

The Future of Periocular Oncology: Fighting the War Against Cancer

Claire Daniel, BSc(Hons) FRCOphth,
Cancer Lead & Adnexal Service Director,
Moorfields Eye Hospital, London, UK
Honorary Consultant Head & Neck Dept.
Guys & St Thomas' Hospital, London, UK



No Disclosures

c.daniel@nhs.net

The History of Cancer Treatment



Ancient Warfare

— The Scalpel !

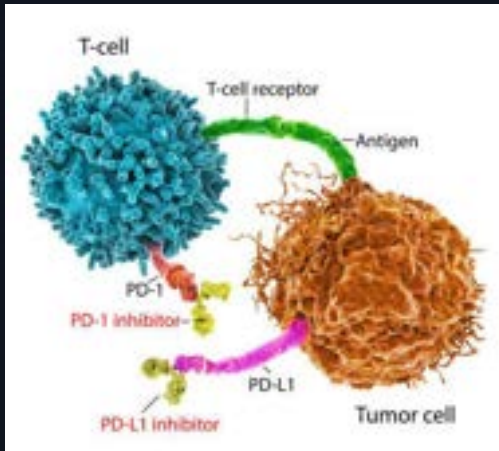
Surgery alone.— radical excision, exenteration, disfigurement accepted as the price of survival.



Cold War

— Nuclear Deterrence

Radiotherapy — massive destructive power, but scorched landscape: dry eye, cataract, radiation retinopathy, lacrimal damage.



Modern Era

-Autonomous Intelligence

Immunotherapy — checkpoint inhibitors (PD-1/PD-L1, CTLA-4). The immune army learns to recognise and destroy cancer cells independently.

1

2

World War I

- Chemical Weapons

Chemotherapy born from mustard gas research.

Toxic to all cells, friend and foe alike — devastating collateral damage.



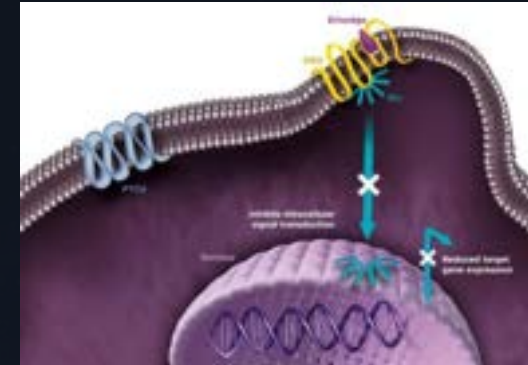
3

4

Gulf War

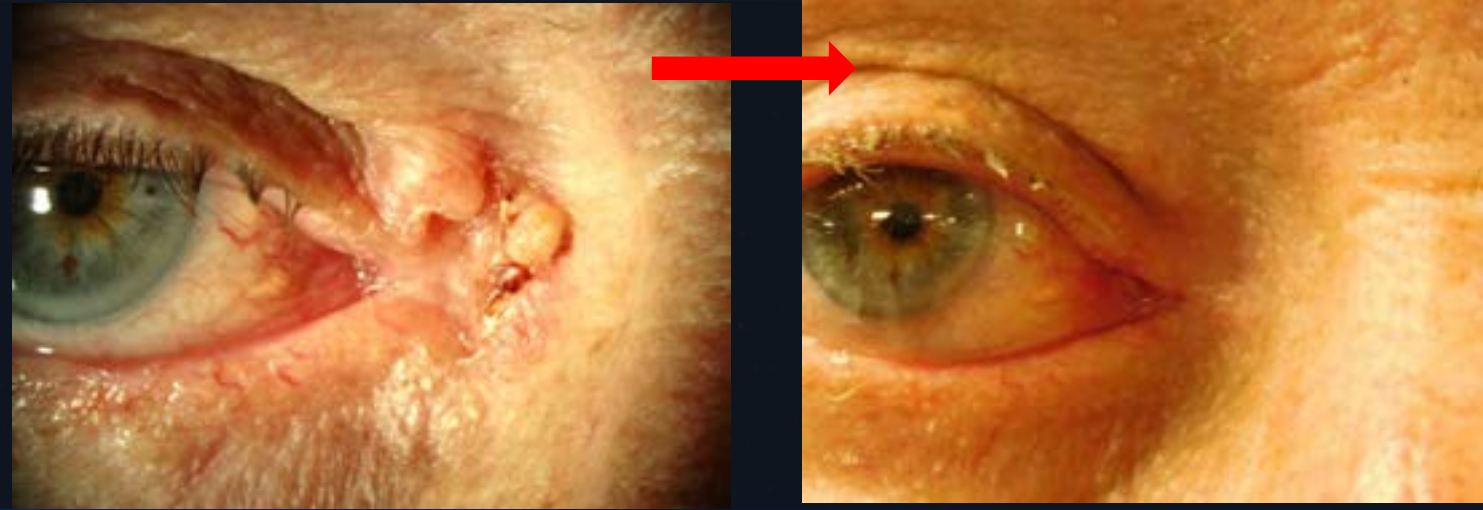
— Precision Missiles

Targeted therapy — Hedgehog inhibitors, EGFR blockers, BRAF/MEK inhibitors. Strike the specific molecular pathway; spare surrounding tissue.



5

Basal Cell Carcinoma: The Most Common Enemy



Know the Enemy

Most common periocular malignancy — **~90% of eyelid cancers.**

Nodular BCC most frequent subtype; morphoeic/infiltrative subtypes carry higher recurrence risk.

Medial canthal location is high-risk — proximity to orbit, lacrimal system, and perineural pathways.

Surgical First Strike

Mohs micrographic surgery — **gold standard** for periocular BCC.

Margin control is critical; conventional excision has higher recurrence rates at this site.

Orbital invasion: multidisciplinary approach mandatory — consider eye-sparing surgery before exenteration.

