention for cancer patients receiving curative treatment. The intervention included remote symptoms and vital sign monitoring, home-based care, and structured communication with oncology teams. Among 196 participants, there was no significant difference in hospital or emergency visits between the intervention and usual care groups. However, the intervention group had fewer urgent clinic visits and showed greater improvement in symptom burden and activities of daily living over time. These findings suggest that home-based supportive care may enhance symptom management and daily functioning, even if it does not reduce hospital admissions.

Comment

Cancer patients often experience a high symptom burden from their disease, as well as adverse effects and toxicities resulting from treatments. These contribute to high utilization of healthcare resources, impaired functional status, and poorer QoL. Interventions, such as symptom monitoring and home-based supportive care models, represent promising approaches aimed at improving patient outcomes[19-21].

Integrating supportive oncology and expertise in symptom management from palliative care teams into cancer patient care is widely regarded as the current standard of care in oncology[22-25]. The home care setting has particular importance in this regard and different approaches have shown promising results[26]. How to effectively design this integration of care is a challenge that the wider oncology community will have to face, depending on particular characteristics of the patient population, healthcare system organization, and available resources[27,28]. Technological developments in the fields of bioinformatics, artificial intelligence, telemedicine, cloud computing, and internet-of-things can provide valuable tools in this regard[29].

Abstract 12006

Summary

The PROTECT study, a multicenter randomized trial, compared 3-week versus 6-week corticosteroid treatments for mild immune-related pneumonitis caused by ICIs. Among 105 patients, the 3-week regimen did not demonstrate non-inferiority to the 6-week treatment, with lower treatment success (66.7% vs. 85.2%) and higher relapse or exacerbation rates (41.1% vs. 24.1%). Although fewer severe adverse events occurred in the shorter treatment group, overall results favored the 6-week regimen. QoL differences were minimal. These findings suggest that shorter steroid courses may be less effective, supporting current guidelines recommending at least 4-6 weeks of treatment.

Comment

Among immune-mediated adverse events (irAEs), immune-mediated pneumonia (IrP) is relatively common. In clinical trials, the reported incidence of IrP is 0-10%, although data indicate a higher incidence in

clinical practice. Corticosteroids are the first-line therapy recommended by guidelines, although the optimal duration of treatment has not yet been defined by randomized clinical trials[30-33].

The management of irAEs is part of the daily practice of oncologists and constitutes a challenge in cancer patient care. With the growing number of ICIs approved in different disease settings, as single-agent or as part of combination regimens, a focus on providing optimized management of irAEs is a key. Important considerations include an effective evaluation of irAE grade, monitoring, effectiveness of the interventions, impact on QoL, and the possibility to resume and adapt the ICI treatment regimen[34].

Abstract 12007

Summary

This global Phase III randomized controlled trial evaluated romiplostim (ROMI), a thrombopoietin receptor agonist, for treating chemotherapy-induced thrombocytopenia (CIT) in patients with gastrointestinal cancers. Among 165 patients, 84% of those receiving ROMI avoided chemotherapy dose modifications due to CIT, compared to 36% in the placebo group. ROMI significantly improved platelet counts and reduced the time to platelet recovery, with a favorable safety profile and minimal adverse events. These findings suggest ROMI is an effective and well-tolerated treatment for CIT, potentially enabling patients to maintain full-dose, on-schedule chemotherapy, addressing a major unmet clinical need in cancer care.

Comment

CIT occurs frequently and can compromise treatment. Full-dose on-time chemotherapy correlates with favorable outcomes, while CIT is often managed with changes to the chemotherapy regimen that compromise dose-intensity. There are no approved standard treatments for CIT - platelet transfusions have limited availability, transient benefits, and are associated with transfusion risks. The thrombopoietin receptor agonist romiplostim ROMI has previously demonstrated safety and efficacy in CIT in a randomized Phase II trial, with an increased platelet count correction rate in the treatment group[35-39].

The management of treatment-related toxicities and the aim to provide optimize dose-intensity while minimizing treatment delays is one of the many challenges faced by oncologists in their practice. Agents, such as ROMI, which provide answers to specific toxicities, provide opportunities to tailor treatment regimens to specific patient needs, contributing to improved outcomes[39].

Conclusion

The selected abstracts highlight the importance of cross-area research in supportive and palliative care, fostering opportunities to develop significant improvements in cancer patients' and survivors' outcomes. A multidisciplinary and integrated approach to patient management has consistently shown promising results. Therefore, it constitutes a standard that should be reflected in healthcare policies and institutional organizational models.

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References

1. Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA. 2008;300:1665-73.
2. Bruera E, Hui D. Integrating supportive and palliative care in the trajectory of cancer: establishing goals and models of care. J Clin Oncol. 2010;28:4013-7.
3. Hui D, Hannon BL, Zimmermann C, Bruera E. Improving patient and caregiver outcomes in oncology: team-based, timely, and targeted palliative care. CA Cancer J Clin. 2018;68:356-76.
4. Hui D. Palliative cancer care in the outpatient setting: which model works best? Curr Treat Options Oncol. 2019;20:17.
5. Glare PA, Semple D, Stabler SM, Saltz LB. Palliative care in the outpatient oncology setting: evaluation of a practical set of referral criteria. J Oncol Pract. 2011;7:366-70.
6. Ostgathe C, Wendt KN, Heckel M, Kurkowski S, Klein C, Krause SW, et al. Identifying the need for specialized palliative care in adult cancer patients - development and validation of a screening procedure based on proxy assessment by physicians and filter questions. BMC Cancer. 2019;19:646.
7. Luis M, Ribeiro C, Sarmento T. Integração dos cuidados paliativos ao longo do percurso da doença oncológica. Rev Assoc Port Cuid Paliativos. 2020;7:8-10.
8. Martins-Branco D, Lopes S, Canario R, Freire J, Feio M, Ferraz-Goncalves J, et al. Factors associated with the aggressiveness of care at the end of life for patients with cancer dying in hospital: a nationwide retrospective cohort study in mainland Portugal. ESMO Open. 2020;5:e000953.
9. Cardoso F, Brennan DJ, Briggs P, Donders G, Panay N, Haseli-Mashhadi N, et al. Efficacy and safety of elinzanetant for vasomotor symptoms associated with adjuvant endocrine therapy: phase 3 OASIS 4 trial. J Clin Oncol. 2025;43:508-8.