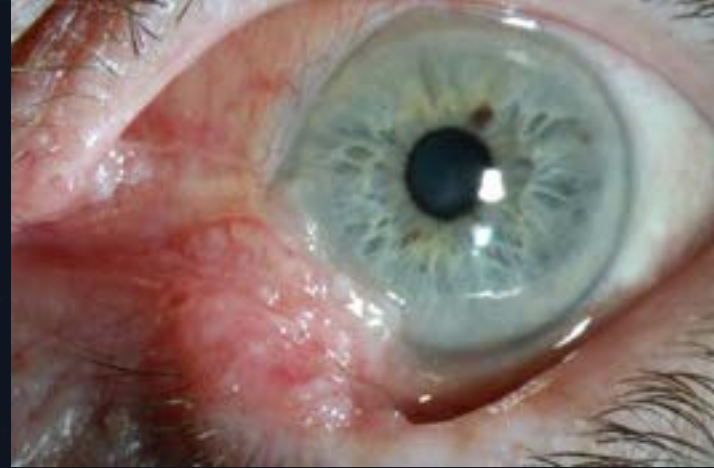
Hedgehog Inhibitors

Advanced/orbital invasion: Hedgehog pathway inhibitors — **vismodegib (Erivedge)** and **sonidegib (Odomzo).**

- Pooled complete response rate **38.4%**, partial response **39.2%** across 764 patients ¹
- Recurrence following discontinuation in **17.4%**; exenteration still required in **28.1%** despite HHI therapy
- **Second-line** for HHI-resistant BCC: cemiplimab (PD-1 inhibitor)

1. Alessa D (2026) Efficacy and safety of vismodegib in periocular and orbital basal cell carcinoma: a systematic review and meta-analysis. Front. Med. 13:1722574. doi: 10.3389/fmed.2026.1722574

Squamous Cell Carcinoma: The Advancing Enemy



Know the Enemy

Second most common periocular malignancy.
Perineural spread to the orbit and skull base is the critical danger

Risk factors: UV exposure, immunosuppression, HPV, prior radiotherapy.

High-risk features: >2cm, poorly differentiated, perineural invasion, depth >6mm.

Or can arise from conjunctival surface (OSSN)

Surgical Strategy & Surveillance

Wide local excision with clear margins — Mohs for high-risk periocular lesions.

Sentinel lymph node biopsy for high-risk lesions (>2cm, poorly differentiated, immunosuppressed patients).

Imaging (MRI orbits/skull base) mandatory if perineural spread suspected.

Red flags for perineural spread: V1 numbness, unexplained ptosis, diplopia in any patient with periocular SCC history

Systemic Arsenal — PD-1 Inhibitors

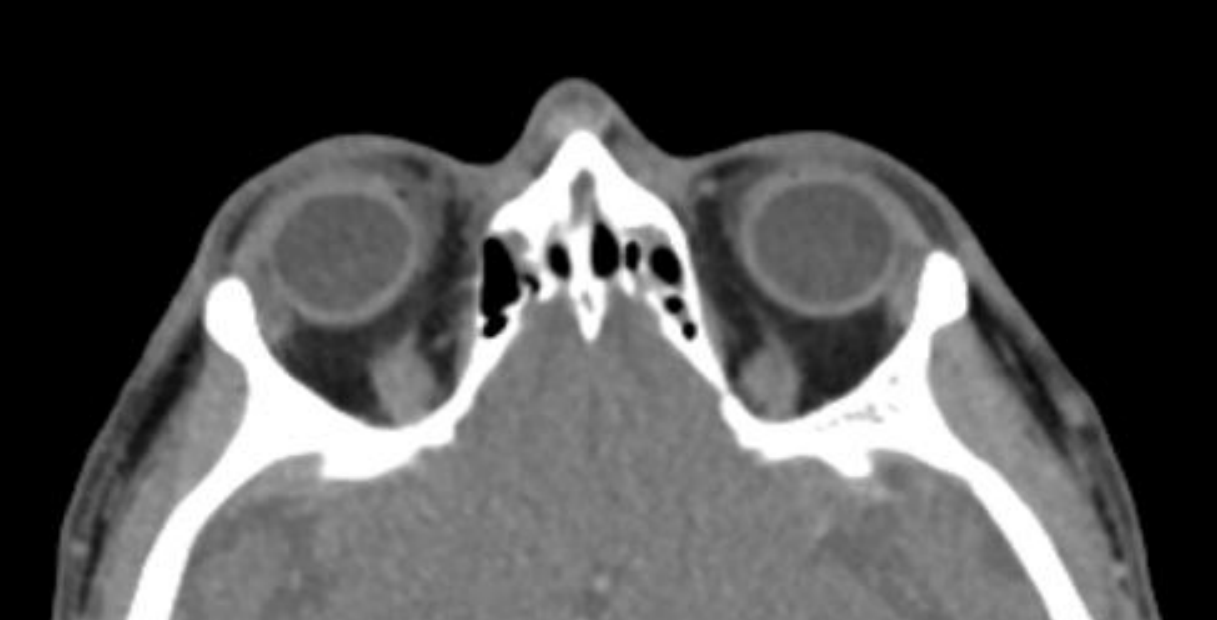
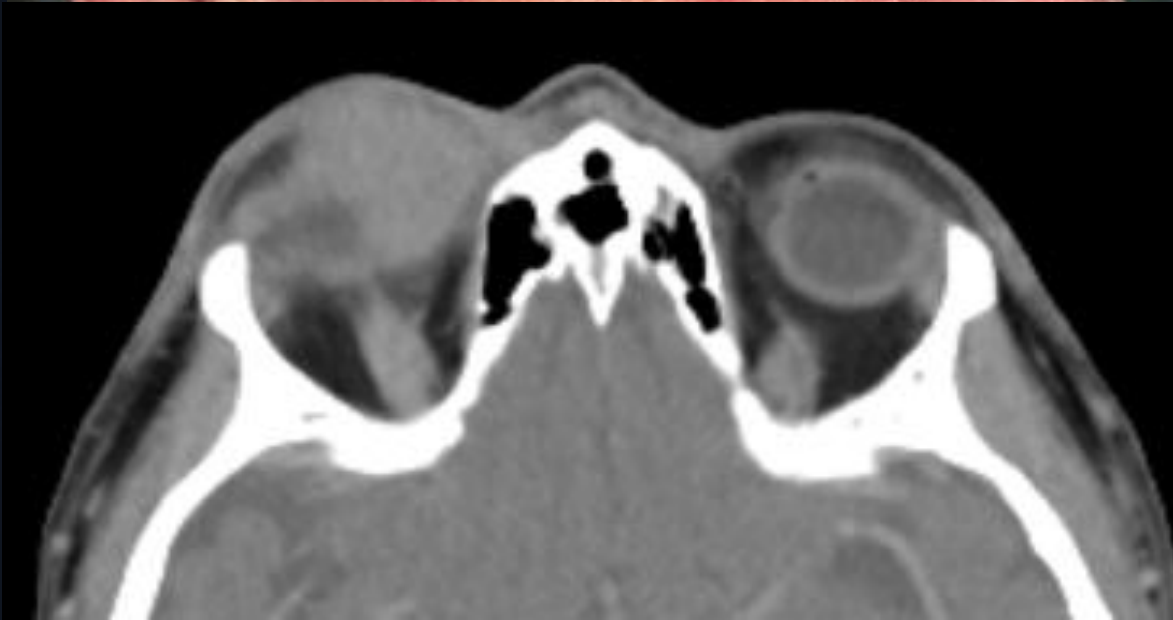
Cemiplimab and pembrolizumab now first-line for locally advanced/unresectable disease.

2026 Moorfields series (n=9):
22% CR, 33% PR, 44% No response²

2025 MD Anderson series 6/10 PR, 4/10 CR with cemiplimab for perineural orbital SCC.³

2. Kanda, M., Jayawickrema, N., Davagnanam, I., Samia-Aly, E., Gupta, T., & Daniel, C. (2026). Cemiplimab in advanced periocular conjunctival and cutaneous squamous cell carcinoma: a United Kingdom case series. *Orbit*, 45(1), 63–73.

3. Lu, T. J., Fan, J., Guimaraes de Sousa, L., Sagiv, O., Hernandez, S., Bolanos Gomez, L., Akhave, N., Ferrarotto, R., & Esmaeli, B. (2025). PD-1 Inhibitors for Periocular Squamous Cell Carcinoma With Perineural Spread to the Orbit and Skull Base. *Ophthalmic Plastic & Reconstructive Surgery*, 41(6), 664–670.



Sebaceous Carcinoma: The Great Masquerader



Know the Enemy

- Arises from **meibomian glands** or **glands of Zeis**
- Mimics chronic blepharitis, chalazion — often misdiagnosed for **months to years**
- **Pagetoid spread** to conjunctiva in up to **44%** of cases — map biopsies are essential
- Association with **Muir-Torre syndrome** (MMR-deficient tumours)

Surgical Strategy

- Wide local excision with **frozen section control**
- Adjuvant radiotherapy for positive margins or lymph node involvement
- Sentinel lymph node biopsy now recommended for tumours **>10mm** or with pagetoid spread
- Conjunctival map biopsies mandatory to assess extent of pagetoid spread **before definitive surgery**

Systemic Options

- Emerging role for **pembrolizumab** in metastatic/MMR-deficient disease
- Muir-Torre syndrome patients (*MLH1*, *MSH2* mutations) may be responsive to **PD-1 blockade**⁴
- No established targeted therapy beyond immunotherapy — **enrol in trials where possible**

4. Woods AD, Grushchak S, Williams KM, Tan A, Kronic AL. Combination treatment of bilateral periocular sebaceous carcinomas with microsatellite instability with neoadjuvant pembrolizumab and Mohs surgery. *Australas J Dermatol*. 2022 Nov;63(4):e345-e349. doi: 10.1111/ajd.13919. Epub 2022 Sep 8. PMID: 36073830; PMCID: PMC9825858.

Conjunctival & Cutaneous Melanoma:

Conjunctival Melanoma

Rare but lethal — 5-year mortality ~25%. Arises from PAM with atypia or de novo.

- Local excision + cryotherapy + topical mitomycin C (MMC) for conjunctival disease
- SLNB for tumours >2mm thickness
- Systemic: BRAF/MEK inhibitors (dabrafenib + trametinib) for BRAF V600E-mutant disease
- PD-1 inhibitors (pembrolizumab, nivolumab) for advanced/metastatic — increased overall survival, local and metastatic disease control, decreased surgical morbidity, avoidance of orbital exenteration ⁵
- Neoadjuvant ipilimumab + nivolumab now being explored for locally advanced disease — Italian Melanoma Intergroup series (2025): 3/4 patients achieved ocular preservation, 1 complete response with surgery deferral

Cutaneous Melanoma of the Eyelid

Treat per cutaneous melanoma guidelines — wide excision, SLNB for 0.8mm Breslow thickness, systemic therapy for stage III/IV.

BRAF status for advanced cases.

Molecular Testing — for systemic disease

- BRAF V600E: dabrafenib + trametinib
- NRAS mutant: MEK inhibitors (trametinib)
- Wild-type: PD-1 ± CTLA-4 blockade
- All advanced cases: test TMB, PD-L1, MSI status





Hong BY, Ford JR, Glitza IC, Torres Cabala CA, Tetzlaff M, Prieto VG, Parker R, Daniel C, Esmali B. Immune Checkpoint Inhibitor Therapy as an Eye-Preserving Treatment for Locally Advanced Conjunctival Melanoma. *Ophthalmic Plast Reconstr Surg*. 2021 Jan-Feb 01;37(1):e9-e13. doi: 10.1097/IOP.0000000000001700. PMID: 32618825; PMCID: PMC7744319.



Merkel Cell Carcinoma



What Is MCC?

Highly aggressive neuroendocrine tumour
eyelid is a common site.
Merkel cell polyomavirus (MCPyV)
implicated in ~**80%** of cases.
Rapid growth, early nodal spread, high
recurrence risk.

Historical Arsenal — Rapid Excision

Wide local excision + adjuvant
radiotherapy.
Chemotherapy for metastatic disease
— poor durable responses.
5-year survival for stage IV historically
<20%.

Modern Weapons — Checkpoint Blockade

Avelumab (anti-PD-L1, FDA-
approved 2017) — first-line for
metastatic MCC;