10. Nipp RD, Johnson PC, Neckermann I, Schneider D, Horick NK, Nurhussien L,et al. Randomized trial of a supportive oncology care at home intervention for patients with cancer receiving curative treatment. J Clin Oncol. 2025;43:11003.
11. Fujimoto D, Abe M, Murotani K, Sato Y, Kijima T, Tamiya M, et al. A multicenter, randomized, controlled, open-label trial to determine the optimal duration of steroid therapy for mild pneumonitis associated with immune checkpoint inhibitors. J Clin Oncol. 2025;43:12006.
12. Al-Samkari H, Munoz C, Geredeli C, Korantzis I, Astorga BG, Arslan C, et al. Romiplostim for chemotherapy-induced thrombocytopenia (CIT) in colorectal, gastroesophageal, and pancreatic cancers: a global, phase 3, randomized, placebo-controlled trial (RCT). J Clin Oncol. 2025;43:12007.
13. Pinkerton JV, Simon JA, Joffe H, Maki PM, Nappi RE, Panay N, et al. Elinzanetant for the treatment of vasomotor symptoms associated with menopause: OASIS 1 and 2 randomized clinical trials. JAMA. 2024;332:1343.
14. Biglia N, Bounous VE, De Seta F, Lello S, Nappi RE, Paoletti AM. Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update. Ecancermedicalscience. 2019;13:909.
15. Smith KL, Verma N, Blackford AL, Lehman J, Westbrook K, Lim D, et al. Association of treatment-emergent symptoms identified by patient-reported outcomes with adjuvant endocrine therapy discontinuation. NPJ Breast Cancer. 2022;8:53.
16. Van Dyk K, Joffe H, Carroll JE. Sleep and endocrine therapy in breast cancer. Curr Opin Endocr Metab Res. 2021;18:165-70.
17. Kingsberg S, Banks V, Caetano C, Janssenswillen C, Moeller C, Schoof N, et al. Real-world evaluation of treatment utilization by women experiencing vasomotor symptoms associated with menopause in the United States and Europe: findings from the REALISE study. Maturitas. 2024;189:108096.
18. Patel R, Klein P, Tiersten A, Sparano JA. An emerging generation of endocrine therapies in breast cancer: a clinical perspective. NPJ Breast Cancer 2023;9:20.
19. Nipp RD, Shulman E, Smith M, Brown PM, Connor Johnson P, Gaufberg E, et al. Supportive oncology care at home interventions: protocols for clinical trials to shift the paradigm of care for patients with cancer. BMC Cancer. 2022;22:383.
20. Nipp RD, El-Jawahri A, Moran SM, D'Arpino SM, Connor Johnson P, Lage DE, et al. The relationship between physical and psychological symptoms and health care utilization in hospitalized patients with advanced cancer. Cancer. 2017;123:4720-7.
21. Nipp RD, Thompson LL, Temel B, Fuh CX, Server C, Kay PS, et al. Screening tool identifies older adults with cancer at risk for poor outcomes. J Natl Compr Canc Netw. 2020;18:305-13.
22. Rebman J, Montague R, Gill DM, Thota R. Integrated supportive oncology program and outcomes for cancer patients at the end of life. JCO Oncol Pract. 2023;19:240.
23. Sanders JJ, Temin S, Ghoshal A, Alesi ER, Ali ZV, Chauhan C, et al. Palliative care for patients with cancer: ASCO guideline update. J Clin Oncol. 2024;42:2336-57.
24. Jordan K, Aapro M, Kaasa S, Ripamonti CI, Scotté F, Strasser F, et al. European Society for Medical Oncology (ESMO) position paper on supportive and palliative care. Ann Oncol. 2018;29:36-43.
25. Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. Lancet Oncol. 2018;19:e588-653.
26. Hwang IY, Woo GU, Lee SY, Yoo SH, Kim KH, Kim MS, et al. Home-based supportive care in advanced cancer: systematic review. BMJ Support Palliat Care. 2024;14:132-48.
27. Bradley N, McConnell T, Blair C, O'Halloran P, Prue G, Lynn F, et al. Integrated palliative care and oncology: a realist synthesis. BMC Med. 2025;23:272.
28. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial. Lancet Respir Med. 2014;2:979-87.
29. HENKO-NET. Available from: https://henko-net.eu
30. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol. 2016;2:160716.
31. Tiu BC, Zubiri L, Iheke J, Pahalyants V, Theodosakis N, Ugwu-Dike P, et al. Real-world incidence and impact of pneumonitis in patients with lung cancer treated with immune checkpoint inhibitors: a multi-institutional cohort study. J Immunother Cancer. 2022;10:e004670.
32. Fujimoto D, Miura S, Yoshimura K, Wakuda K, Oya Y, Haratani K, et al. A real-world study on the effectiveness and safety of pembrolizumab plus chemotherapy for nonsquamous NSCLC. JTO Clin Res Rep. 2021;3:100265.
33. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol. 2017;35:709-17.
34. Verheijden RJ, van Eijs MJ, May AM, van Wijk F, Suijkerbuijk KP. Immunosuppression for immune-related adverse events during checkpoint inhibition: an intricate balance. NPJ Precis Oncol. 2023;7:41.
35. Al-Samkari H, Parnes AD, Goodarzi K, Weitzman JI, Connors JM, Kuter DJ. A multicenter study of romiplostim for chemotherapy-induced thrombocytopenia in solid tumors and hematologic malignancies. Haematologica. 2021;106:1148-57.
36. Soff GA, Miao Y, Bendheim G, Batista J, Mones JV, Parameswaran R, et al. Romiplostim treatment of chemotherapy-induced thrombocytopenia. J Clin Oncol. 2019;37:2892-8.
37. Al-Samkari H. Treatment of chemotherapy-induced thrombocytopenia with monotherapy versus combination therapy: the devil is in the details. Res Pract Thromb Haemost. 2023;7:102250.
38. Wu Y, Aravind S, Ranganathan G, Martin A, Nalysnyk L. Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database, 2000-2007. Clin Ther. 2009;31 Pt 2:2416-32.
39. Havrilesky LJ, Reiner M, Morrow PK, Watson H, Crawford J. A review of relative dose intensity and survival in patients with metastatic solid tumors. Crit Rev Oncol Hematol. 2015;93:203-10.

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ORIGINAL ARTICLE

Testing positive after genetic testing for hereditary cancer: what's next?

Resultado positivo num teste genético para cancro hereditário: quais os próximos passos?

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Abstract

Background: *The growing integration of genetic testing into clinical oncology practice has led to the identification of a growing number of individuals carrying pathogenic variants associated with hereditary cancer.* **Objectives:** *These cases require a multidisciplinary and personalized approach; however, access to structured follow-up care remains unstandardized in Portugal.* **Methods:** *To discuss existing organizational models and establish consensus on an optimal infrastructure, the Hereditary Cancer Group of the Portuguese Society of Oncology organized a workshop in September 2023, involving representatives from various healthcare units across the country.* **Results:** *This document, arising from that meeting, proposes the implementation of a structured follow-up model for individuals at genetic risk of cancer. It aims to ensure equitable access to specialized care and to strengthen collaboration with General and Family Medicine. This coordination faces significant challenges, including the transmission of genetic information and limited access to imaging prescriptions, such as magnetic resonance imaging. Despite advances in molecular testing for hereditary cancer diagnosis, the clinical follow-up infrastructure – particularly in terms of multidisciplinary teams, genetic information management, equipment availability, and human resources – has not kept pace. Nevertheless, several centers have begun establishing multidisciplinary teams comprising various medical specialties, specialized nurses, and other health professionals who play a key role in managing patients' care pathways. A central priority is to define the role of the case navigator and ensure continuous patient contact throughout the care journey. This document presents a set of proposals aimed at fostering care organization and integration, technological solutions, the implementation of case navigators, and the dissemination of updates from European reference networks nationwide.*

Keywords: *Hereditary cancer. Genetic testing. Multidisciplinary care. Healthcare coordination.*

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Resumo

Introduçao: *A crescente integração dos testes genéticos na prática clínica em Oncologia tem permitido identificar mais indivíduos com variantes patogénicas associadas ao cancro hereditário.* **Objetivos:** *Estes casos exigem uma abordagem multidisciplinar e personalizada, mas o acesso a cuidados de seguimento estruturados continua por normalizar em Portugal.* **Métodos:** *Com o objetivo de discutir modelos organizativos e estabelecer consenso sobre uma infraestrutura ideal, o Grupo de Cancro Hereditário da Sociedade Portuguesa de Oncologia promoveu, em setembro de 2023, um workshop com representantes de várias unidades de saúde do país.* **Resultados:** *Este documento, resultante do encontro, propõe um modelo de acompanhamento estruturado para indivíduos com risco genético de cancro, promovendo acesso equitativo a cuidados especializados e reforçando a colaboração com a Medicina Geral e Familiar. Essa articulação enfrenta desafios, como a transmissão de informação genética e limitações na prescrição de exames, nomeadamente ressonâncias magnéticas. Apesar da evolução nos testes moleculares, os recursos necessários ao seguimento clínico – nomeadamente equipas multidisciplinares, gestão da informação genética, acesso a equipamentos e recursos humanos – não acompanharam esse progresso. Ainda assim, vários centros estão a criar equipas multidisciplinares, compostas por diversas especialidades médicas, enfermeiros especializados e outros profissionais, que têm sido fundamentais na gestão do percurso destes doentes. Uma das prioridades é definir quem assume o papel de gestor de caso e como garantir um contacto contínuo com o doente ao longo do percurso assistencial. Este documento apresenta propostas que visam promover a organização e integração de cuidados, soluções tecnológicas, o gestor de cuidados e a disseminação das atualizações das redes europeias de referência.*

Palavras-chave: *Cancro hereditário. Teste genético. Cuidados multidisciplinares. Coordenação em saúde.*

Introduction

The growing integration of genetics into clinical oncology practice has led to an increase in the number of individuals (both cancer survivors and those without prior oncological diagnoses) identified with genetic variants associated with hereditary cancer. These individuals require a multidisciplinary approach to manage their cancer risk, and various structures have been established across national institutions. However, not all patients, across the country, have access to integrated follow-up care. A national study presented in 2019, involving 611 respondents from 31 healthcare units, found that 45% of hospital units had specific structures for monitoring families at risk of hereditary cancer[1]. The same survey suggested that most of the National Health Service (Sistema Nacional de Saúde [SNS]) hospitals have the technical capacity to address and monitor major hereditary cancer syndromes. However, there appears to be a lack of common national organization to ensure care accessibility and effective coordination among various healthcare structures, including the primary care setting.