durable responses in ~**33% at 2
years.**

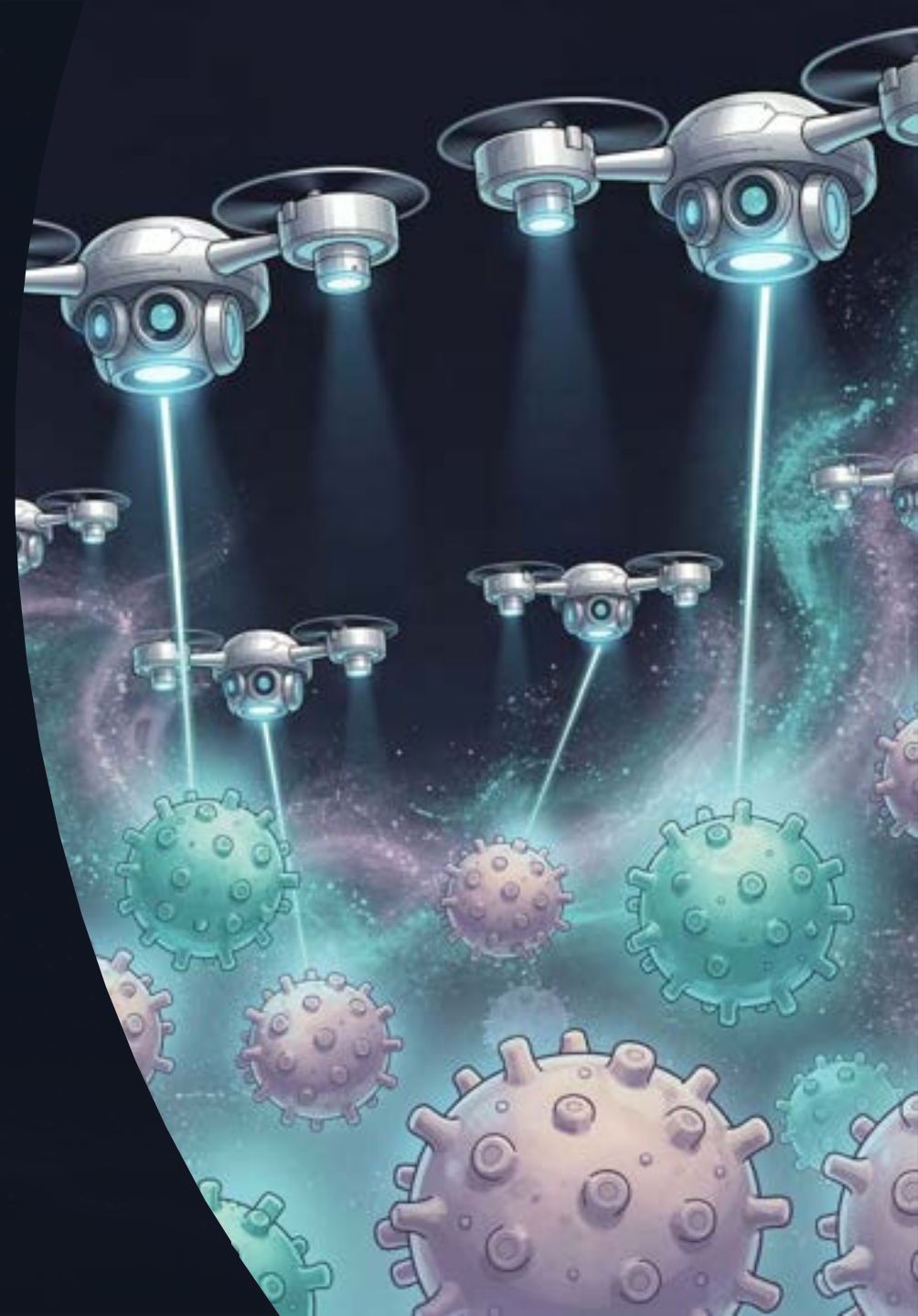
Pembro and nivo also may help.
Neoadjuvant immunotherapy trials
ongoing for localised disease.

Kok L.T., Nghiem A.Z., Uddin J.M. Gupta T, Daniel C.
Management and outcomes of periorbital Merkel cell carcinoma: a tertiary eye centre
experience. Eye **39**, 1011–1014 (2025). <https://doi.org/10.1038/s41433-025-03649-w>

c.daniel@nhs.net

New Weapons on the Horizon

The “Drone Age” of Periocular Oncology



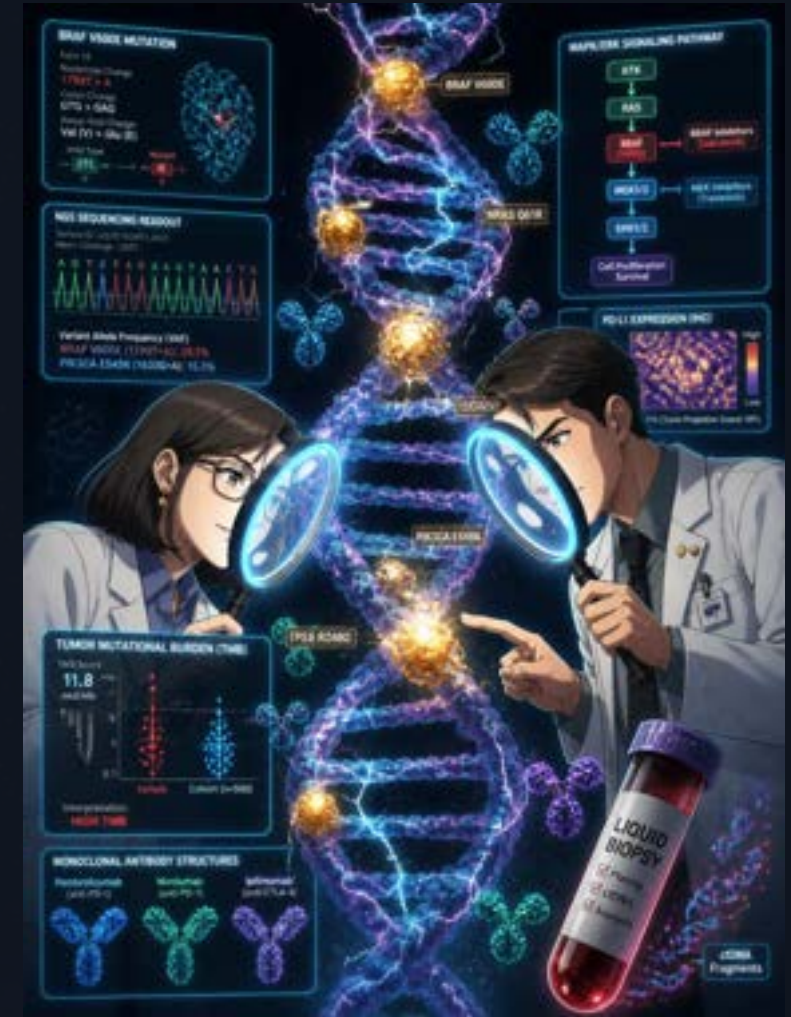
Next-Generation Treatments: The Drone Age of Oncology



Molecular Profiling & Biobanking; Mapping the Enemy's (DNA) Plans

Intelligence planning — TMB, PD-L1, MSI identify which patients will respond to immunotherapy before treatment begins.

- NGS panels identify actionable mutations (BRAF, NTRK, EGFR, HER2, MMR, TMB, MSI) from a single biopsy.
- Biobanking enables trial eligibility screening and future biomarker discovery.
- Molecular tumour boards: match NGS results to targeted therapy or trial
- Key targets: BRAF V600E (melanoma), NTRK fusions (lacrimal ACC), PD-L1/TMB (SCC, MCC), CD19/CD20 (lymphoma)
- Understanding of tumour microenvironment ⁶



6. Booth L et al. Circulating B cell and T cell activation states predict clinical outcomes in melanoma and reveal dynamic immune reinvigoration with checkpoint inhibitor immunotherapy. Journal for ImmunoTherapy of Cancer. 2026;14:e015585. <https://doi.org/10.1136/jitc-2026-015585>

c.daniel@nhs.net



Combination Immunotherapy

Coordinated multi-domain attack — dual checkpoint blockade (nivolumab + ipilimumab) showing superior responses in melanoma and MCC.



Neoadjuvant Therapy — Pre-Emptive Strike before surgery: shrink the tumour, preserve the eye, then operate.

- Vismodegib pre-op for BCC — enables Mohs where exenteration was previously inevitable
- Cemiplimab neoadjuvant for SCC — complete responses allowing surgery cancellation
- Cisplatin + proton beam RT for lacrimal gland ACC — eye-sparing outcomes
- Ipi + nivo for conjunctival melanoma — Italian Melanoma Intergroup 2025: 3/4 achieved ocular preservation ⁷

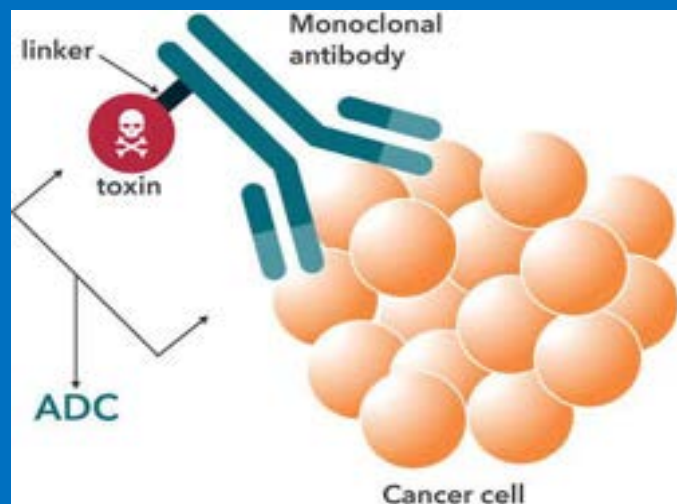




Antibody-Drug Conjugates (ADCs)

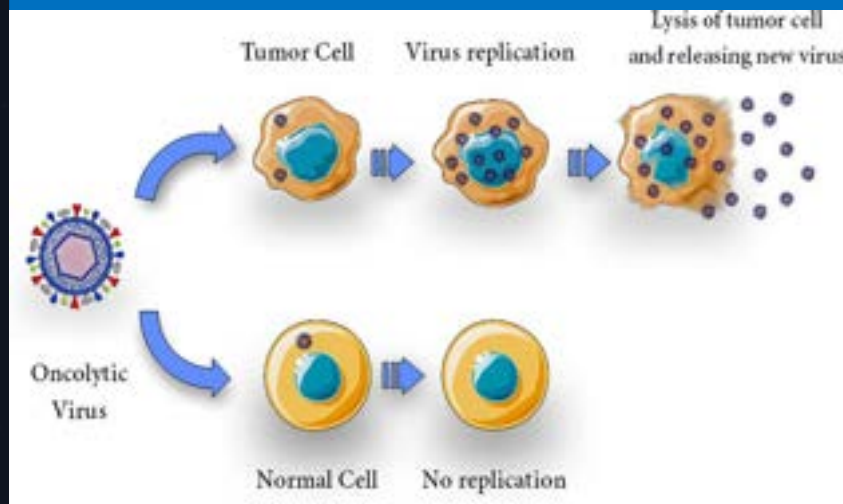
Precision-guided missiles — monoclonal antibody delivers cytotoxic payload directly to tumour surface antigen.

Tebentafusp active in uveal melanoma;
ADCs targeting **HER2**, **TROP-2** in development for periocular SCC and lacrimal gland tumours.



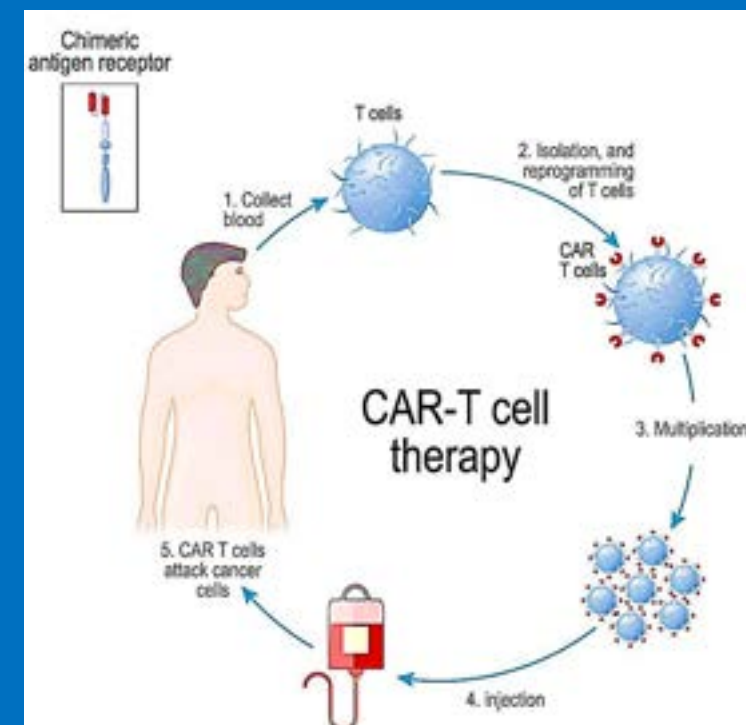
Oncolytic Virotherapy

Biological warfare turned in our favour — engineered viruses selectively infect and lyse tumour cells while stimulating immune response. T-VEC approved for melanoma; periocular trials ongoing.



CAR-T Cell Therapy

Autonomous drone swarms — genetically engineered T-cells programmed to seek and destroy specific tumour antigens. Active trials in ocular adnexal lymphoma (CD19, CD20 CAR-T).