This study was driven by the need to harmonize two realities:

1. Existing evidence on the potential impact of cancer risk management in reducing morbidity and mortality in these individuals[2-5], as well as its effect on quality of life and family adjustment[6].
2. Challenges on the healthcare system due to the progressive increase in pathogenic variant (PV) carriers requiring specialized care. This increase is a consequence from the recent improvement in molecular genetic testing and the routine implementation of multigene panels[7]. In centers implementing programs based on the Mainstream Genetics model[8,9], the referral pathway for at-risk relatives to genetic consultations is not uniform.

The universe of hereditary cancer families is heterogeneous, and risk management may involve multidisciplinary teams with multiple specialties, including in the case of rare syndromes (e.g., Birt-Hogg-Dubé, Cowden, Li-Fraumeni), implying collaboration across multiple healthcare structures.

Objectives

General objective

The objective of the study was to develop a national framework ensuring a comprehensive and coordinated approach for the accurate identification and appropriate follow-up of individuals carrying PVs associated with hereditary cancer risk, across the country.

Specific objectives

- Promote the development of evidence-based follow-up guidelines.
- Clarify the roles of various medical specialties and other health care professionals, as well as of the structures needed to ensure timely access to genetic counseling, testing, and risk management.
- Define care pathways for these individuals.

Methods

Although health structures, in different formats, already provide care for hereditary cancer families and individuals, there is a critical need to share experiences and knowledge across different stakeholders, to harmonize access to adequate care across the National Health Service (currently comprising local health units and the IPO Hospital Group) and private units.

On the 29th September 2023, the Hereditary Cancer Group (HCG) of the Sociedade Portuguesa de Oncologia (SPO) organized a workshop in Lisbon to discuss the existing organizational models and proposals to improve care. The workshop format allowed the discussion of the pre-existing models of care in the different health structures across the country (presented in the first half), and also for a general discussion intending that, at the end, a proposal for a national framework regarding structure and core guidelines for the appropriate follow-up of these individuals was done.

The HCG invited healthcare workers from across the country, as well as patient associations and representatives from the National Oncological Plan (PNDO-DGS). Due to challenges in coordination with Primary Care, specialists in General and Family Medicine from across the country were also invited.

Results

Participants

Forty-four healthcare professionals (from public and private hospitals and from Primary Care Units) and three patient associations participated, sharing data and discussing existing organizational models in Portugal (Supplementary material, I and II). Furthermore, present were the then SPO President (Prof. Dr. Miguel Abreu), the former Director-General of Health (Dr. Graça Freitas), and Prof. Dr. Isabel Fernandes, representing the National Program for Oncological Diseases (PNDO_DGS).

Scope and strategic definition

The opening session highlighted the need to characterize the target population and to evaluate the current clinical practice. This would allow the strategic planning to ensure an equitable, patient-centered governance model.

For the current version of this document, (Portuguese version available in: www.cancrohereditario.pt/pt/eventos/gestao-de-risco-e-seguimento-dos-individuos-portadores-de-variantes-patogenicas-associadas-a-cancro-hereditario/), seven institutions provided aggregate data on individuals identified with PVs associated with hereditary cancer risk. In those 7 centers (IPO Lisboa, IPO Porto, IPO Coimbra, ULS S. João, ULS Alto Ave, Hospital Nelio Mendonça and ULS de Braga), a total of 8,105 individuals with PVs were identified, with the majority being mutations in *BRCA1*, *BRCA2*, and *PALB2* genes (4,171), 1,835 in mismatch repair (*MMR*) genes (associated with Lynch syndrome), 662 in genes linked to colorectal polyposis syndromes, 131 in *TP53*, 129 in *CDH1*, 52 in *PTEN*, and 1,132 in other moderate- and high-penetrance genes associated with hereditary cancer risk.

Operational structures in Portugal

To establish the starting point for discussion, several health professionals from already implemented operational structures in the country presented data regarding their experience. Speakers from IPO Lisboa (Isália Miguel, Isadora Rosa, and Paula Rodrigues), ULS São João (Susy Costa, Luzia Garrido, Sandra Silva-Soares), ULS Alto Ave (Carolina Carvalho), Dr. Nélio Mendonça Hospital (Sara Camara, Rosa Neto-Silva), and IPO Porto (Pedro Souteiro and João Silva) structured their presentations as follows:

1. How is the follow-up of individuals with positive genetic tests organized in your center?
2. How do PV carriers access follow-up care?
3. Are healthy PV carriers included in follow-up care?
4. What challenges do you identify?

The information collected is summarized in table 1.

Table 1. A Portuguese national portrait regarding cancer risk management

Question	Response
1. How is the follow-up of individuals with positive genetic tests organized?	Across various centers, specialized structures–Familial Cancer Risk Clinics, Oncogenetics consultations – have been established to monitor individuals either based on the predominant oncologic phenotype, or identified hereditary syndrome within their families (e.g., breast/ovarian/prostate cancer; gastrointestinal tumors; melanoma; pediatric hemato-oncology; pediatric gastroenterology; endocrinology syndromes, and others included in Medical Oncology management). In some institutions, multidisciplinary case discussions are regularly scheduled to address complex or atypical cases; review Variants of uncertain significance, and update management guidelines (e.g., Multidisciplinary Oncogenetics Group meetings, regular discussions between clinicians and molecular biologists). However, the extent to which individuals with a positive genetic test–particularly those without a cancer diagnosis–are effectively integrated in follow-up by existing structures remains unclear.
2. How do PV carriers access follow-up care?	Access is typically facilitated through referral by the oncogenetics clinic or the physician responsible for the genetic diagnosis, directing patients to familial cancer risk clinics or specific consultations, either within the same institution or to centers where such follow-up is available. Despite the growing number of individuals identified as at-risk and the complex, multidisciplinary nature of their care needs, hospitals did not have a proportional increase in specialized resources (infrastructure, equipment, and human resources). Consequently, healthcare professionals must coordinate internally or refer patients to other centers to ensure appropriate follow-up.
3. Are healthy PV carriers included in follow-up care?	In general, it is assumed that all carriers with a cancer diagnosis are followed through oncology consultations, with varying levels of integration into institutional surveillance and risk-reduction frameworks. For unaffected carriers (without a previous cancer diagnosis), follow-up is offered in many centers via structured familial risk clinics or specific medical oncology, endocrinology, and/or pediatric consultations. Some centers initially focused on patients with cancer and a positive genetic test, but are now working to expand follow-up services to include asymptomatic carriers.
4. What challenges have been identified?	Inadequate physical infrastructure; Shortage of dedicated human resources (e.g., clinical geneticists, gastroenterologists, anesthesiologists, specialized nurses); Increasing demand for genetic testing, challenging timely access and response; High cost of genetic testing; Difficulties in implementing surveillance protocols, particularly for endoscopic procedures (especially those requiring anesthesia), radiological exams (due to equipment limitations and long waiting times), and access to specialized consultations; Reluctance or refusal of some carriers to inform at-risk relatives of their genetic status; Lack of clear discharge criteria or referral pathways from specialized clinics; Insufficient surgical capacity and long waiting times for risk-reducing (prophylactic) surgeries.

IPO Lisboa

Since 2006, specific consultations (breast, ovarian, prostate, colorectal, and melanoma) have functioned within a specific structure dedicated to these patients: the Cancer Family Risk Clinic (Clínica de Risco Familiar [CRF]). At CRF, the different groups share space, administrative services, and collaboration with specialized Nursing, Medical Genetics, Psychology and Molecular Biology. Common to all CRF multidisciplinary groups is the close coordination with the molecular diagnostics team, enabling individualized interventions in systemic therapy decisions and risk-reducing surgeries (for both cancer patients and healthy carriers). The core team at CRF integrates multidisciplinary groups with several other medical specialities (Breast Surgeons, Gynecological Oncology, Plastic and Reconstructive Surgery, Urology). IPO Lisboa is part of the European Genturis network[10] in thematic Groups 2 (Lynch syndrome and polyposis), 3 (Breast and Ovarian) and 4 (other hereditary syndromes).

Breast, ovarian, and prostate cancer family risk consultation

Access to the consultation is made through referral from other clinics and units from IPO Lisboa and from other external public or private units. This multidisciplinary group includes dedicated nursing for patient and family management throughout the process, and also oncologists, geneticists, and the molecular diagnostics group (an integral part of the multidisciplinary team). Based on evidence and actionable results, most tests prescribed in 2023 for breast, ovarian, and prostate cancer patients included genes *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *RAD51C*,

RAD51D, *STK11*, *TP53*, and *MMR* genes. The detection rate was approximately 10-11%. For reanalyses (multigene panel reanalyses in patients previously tested only for *BRCA1/2),* the positivity rate was 8% (30/386) (2023 data). The surveillance protocol for these carriers was presented, along with Genturis[10-12], European Society for Medical Oncology (ESMO)[11], and National Comprehensive Cancer Network (NCCN)[13] recommendations, included in the internal protocols.

Colorectal cancer family risk consultation

The colorectal cancer family risk consultation follows patients with non-polyposis and polyposis hereditary syndromes. Lynch syndrome is associated with an autosomal dominant defect in the MMR system, leading to accelerated carcinogenesis and early-onset cancers (colorectal, endometrial, ovarian, gastric, small intestine, urothelial, central nervous system [CNS], pancreatic, and biliary). Surveillance significantly reduces colorectal cancer risk. The surveillance protocol for these carriers was presented, along with ESMO[14], NCCN[15], and EHTG/ESCP[16] recommendations. In APC-associated polyposis, a defect in the Wnt signaling pathway results in an autosomal dominant syndrome with an 80-100% lifetime colorectal cancer risk and extracolonic manifestations (small intestine, CNS, thyroid, liver, stomach, and pancreas). The institutional surveillance protocol was presented and compared with NCCN recommendations[14].

ULS São João (Porto)

This local health unit has an Oncogenetics consultation that works in coordination with various teams involved in diagnostics and surveillance. ULS São João is the only public center in Portugal offering access to Preimplantation Genetic Testing for Monogenic (PGT-M) Disorders. It is also a Genturis center[10] for thematic Groups 1 (Neurofibromatosis), 2 (Lynch syndrome and polyposis), 3 (Breast and Ovarian), and 4 (other hereditary syndromes).

Oncogenetics consultation

Patients are referred to the ULS São João Oncogenetics outpatient unit, either from other services of ULS São João or from external public or private health services. After identifying carriers (affected or unaffected), they are referred to various High-Risk Consultations based on the identified PV. The Breast and Ovarian Cancer High-Risk Consultation, managed by surgical oncologists, follows individuals with syndromes associated with PVs in *BRCA1*, *BRCA2*, *PALB2*, *CDH1* (females), *PTEN*, *CHEK2* (females), *ATM* (females), *BRIP1*, *RAD51C*, *RAD51D*, and *BARD1*. The Gastrointestinal Tumors High-Risk Consultation, also managed by surgical oncologists, follows individuals with syndromes associated with PVs in *CDH1* (both sexes), *CHEK2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *APC*, *MUTYH*, and *STK11*. The Medical Oncology High-Risk Consultation, managed by oncologists, follows individuals with syndromes associated with PVs in *ATM* (males), *CHEK2* (males), *DICER1*, *FH*, *FLCN*, *NF1*, *TP53*, *PTEN*, *RB1*, *RET*, SDHs, SUFU, and VHL.

In 2019, a Multidisciplinary Oncogenetics Group Consultation was established to discuss criteria for expanding genetic studies in families with undiagnosed hereditary syndromes and surveillance protocols for carriers of variants in moderate- and low-penetrance genes. The multidisciplinary group includes dedicated nurses, oncologists, geneticists, and surgical oncologists responsible for High-Risk Consultations. Carriers of variants of unknown significance (VUS) are reassessed every 2-3 years, with VUS reclassification requested from the original laboratory at no additional cost. Surveillance follows ERN-Genturis[10,11,16-30], ESMO[11,14], and NCCN[13,15] guidelines. Pediatric carriers are followed in High-Risk Pediatric Hemato-Oncology and Gastroenterology.

PGT-M

ULS São João is the only public center in Portugal performing PGT-M for PV carriers at risk of transmitting variants to the offspring. It receives nationwide patients, who are eligible for the procedure. Dr. Sandra Silva-Soares explained why genetic counseling is important to inform couples about transmission risks and available interventions (e.g., prenatal diagnosis or PGT-M). Early referral (inter-hospital or via email: umr@ulss-joao.min-saude.pt) with clinical details, variant reports, and carrier data was emphasized. For variants in unauthorized pre-implantation genes, approval from the National Council for Medically Assisted Reproduction (Comissão Nacional de Procriação Medicamente Assistida, [CNPMA] - www.cnpma.org.pt/) is required and then handled by the reproductive medicine center after verifying inclusion criteria. Most new gene variants require pre-genetic tests and embryonic diagnostics at Universitaire Ziekenhuis Brussel (not feasible in Portugal).

Key challenges include:

- Age limit for women (40 years) for assisted reproductive techniques in the SNS.
- A 14-month waiting list for treatment.
- Inability to perform PGT-M for independent reproduction due to the inability to create pre-genetic tests for variant identification in embryos (donor genetic information unavailable in the SNS).
- Individuals with healthy children without the PV lack eligibility for the procedure in the SNS.

ULS Alto Ave (Guimarães)

Until 2019, high-risk patients had to be referred to a different city to access genetic testing at the Medical Genetics Consultation at ULS Braga. In 2020, ULS Alto Ave implemented two hereditary cancer risk consultations: one for gastrointestinal syndromes (2020); for the other syndromes a Cancer Family Risk consultation was set up in 2021. In 2022, ULS Alto Ave had its own Medical Genetics consultation that allows for better access to genetic testing. The Cancer Family Risk consultation, managed by Medical Oncology, initially managed only patients with positive genetic tests and prior oncological diagnoses. Since 2023, it has included healthy carriers with positive genetic tests in surveillance. An internal document, disseminated through ULS Alto Ave, outlines objectives, prescribed multigene panels, and the informed consent for genetic testing (based on a national guideline from the Directorate-General of Health, DGS).

Dr. Nélio Mendonça hospital (Funchal)

Since 2018, the Breast and Ovarian Cancer Family Risk Consultation has collected data on carriers of genetic predispositions or relevant family histories, even if untested. After 2019, with Medical Genetics collaboration, proactive testing was implemented in diagnostic and predictive settings. Before, since 2011, a Polyposis and Family Risk Consultation was operating with similar objectives (specific surveillance for high-risk patients). On June 20, 2022, the Family Risk Clinic was officially established, including both teams plus Medical Genetics. Clinical links are identified within the hospital (Dermatology, Imaging, Plastic Surgery, etc.) and collaborate with the Family Risk Clinic in patient management. A nurse with specialized training in this area was assigned to the clinic, managing genograms, genetic archives, and an email account that serves as an interface with patients and other healthcare professionals.

IPO Porto

The IPO Porto Genetics Consultation coordinates with the Genetics Laboratory and with the various other consultations involved in managing the risk of PV carriers associated with hereditary cancer. The Endocrinology-Family Risk Consultation was presented as an example.

Endocrinology-family risk consultation

Several endocrine neoplasms (medullary thyroid carcinomas, pheochromocytomas/paragangliomas, pituitary, and parathyroid tumors) can occur in familial genetic syndromes. The Endocrinology Family Risk Consultation at IPO Porto started its activity in 2022, in coordination with the Medical Genetics Service, which refers asymptomatic carriers identified through cascade family screening. Surveillance for hereditary endocrine neoplasms requires clinical, imaging, and analytical monitoring, often involving dynamic laboratory tests in endocrinology. Centralizing these individuals in a dedicated consultation has standardized procedures through surveillance protocols, promoted clinical research, and balanced early neoplasm detection with avoiding iatrogenic and psychologically stressful diagnostic procedures.