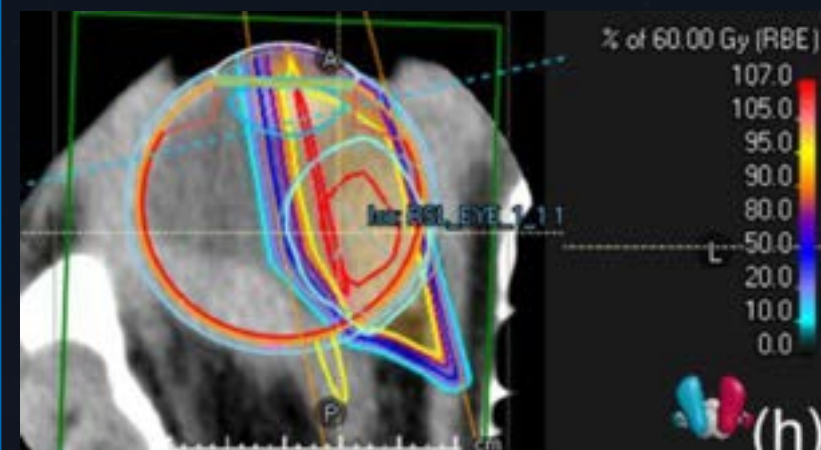
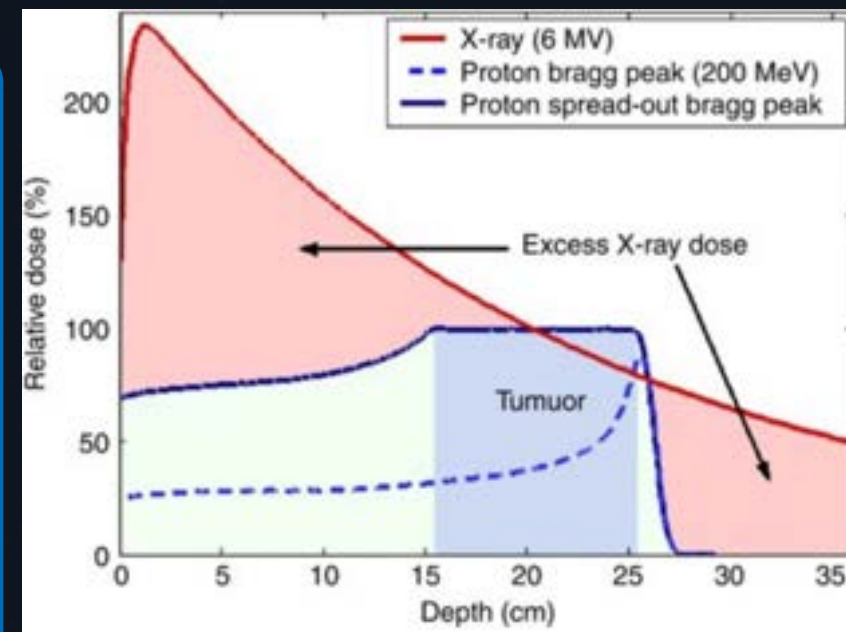


Precision Radiotherapy

Proton Beam Radiotherapy — Maximum Precision

The Bragg Peak advantage: proton beams deposit maximum dose at a precise, programmable depth — then stop. Near-zero exit dose beyond the tumour.

- Now standard of care for lacrimal gland adenoid cystic carcinoma (ACC) and selected orbital tumours at specialist centres
- Reduces radiation-induced cataract, dry eye, and retinopathy compared to conventional photon RT
- Eye-sparing alternative to exenteration when combined with neoadjuvant chemotherapy
- UK centres: University College London Hospital (UCLH), Clatterbridge Hospital, Liverpool.



Precision Radiotherapy

IMRT & Stereotactic Radiotherapy

— Smart Targeting

Intensity-Modulated Radiotherapy (IMRT): computer-optimised multi-beam delivery that sculpts the dose around the tumour, sparing adjacent critical structures. Now widely available across UK oncology centres.

Stereotactic Radiosurgery (SRS) / SBRT: ultra-precise high-dose delivery in 1–5 fractions. Used for orbital metastases, lymphoma, and selected primary tumours.

CyberKnife and Gamma Knife platforms available at specialist UK centres.

The Evolution — From Nuclear to Surgical Strike

- Conventional RT (1950s–80s): broad field, significant collateral damage — cataract, dry eye, retinopathy, lacrimal damage
- 3D-CRT (1990s): shaped fields, improved sparing
- IMRT (2000s): dose sculpting around critical structures
- Proton beam / SBRT (2010s–present): sub-millimetre precision, near-zero exit dose — the bunker-busting munition of modern oncology



AI & Liquid Biopsy: Battlefield Surveillance

Artificial Intelligence

- AI-assisted dermoscopy and anterior segment imaging for early detection of conjunctival melanoma, PAM, and eyelid malignancies
- Deep learning models achieving **dermatologist-level accuracy** in BCC/SCC detection
- AI-guided **surgical margin assessment in real time** — emerging capability
- Biobank matching

Liquid Biopsy – circulating tumour DNA (ctDNA)

- ctDNA detects minimal residual disease, monitors treatment response, identifies resistance mutations — **without repeat biopsy**
- Particularly promising for **conjunctival melanoma and MCC** post-treatment surveillance





Explore content ▾ About the journal ▾ Publish with us ▾ Subscribe

nature > news > article

NEWS | 20 August 2026 | Correction 20 August 2026

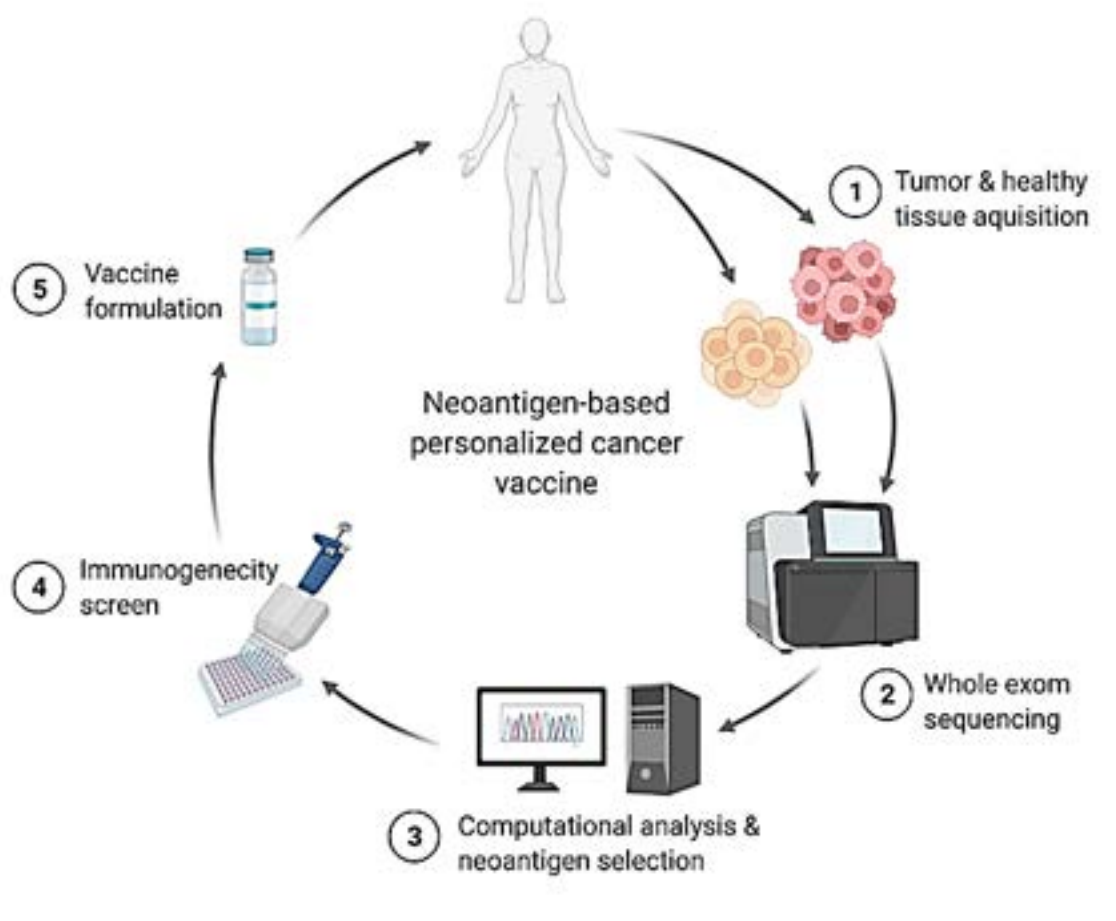
Moderna cancer vaccine stops melanoma returning: what's next for personalized treatments?