Role of nursing

Two nurses (from ULS São João and IPO Lisboa) emphasized nurses' role in managing the care needs of at-risk individuals throughout their care pathway. Experiences at the two institutions differ slightly. At ULS São João, the nurse participates in the Breast Oncology Group Consultation, identifies patients eligible for genetic testing, and serves as a liaison with the multidisciplinary team, and participates in the referral to High-Risk Consultations. At ULS São João, the nurse also identifies priority cases for timely genetic diagnosis to optimize therapeutic decisions, manages cascade testing for at-risk relatives, and maintains family records as per current Portuguese legislation. The concept of a "nurse navigator" was explored.

At IPO Lisboa, the nursing team collaborates with the medical team to prioritize requests, ensuring timely genetic diagnosis for patients with short-term

therapeutic implications. Beyond creating initial files and genograms, they facilitate coordination between consultations (e.g., scheduling risk consultations after identifying a cancer-associated variant), manage cascade testing for at-risk relatives, and collaborate, during the follow-up in surveillance protocol compliance. The nursing team participates in the core team with the Molecular Pathology Unit, and has a close collaboration with the Psychology Unit, assessing distress in *BRCA1/2* carriers.

Medical genetics

Medical Genetics specialists are essential for pre- and post-test counseling and for developing surveillance plans. In most healthcare structures, they do not participate in active follow-up of PV carriers and their surveillance, after test results. They remain involved in identifying relatives, managing reproductive options (e.g., PGT-M), and participating in multidisciplinary case discussions, variant analysis, and guideline development[31].

Discussion

The open discussion highlighted the following points:

Coordination with general and family medicine (GFM)

Given that GFM has more training in prevention and health promotion than most hospital medical specialties; its collaboration is not only desirable but mandatory. GFM's holistic approach spans the entire life cycle, including preventive care for those at increased risk, such as the individuals addressed in this document. Keeping up with specialized, updated knowledge can be challenging for GFM, requiring ongoing dialogue with colleagues specializing in these conditions, especially given the low prevalence of PV carriers associated with hereditary cancer in each of the patient files under the care of a specific GFM. GFM faces three main challenges in managing preventive care for PV carriers:

- Difficulty in the communication of clinical information to patients regarding their genetic risk
- Challenges in maintaining updated specialized knowledge about genetic risk and the low number of PV carriers in each patient list.
- Barriers to accessing complementary diagnostic and therapeutic resources (CDTRs) and integrating care.

The difficulty in transmitting clinical information about genetic risk results from legal limitations on recording genetic information in electronic health records. The requirement to separate genetic information to prevent discrimination, as stipulated in current legislation [Law No. 12/2005 of January 26 (Personal Genetic Information and Health Information) and its regulation, Decree-Law No. 131/2014 of August 29], complexifies the follow-up for carriers without prior cancer diagnoses, as no platforms or archives enable electronic sharing between genetics or risk clinics and GFM. Although confidential notes can be added to electronic medical records, these are only accessible to the registering physician, hindering follow-up if the physician leaves the practice. A proposal during the discussion was to seek feedback from the Shared Services of the Ministry of Health (SPMS) to enable controlled access to genetic information in the electronic health record, restricted to those managing patient risk in hospital or primary care settings, ensuring secure data use.

GFM faces barriers to prescribing necessary CDTRs (some only available or requested at the hospital level like MRI) for early cancer detection and care integration. To address these, bidirectional training on primary care and hospital procedures, identifying contact points, and coordinating hereditary cancer risk management should be implemented, specifying what can be done in primary care, what can be shared, what must be hospital-based (e.g., risk-reducing surgeries), and what can primarily be managed in primary care (e.g., follow-up of women with a *BRCA1/2* PV post-risk-reducing surgeries). The current reform of the National Health Service, with the generalization of the Local Health Unit model, can solve this problem, liberalizing access to complementary diagnostic means, making these accessible to GFM.

Coordination in care of high risk individuals

Some hereditary cancer syndromes are so complex that, to manage risk in individuals affected, good coordination between a Risk Clinic and Primary Care would not be enough. Indeed, for some patients, the system has to work in a national network (e.g., only one public hospital offers PGT-M). This underscores the need for agreed-upon follow-up guidelines, awareness of available network services, and criteria for effective referrals to other centers when necessary.

Infrastructure

The increasing identification of individuals with positive genetic tests has not been accompanied by proportional increases in structural resources for their follow-up, particularly regarding multidisciplinary structures, genetic information management, access to equipment [breast MRI, abdominal MRI/MRCP, whole-body MRI, colonoscopy equipment and operating rooms], and human resources. This has led some Medical Genetics or Oncology services, where mainstream genetics programs are implemented, to send positive cases to centers with established multidisciplinary groups. However, these reference centers also face exponential increases in identified at-risk individuals and have serious difficulties in accommodating promptly externally referred patients.

Indeed, there is an increasing pressure on existing structures, but new teams have also been progressively implemented in places where they did not previously exist, such as ULS Alto Ave, Dr. Nélio Mendonça Hospital, ULS Trás-os-Montes e Alto Douro, ULS Almada-Seixal, and ULS Braga (the latter two in 2024). These units initially focused on managing cancer patients, considering their genetic specificities, but some have progressively extended their scope to unaffected relatives with positive tests.

The minimum infrastructure facilities needed for healthcare institutions identifying these patients were discussed. No consensus was reached on whether a dedicated physical space was necessary. While ideal for archiving, administrative support, patient care managers (e.g., nurse navigators or other patient navigators), and multidisciplinary meetings, space limitations may make this unfeasible. Functional team coordination was deemed essential. Each site should define a team considering clinical guidelines and patient's needs, tailored to the structure's specifics and leveraging its professional resources. These teams include various specialties, varying by hereditary syndrome follow-up needs. Ideally, the patient's physician should be part of these teams, which should include specialists as "connecting links" across services and structures involved in the patient's care pathway.

Patient care manage/patient navigator

Specialized nursing plays a critical role in managing the care pathway of these patients and their families, as highlighted during the meeting. After identifying a PV and developing a surveillance plan, the patient care manager addresses questions and operationalizes the plan over time. While nursing typically assumes this role, other professionals (e.g., genetic counselors, psychologists) also fulfill this role in some centers. The priority is defining who serves as the patient care manager in each healthcare unit and how patients can contact them throughout their care journey, ensuring guidance beyond scheduled consultations and procedures. Each patient should receive a card identifying their care manager and contact details, including the email of the multidisciplinary team's structure.

Guidelines

Given the multiplicity of hereditary syndromes and follow-up guidelines from various national and international societies (e.g., Gastroenterology, Gynecologic Oncology) (ERN-Genturis[10,11,16-30], ESMO[11,14], NCCN[13,15]), it is proposed that ERN-Genturis [10,11,16-30] and ESMO[11,14] guidelines be followed where available, resorting to others for specific cases not covered. Existing national guidelines are included in multidisciplinary case discussions but are rarely organized into comprehensive guidelines. Several multidisciplinary structures have approved surveillance protocols, though their frequent updating is challenging. The importance of an updated, individualized, and dynamic surveillance plan for each patient, serving as a "passport" for navigating healthcare structures, was emphasized. This dynamism reflects both guideline updates and changes in patient risk (e.g., post-risk-reducing surgeries)[32].

Proposals/challenges

The main proposals to organize hereditary cancer risk management for at-risk patients and foster synergies among healthcare providers include:

- Integration of genetic testing teams dedicated to risk management.
- At the individual level, each patient should have updated information about their genetic status and risk management plan.
- Network between different health structures and between hospitals and primary care depend on technological solutions probably dependent on SPMS.
- Regardless of national consensus (e.g., from Portuguese societies or specific multidisciplinary groups), the SPO HCG should provide links to the

latest Genturis[10], ESMO[11,14], and NCCN[13,15] guidelines on its website.
- Implement the patient care manager role across centers.
- Each patient's genetic status and plan should ideally be expressed in a standardized document, like a passport, promoted by the SPO HCG.
- National centers in European networks (e.g., ERN-Genturis) should collaborate in disseminating relevant updates and opportunities for national collaboration.

Several structures involved in genetic testing and follow-up of patients with confirmed genetic risk were implemented after the September 2023 workshop (e.g., ULSTMAD and ULS Braga). Maintaining a good network communication is essential, as structures are overburdened (particularly in CDTR access). Sharing organizational experiences within the healthcare system is desirable to reduce duplication and optimize the management required for individuals at risk of hereditary cancer.

Following this initiative, in December 2023, DL No. 13227/2023 was published in the Diário da República, approving the National Cancer Control Strategy, Horizon 2030. For the 1st time, under the early detection pillar, it was included a national strategic determination to establish an expert panel to support the development of Oncological Screening Standards for Hereditary Syndromes associated with increased cancer risk, particularly for *BRCA1/2*-associated breast cancer and Lynch syndrome-associated colorectal cancer. This legislative measure, linked to the National Program for Oncological Diseases, is a critical step toward integrating oncological screening for hereditary syndromes into the national healthcare system.

Conclusion

The participation of various professional groups from different SNS structures and patient associations enabled the identification of limitations in hereditary cancer risk management in Portugal and the proposal of intervention areas. This process is dynamic, requiring ongoing intra- and inter-institutional communication channels and collaboration with scientific societies and patient associations to integrate guidelines on organization, infrastructure, and technical follow-up. The implementation of screening for two major adult hereditary cancer syndromes, as outlined in DL No. 13227/2023, is recognized as a decisive step toward integrating hereditary cancer risk management at the national level.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Available from: https://www.medis.pt/mais-medis/cancro/cancro-hereditario-so-45-2 das-unidades-hospitalares-tem-estrutura-para-seguir-familias-e-doentes [Last accessed on 2024 Feb 15].
2. Roebothan A, Smith KN, Seal M, Etchegary H, Dawson L. Specialty care and counselling about hereditary cancer risk improves adherence to cancer screening and prevention in newfoundland and labrador patients with BRCA1/2 pathogenic variants: a population-based retrospective cohort study. Curr Oncol. 2023;30:9367-81.
3. Villani A, Shore A, Wasserman JD, Stephens D, Kim RH, Druker H, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol. 2016;17:1295-305.
4. Barrow P, Khan M, Lalloo F, Evans DG, Hill J. Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome. Br J Surg. 2013;100:1719-31.
5. Dullens B, de Putter R, Lambertini M, Toss A, Han S, Van Nieuwenhuysen E, et al. Cancer surveillance in healthy carriers of germline pathogenic variants in BRCA1/2: a review of secondary prevention guidelines. J Oncol. 2020;2020:9873954.
6. Gomes P, Pietrabissa G, Silva ER, Silva J, Matos PM, Costa ME, et al. Family adjustment to hereditary cancer syndromes: a systematic review. Int J Environ Res Public Health. 2022;19:1603.
7. Calabrese A, von Arx C, Tafuti AA, Pensabene M, De Laurentiis M. Prevention, diagnosis and clinical management of hereditary breast cancer beyond BRCA1/2 genes. Cancer Treat Rev. 2024;129:102785.
8. Alves IT, Condinho M, Custódio S, Pereira BF, Fernandes R, Gonçalves V, et al. Genetics of personalized medicine: cancer and rare diseases. Cell Oncol (Dordr). 2018;41:335-41.
9. Beard C, Monohan K, Cicciarelli L, James PA. Mainstream genetic testing for breast cancer patients: early experiences from the Parkville Familial Cancer Centre. Eur J Hum Genet. 2021;29:872-80.
10. ERN GENTURIS. Available from: https://www.genturis.eu [Last accessed on 2024 Nov 09].
11. Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34:3347.
12. McDevitt T, Durkie M, Arnold N, Burghel GJ, Butler S, Claes KB, et al. EMQN best practice guidelines for genetic testing in hereditary breast and ovarian cancer. Eur J Hum Genet. 2024;32:479-88.
13. NCCN Clinical Practice Guidelines - Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic; 2025. Available from: https://www.nccn.org

14. Stjepanovic N, Moreira L, Carneiro F, Balaguer F, Cervantes A, Balmaña J, et al. Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30:1558-71.
15. NCCN Clinical Practice Guidelines - Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric; 2024. Available from: https://www.nccn.org
16. Seppälä TT, Latchford A, Negoi I, Sampaio Soares A, Jimenez-Rodriguez R, Sánchez-Guillén L, et al. European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. Br J Surg. 2021;108:484-98.
17. Blair VR, McLeod M, Carneiro F, Coit DG, D'Addario JL, van Dieren JM, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020;21:e386-97.
18. Tischkowitz M, Colas C, Pouwels S, Hoogerbrugge N, PHTS Guideline Development Group, European Reference Network GENTURIS. Cancer Surveillance Guideline for individuals with PTEN hamartoma tumour syndrome. Eur J Hum Genet. 2020;28:1387-93.
19. Crosbie EJ, Ryan NA, Arends MJ, Bosse T, Burn J, Cornes JM, et al. The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. Genet Med. 2019;21:2390-400.
20. van Leerdam ME, Roos VH, van Hooft JE, Balaguer F, Dekker E, Kaminski MF, et al. Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2019;51:1082-93.
21. Monahan KJ, Bradshaw N, Dolwani S, Desouza B, Dunlop MG, East JE, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut. 2020;69:411-44.
22. Zaffaroni G, Mannucci A, Koskenvuo L, de Lacy B, Maffioli A, Bisseling T, et al. Updated European guidelines for clinical management of familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), gastric adenocarcinoma, proximal polyposis of the stomach (GAPPS) and other rare adenomatous polyposis syndromes: a joint EHTG-ESCP revision. Br J Surg. 2024;111:znae070.
23. van Leerdam ME, Roos VH, van Hooft JE, Dekker E, Jover R, Kaminski MF, et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2019;51:877895.
24. Wagner A, Aretz S, Auranen A, Bruno MJ, Cavestro GM, Crosbie EJ, et al. The management of Peutz-Jeghers syndrome: European Hereditary Tumour Group (EHTG) guideline. J Clin Med. 2021;10:473.
25. Bakhuizen JJ, Hanson H, van der Tuin K, Lalloo F, Tischkowitz M, Wadt K, et al. Surveillance recommendations for DICER1 pathogenic variant carriers: a report from the SIOPE Host Genome Working Group and CanGene-CanVar Clinical Guideline Working Group. Fam Cancer. 2021;20:337-48.
26. Geilswijk M, Genuardi M, Woodward ER, Nightingale K, Huber J, Madsen MG, et al. ERN GENTURIS clinical practice guidelines for the diagnosis, surveillance and management of people with Birt-Hogg-Dubé syndrome. Eur J Hum Genet. 2024;32:1542-50.
27. Carton C, Evans DG, Blanco I, Friedrich RE, Ferner RE, Farschtschi S, et al. ERN GENTURIS tumour surveillance guidelines for individuals with neurofibromatosis type 1. EClinicalMedicine. 2023;56:101818.
28. Legius E, Messiaen L, Wolkenstein P, Pancza P, Avery RA, Berman Y, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med. 2021;23:15061513.
29. Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG, European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet. 2020;28:1379-86.
30. Binderup ML, Smerdel M, Borgwadt L, Beck Nielsen SS, Madsen MG, Møller HU, et al. von Hippel-Lindau disease: updated guideline for diagnosis and surveillance. Eur J Med Genet. 2022;65:104538.
31. Costa C, Lemos MS, Azevedo LF, Paneque M. Service provision of genetics health care in Portugal. J Community Genet. 2023;14:101-13.
32. Available from: https://www.gustaveroussy.fr/fr/programme-apres-cancer-interval [Last accessed on 2025 Feb 23].

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CASE REPORT

The role of Epstein-Barr virus in nasopharyngeal carcinoma: a case report

O papel do vírus Epstein-Barr no carcinoma nasofaríngeo: um relato de caso

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Abstract

Nasopharyngeal carcinoma (NPC) has a strong association with Epstein-Barr virus (EBV) infection. We present the case of a 45-year-old male with non-keratinizing NPC cT1N2M0 and serum EBV DNA positivity (1.4 × 10^3 copies/mL) in April 2022. He underwent three cycles of cisplatin/gemcitabine until October 2022 and was submitted to chemoradiotherapy, obtaining a partial imaging response and undetectable EBV DNA. In April 2023, he presented with bone and lymph node metastases, with EBV DNA < 250 copies/mL. He underwent palliative chemotherapy with carboplatin/paclitaxel and, after six cycles of treatment, showed concomitant disease progression with an increase in EBV viral load. He began treatment with nivolumab but maintained an increase in EBV DNA, and after two cycles, disease progression was confirmed, and rechallenge with gemcitabine was proposed. He obtained a partial response and EBV DNA < 250 copies/mL. Thus, monitoring plasma EBV DNA can play a role in surveillance and in assessing the response to Nicole Conradie therapy.