Promising trial results suggest cancer vaccines work and could be used to target other tumours.

MEAN VACCINE

STREAM CNBC+

Bespoke Cancer Vaccinations:



Tumour Vaccination — Biological Weapons

Bespoke vaccines manufactured from each patient's own tumour fingerprint.

- mRNA-4157/V940 (Moderna + MSD): 44% reduction in melanoma recurrence vs pembrolizumab alone (KEYNOTE-942)
- Relevant to periocular melanoma and high-risk MCC — trials expanding
- Dendritic cell vaccines: active trials in uveal and conjunctival melanoma
- Vaccine + checkpoint inhibitor: synergistic attack — prime the response, remove the brakes
- Future: off-the-shelf shared neoantigen vaccines — weeks to hours

Grimmett, E., Al-Share, B., Alkassab, M.B. *et al.* Cancer vaccines: past, present and future; a review article. *Discov Onc* 13, 31 (2022).
<https://doi.org/10.1007/s12672-022-00491-4>

c.daniel@nhs.net

The Coalition of Forces: Multidisciplinary Teams

Field Commander

The **ophthalmologist** — first to see the patient; responsible for early recognition, biopsy, and urgent referral. Your clinical suspicion is the intelligence that triggers the entire campaign.

NATO Alliance — The MDT

Oculoplastic surgeon
Dermatologist
Oncologist
Radiation oncologist
Pathologist
Radiologist

The War Room — Tumour Board

Every periocular malignancy beyond simple BCC should be discussed at a **specialist tumour board** before definitive treatment. Decisions made in isolation lead to under-treatment, over-treatment, and missed opportunities for eye preservation.

Forward Reconnaissance — SLNB

Recommended for: high-risk BCC, SCC >2cm, sebaceous carcinoma >10mm, conjunctival melanoma >2mm, and MCC.

Identifies microscopic nodal disease before it becomes macroscopic — changes staging and systemic treatment decisions.

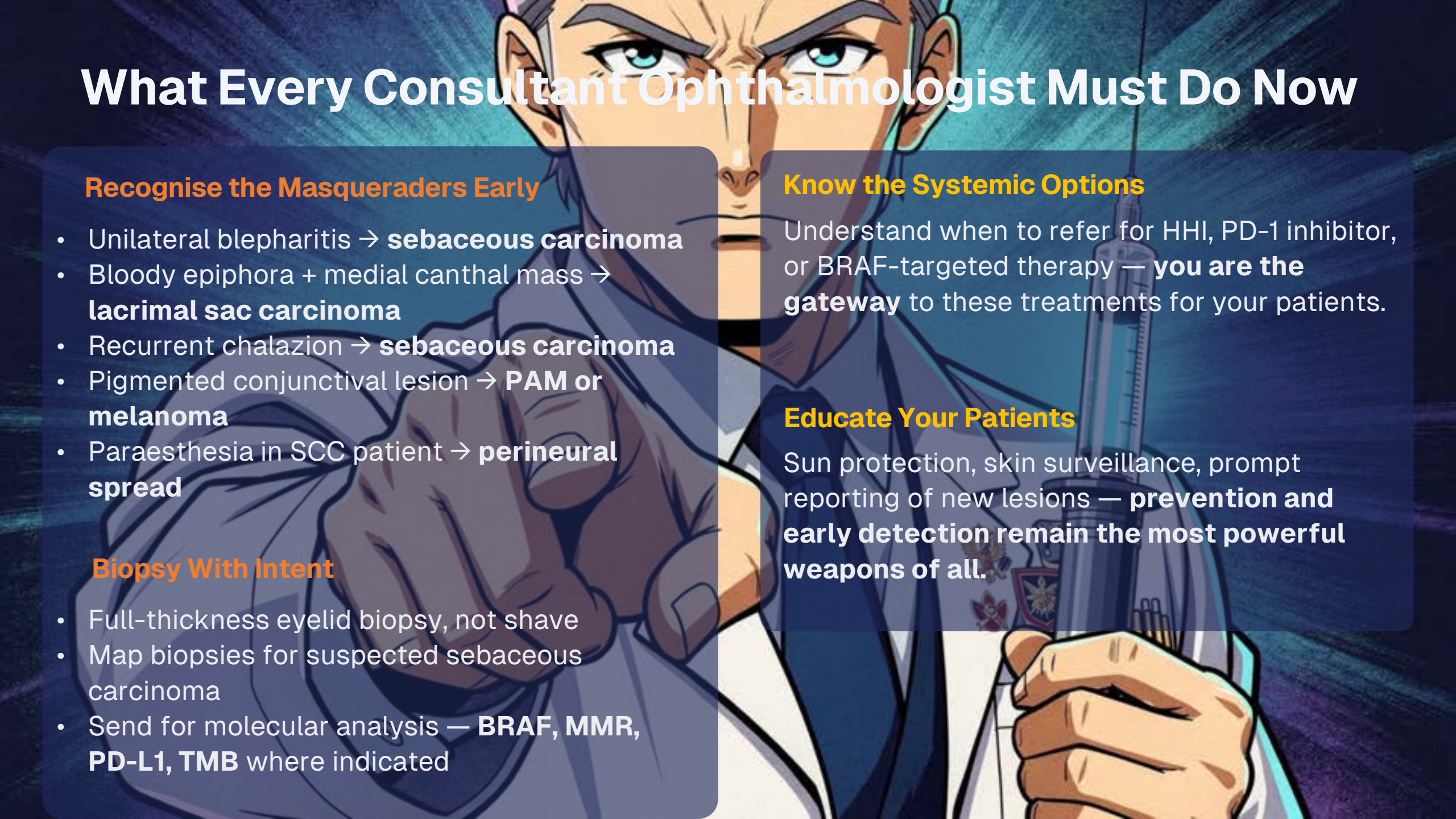
Supply Lines — Referral Pathways

Know your regional specialist centre.

Establish **clear, fast referral pathways** for advanced periocular malignancy.