Keywords: *Nasopharyngeal carcinoma. Epstein–Barr virus infections. Herpesvirus 4. Human. Early detection of cancer.*

Resumo

O carcinoma da nasofaringe (CN) tem uma forte associação com a infeção pelo vírus Epstein-Barr (EBV). Apresentamos o caso de um homem de 45 anos com CN não queratinizante cT1N2M0 e positividade sérica do DNA de EBV (1.4x10^3 cópias/mL) em 04/2022. Realizou 3 ciclos de cisplatina/gemcitabina até 10/2022 e foi submetido a quimiorradioterapia, tendo obtido resposta imagiológica parcial e ADN do EBV indetetável. Em 04/2023 apresentou metastização óssea e ganglionar com DNA do EBV < 250 cópias/mL. Foi submetido a quimioterapia paliativa com carboplatina/paclitaxel e, após 6 ciclos do tratamento, apresentou progressão de doença concomitante com aumento da carga vírica do EBV Iniciou tratamento com Nivolumab mas manteve aumento do DNA do EBV e, após 2 ciclos, confirmou-se progressão da doença, tendo sido proposto rechallenge com gemcitabina. Obteve resposta parcial e DNA EBV < 250 cópias/mL. Assim, a monitorização do DNA EBV plasmático pode ter papel na vigilância e na avaliação de resposta à terapêutica do CN.

Palavras-chave: *Carcinoma da nasofaringe. Infeções pelo vírus Epstein-Barr. Herpesvírus 4. Humano. Deteção precoce de cancro.*

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Introduction

Nasopharyngeal carcinoma (NPC) is classified into three subtypes: keratinizing squamous cell carcinoma (type 1), non-keratinizing squamous cell carcinoma (type 2), and undifferentiated carcinoma (type 3)[1,2]. The initial symptoms of NPC may be subtle, with an estimated delay of approximately 6 weeks between symptom onset and the first medical evaluation[1]. Approximately 70% of patients present with advanced-stage disease at diagnosis[1]. The gold-standard diagnostic procedure for NPC is nasopharyngeal endoscopy with histological biopsy[2].

NPC exhibits unique characteristics, particularly its association with Epstein-Barr virus (EBV) infection, especially in subtypes 2 and 3[1,2]. EBV is classified as a Group 1 carcinogen by the International Agency for Research on Cancer, indicating sufficient evidence of carcinogenicity in humans[2]. Ninety percent of the global population harbors a persistent, asymptomatic EBV infection. In regions where NPC is endemic, EBV accounts for 95% of NPC incidence and 100% of NPC-related mortality[1]. The majority of NPC cases occur in East and Southeast Asia (70%), followed by South and Central Asia (6.3%), North Africa (2.6%), and Southern Africa (2.4%)[1].

In cases of NPC, EBV detection in histological samples through *in situ* hybridization is recommended[2]. Furthermore, a correlation has been established between plasma EBV DNA concentration and disease stage, clinical outcomes, and overall survival[1,2]. Incorporating this assessment into the tumor, node, metastasis (TNM) staging system appears to enhance its prognostic accuracy[1,2].

In this article, we present the case of a male patient diagnosed with NPC and the monitoring of EBV DNA throughout his clinical course.

Case report

A 45-year-old male was referred to our oncology center with a 2-month history of fever, night sweats, and a left cervical mass. Cervical computed tomography (CT) revealed an extensive conglomerate of lymphadenopathy involving levels II, III, IV, and V on the left side, with no evidence of a primary neoplasm. Excisional biopsy of one of the lymph nodes revealed metastatic undifferentiated carcinoma originating from the upper aerodigestive tract.

The patient underwent positron emission tomography-CT (PET-CT), which demonstrated increased uptake in the nasopharynx and the cervical lymph node conglomerate. Nasopharyngeal biopsy confirmed a diagnosis of non-keratinizing undifferentiated NPC, positive for EBV-encoded RNA and negative for p16. Clinical staging was cT1N2M0 (stage III). Plasma EBV DNA was positive (1.4×10^3 copies/mL).

The patient completed three cycles of cisplatin (100 mg/m^2) and gemcitabine (1250 mg/m^2) every 21 days until October 2022, with a favorable metabolic response on PET-CT and undetectable plasma EBV DNA levels (Fig. 1). Following multidisciplinary discussion, the patient underwent concurrent chemoradiotherapy (CRT), consisting of radiotherapy to the primary tumor and cervical lymph nodes (total dose of 70 Gy in 35 fractions) and cisplatin (100 mg/m^2) every 21 days for three cycles, completed in January 2023.

Three months after completing CRT, a new PET-CT revealed bone and lymph node metastases. Lymph node biopsy confirmed metastasis of the previously diagnosed NPC. At this time, plasma EBV DNA was < 250 copies/mL. He initiated chemotherapy with carboplatin area under the curve (AUC 6) and paclitaxel (175 mg/m^2), completing six cycles by October 2023. The main toxicity observed was grade 2 sensory peripheral neuropathy (per CTCAE v5.0).

Post-treatment PET-CT showed disease progression with *de novo* hepatic metastases, and plasma EBV DNA became positive (7.8×10^3 copies/mL). The patient began a new line of treatment with nivolumab (480 mg every 28 days). After the second cycle, the patient was hospitalized for persistent fever and started on broad-spectrum antibiotics. However, no microbiological agents were identified, and a significant increase in plasma EBV DNA copies was observed (1.0×10^6 copies/mL).

Cervico-thoraco-abdominal CT (CTA) revealed disease progression (lymphatic, bone, and hepatic), with no evidence of infectious focus. After discussion within the medical oncology team and with the patient, rechallenge with gemcitabine (1000 mg/m^2 on days 1, 8, and 15 every 28 days) was proposed.

Following the first cycle, the patient experienced sustained apyrexia and clinical improvement (reduction in pain and anorexia). After the third cycle, imaging showed a partial response, and there was a decrease in EBV viral load (< 250 copies/mL) (Fig. 2). Due to grade 3 hematologic toxicity (per CTCAE v5.0), the gemcitabine dose was reduced to 750 mg/m^2 after the third cycle.

After the fifth cycle of treatment, the patient developed a fever and was diagnosed with a severe acute

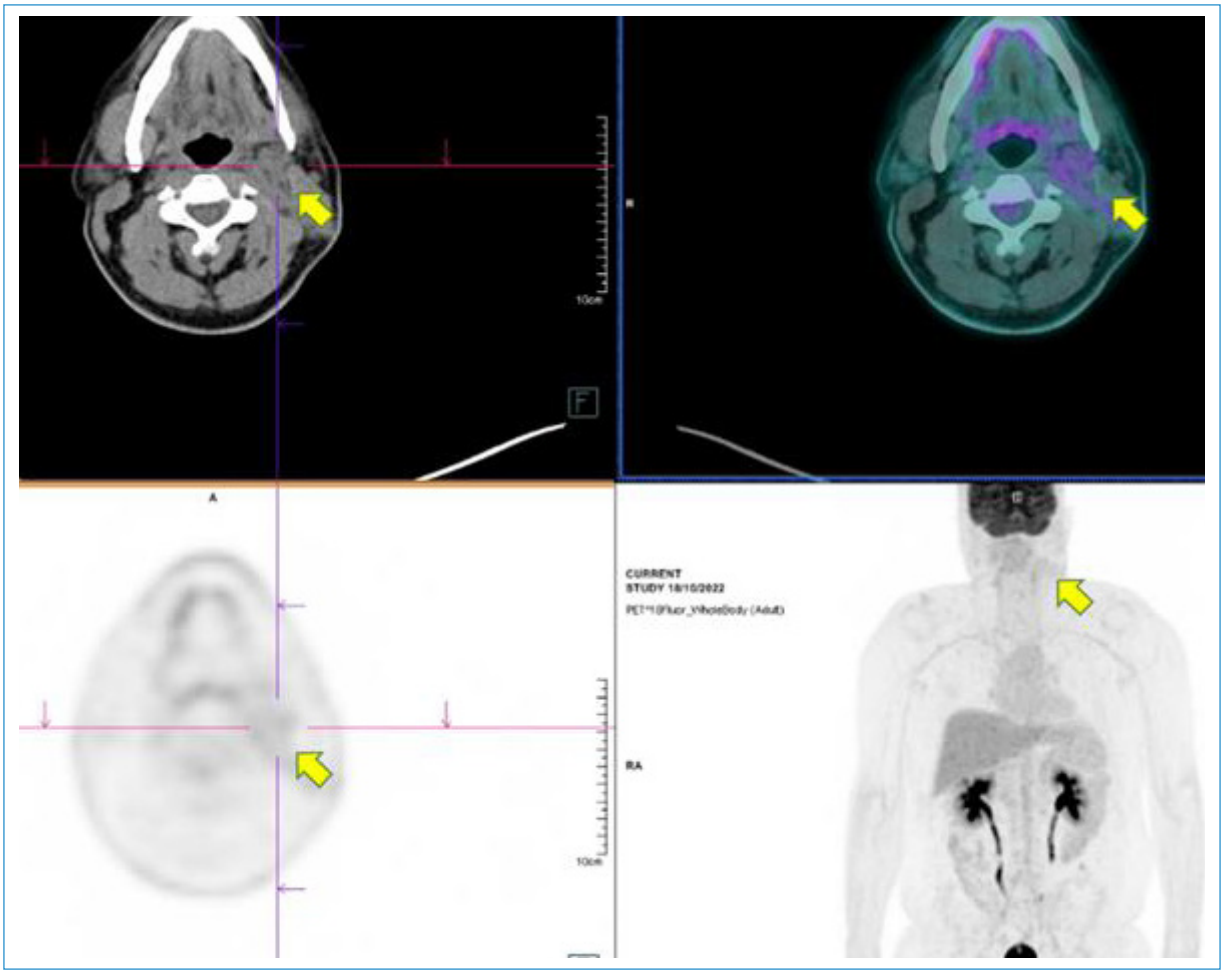


Figure 1. Imaging assessment by positron emission tomography-computed tomography following chemoradiotherapy, showing dimensional and metabolic regression of the left cervical lymph node conglomerate (yellow arrows), compared to the baseline scan.

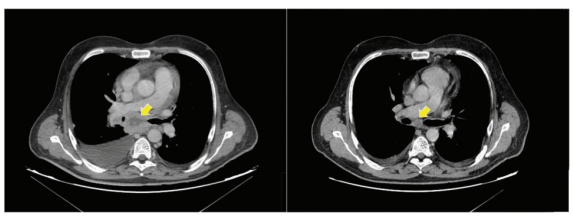


Figure 2. Partial response of lymph node disease (yellow arrow); computed tomography from January 2024 on the left and March 2024 on the right.

respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A CTA performed in June 2024 revealed disease progression (lymph nodes and liver). Due to worsening general condition and persistent fever, the patient was hospitalized for further investigation. He was diagnosed with sepsis of undetermined origin and multiorgan dysfunction (respiratory and renal). Despite the therapeutic measures, the patient's clinical condition continued to deteriorate, and he passed away during hospitalization.

Discussion

The pathogenesis of NPC is influenced by environmental factors (such as tobacco use, alcohol consumption, and diet), host-related factors (including male sex, genetic predisposition, and ethnicity), and EBV infection[1].

Between 5% and 15% of patients who undergo radical treatment for NPC will experience locoregional recurrence, and 15-30% will develop distant metastases[1]. The risk of recurrence following curative-intent radiotherapy follows a bimodal pattern, with peaks at approximately 1.5 and 3.5 years of follow-up[2]. Plasma EBV DNA detection is thought to enable the early identification of

Table 1. Temporal evolution of EBV viral load

Date	June 2022	October 2022	April 2023	October 2023	January 2024	March 2024	May 2024
Viremia (copies/mL)	1.40×10^3	ND	< 250	7.80×10^3	1.0×10^6	< 250	572
Response evaluation	Baseline	Metabolic response (PET)	DP	DP	DP	PR	NA

NA: not assessed; ND: not detected; PD: progressive disease; PR: partial response.

disease recurrence during follow-up (level of evidence V, grade of recommendation B)[2]. Therefore, plasma EBV DNA quantification should be considered 1-4 weeks after radiotherapy (level of evidence II, grade of recommendation B) and annually thereafter (level of evidence V, grade of recommendation B)[2].

In addition, plasma EBV DNA concentration is a prognostic factor for distant metastases in patients eligible for surgical treatment, and both its concentration and clearance rate during therapy are prognostic indicators in patients receiving first-line palliative treatment[2].

Immunotherapy is a promising treatment option for unresectable or metastatic NPC, partly due to the high expression of EBV-related antigens and CD4+/CD8+T-cell target proteins[3]. Immunotherapy may be active (e.g., vaccination, immune checkpoint inhibitors [ICIs]) or passive (e.g., adoptive transfer of autologous EBV-targeting cytotoxic T lymphocytes)[3]. The most recent update of the European guidelines includes ICIs in combination with chemotherapy as a first-line palliative treatment, whereas ICI monotherapy remains a second-line option[4].

Early diagnosis of NPC remains a challenge due to its deep anatomical location and non-specific symptoms[1]. As such, EBV testing has been investigated as a screening tool in endemic regions and high-risk individuals (particularly men aged 30-59 years), demonstrating utility in detecting early asymptomatic NPC. Even small tumors may release sufficient DNA into the circulation to allow detection[5,6].

Serological evaluation of anti-EBV capsid antigen (viral capsid antigen immunoglobulin A [IgA]), anti-EBV nuclear antigen IgA, and early antigen IgA, when combined, shows high sensitivity and specificity (91-96%) for screening purposes, although the positive predictive value (PPV) remains low (< 10%)[1,5].

EBV viremia detection has also been studied as a screening method, with high specificity and sensitivity (97% and 99%, respectively), though it is associated with higher costs and the need for advanced laboratory infrastructure[5,7]. Detection of methylation patterns in circulating DNA appears to be a promising method, given the high PPV reported in studies of other malignancies[1,7].

Conclusion

This case report aimed to illustrate how EBV viremia monitoring may be relevant in detecting disease progression or recurrence (Table 1). Thus, monitoring plasma EBV DNA concentration may contribute to a more personalized treatment approach for patients with NPC. We also aimed to highlight the challenges in selecting subsequent lines of therapy following first-line treatment failure in metastatic NPC.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution’s confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Su ZY, Siak PY, Leong CO, Cheah SC. The role of epstein-barr virus in nasopharyngeal carcinoma. Front Microbiol. 2023;14:1116143.
2. Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, et al. Nasopharyngeal carcinoma: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32:452-65.
3. Huang H, Yao Y, Deng X, Huang Z, Chen Y, Wang Z, et al. Immunotherapy for nasopharyngeal carcinoma: current status and prospects (Review). Int J Oncol. 2023;63:97.
4. Bossi P, Chan AT, Even C, Machiels JP, ESMO Guidelines Committee. ESMO-EURACAN clinical practice guideline update for nasopharyngeal carcinoma: adjuvant therapy and first-line treatment of recurrent/metastatic disease. Ann Oncol. 2023;34:247-50.
5. Yuan Y, Ye F, Wu JH, Fu XY, Huang ZX, Zhang T. Early screening of nasopharyngeal carcinoma. Head Neck. 2023;45:2700-9.
6. Chan KC, Woo JK, King A, Zee BC, Lam WK, Chan SL, et al. Analysis of plasma epstein-barr virus DNA to screen for nasopharyngeal cancer. N Engl J Med. 2017;377:513-22.
7. Siak PY, Heng WS, Teoh SS, Lwin YY, Cheah SC. Precision medicine in nasopharyngeal carcinoma: comprehensive review of past, present, and future prospect. J Transl Med. 2023;21:786.