Delays cost eyes and lives. Treatments must be multidisciplinary, aiming to eliminate cancer with the least ocular morbidity possible.

What Every Consultant Ophthalmologist Must Do Now



Recognise the Masqueraders Early

- Unilateral blepharitis → **sebaceous carcinoma**
- Bloody epiphora + medial canthal mass → **lacrimal sac carcinoma**
- Recurrent chalazion → **sebaceous carcinoma**
- Pigmented conjunctival lesion → **PAM or melanoma**
- Paraesthesia in SCC patient → **perineural spread**

Biopsy With Intent

- Full-thickness eyelid biopsy, not shave
- Map biopsies for suspected sebaceous carcinoma
- Send for molecular analysis — **BRAF, MMR, PD-L1, TMB** where indicated

Know the Systemic Options

Understand when to refer for HHI, PD-1 inhibitor, or BRAF-targeted therapy — **you are the gateway** to these treatments for your patients.

Educate Your Patients

Sun protection, skin surveillance, prompt reporting of new lesions — **prevention and early detection remain the most powerful weapons of all.**

Engage With Clinical Trials: Join the Fight



Cutaneous & Periocular SCC

- NCT06580054 — Pembrolizumab for locally advanced/recurrent orbital & periocular cSCC (Phase II, University of Michigan; actively recruiting)
- INCEPT Trial (2025-523633-25-00, CTIS) — Cemiplimab as organ-preservation strategy in locally advanced cSCC; 10 European sites, recruitment pending
- NKI-AVL Trial (2024-516152-17-00, CTIS) — Immunotherapy alone (without surgery) for locally advanced cSCC; Netherlands Cancer Institute, recruiting since April 2025

Engage With Clinical Trials: Join the Fight

Melanoma (Ocular & Periocular)

- ATOM Trial (NCT06246149 / 2023-510333-28-00, CTIS) — EORTC Phase III: adjuvant tebentafusp vs observation after surgery/radiation for uveal melanoma; 9 EU countries, 20 sites, recruiting since August 2025
- Roginolisib Trial (2024-514333-37-00, CTIS) — Phase II: PI3K δ inhibitor roginolisib vs investigator's choice in advanced uveal melanoma; 10 EU sites, recruiting
- Neoadjuvant Nivolumab + Ipilimumab for High-Risk Uveal Melanoma (2025-524953-15-00, CTIS) — Phase I, Herlev Hospital Denmark, recruiting from June 2026
- Sentinel Lymph Node Biopsy in Ocular Surface & Adnexal Cancers (BLS, NCT05797415) — Prospective observational study covering conjunctival melanoma, MCC, sebaceous carcinoma, SCC; Gemelli IRCCS Rome, recruiting

Merkel Cell Carcinoma

- NeoMatryx (NCT07387198 / 2025-522091-84-00, CTIS) — Neoadjuvant cemiplimab vs placebo before SLNB in stage I–II MCC; Phase II, 15 European sites, recruiting from May 2026
- PANDORA Trial (2022-500988-12-00, CTIS) — Pembrolizumab + chemotherapy as first-line for advanced MCC; Phase II, Italy, recruiting

How to Get Involved

Check
clinicaltrials.gov
or
ctis.eu

for current UK/EU eligibility

- Many trials accept referrals from specialist oculoplastic and ocular oncology centres
- Contact your regional specialist centre to discuss trial eligibility for your patients
- Biobank fresh tissue at diagnosis — enables future trial eligibility screening

Our Aims For The Future;

- **Eye Preservation Over Exenteration**
- **Cure Without Collateral Damage**
- **Earlier Detection, Earlier Intervention**
- **Better Surveillance**
- **A Unified Front**



Sources & References

Immune Checkpoint Inhibitors for Ocular Adnexal & Periocular Tumours

doi.org/10.4103/tjo.tjo-d-24-00130

Efficacy and Safety of Vismodegib in Periocular and Orbital BCC: Systematic Review & Meta-Analysis

[Frontiers in Medicine, 2026](#)

PD-1 Inhibitors for Periocular SCC With Perineural Spread to the Orbit and Skull Base

doi.org/10.1097/iop.0000000000002944

Avelumab as an Emerging Therapy for Eyelid and Periocular Merkel Cell Carcinoma

[PMC7101017](#)

Targeted Therapy in Ophthalmic Oncology: The Current Status

doi.org/10.1016/j.apjo.2024.100062

Recent Developments in the Management of Orbital and Periocular Neoplasms

[Houston Methodist Scholars](#)

Neoadjuvant Chemotherapy ± EGFR / Anti-PD-1 for Lacrimal Sac & Nasolacrimal Duct Carcinomas

doi.org/10.1080/08820538.2024.2324057

Personalised Treatment Concepts in Extraocular Cancer

doi.org/10.1016/j.aopr.2024.02.003

Pembrolizumab for Locally Advanced/Recurrent Orbital or Periocular Cutaneous SCC (NCT06580054)

[ClinicalTrials.gov NCT06580054](#)

NeoMatryx Trial — Neoadjuvant Cemiplimab in Stage I–II Merkel Cell Carcinoma (NCT07387198 / CTIS 2025-522091-84-00)

ctis.eu/trial/2025-522091-84-00

PANDORA Trial — Pembrolizumab + Chemotherapy in Advanced MCC (CTIS 2022-500988-12-00)

ctis.eu/trial/2022-500988-12-00

ATOM Trial (EORTC 2022-MG) — Adjuvant Tebentafusp vs Observation in Uveal Melanoma (NCT06246149 / CTIS 2023-510333-28-00)

ctis.eu/trial/2023-510333-28-00

Roginolisib Phase II in Advanced Uveal Melanoma (CTIS 2024-514333-37-00)

ctis.eu/trial/2024-514333-37-00

Sentinel Lymph Node Biopsy in Ocular Surface & Adnexal Cancers — BLS Study (NCT05797415)

ichgcp.net/clinical-trials-registry/NCT05797415

INCEPT Trial — Cemiplimab as Organ-Preservation Strategy in Locally Advanced cSCC (CTIS 2025-523633-25-00)

ctis.eu/trial/2025-523633-25-00

NKI-AVL Trial — Immunotherapy Alone for Locally Advanced cSCC (CTIS 2024-516152-17-00)

ctis.eu/trial/2024-516152-17-00

Moorfields' New Hospital Build Opening 2027



The Future of Periocular Oncology: Fighting the War on Cancer



Claire Daniel, BSc(Hons) FRCOphth,
Cancer Lead & Adnexal Service Director,
Moorfields Eye Hospital, London, UK
Honorary Consultant Head & Neck Dept.
Guys & St Thomas' Hospital, London, UK



c.daniel@nhs.net