Organ Preservation and Induction Chemotherapy in Head and Neck Cancer: MACH-NC Update and Beyond

50th ICRO Sun PG Teaching Program

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Why This Topic Matters – Relevance for Residents

Shifts the Paradigm: Transforms curative HNSCC care from mutilating surgery to function-preserving approaches without compromising survival

Evidence-Based Learning: Trials like VA, EORTC, RTOG 91-11, and TAX studies underpin treatment decisions; understanding their *rotionale*, design, and limitations builds critical appraisal skills

Balance Between Cure and Quality of Life: Residents must learn how to individualize therapy—when to preserve, *when not to*

Evolving Standards: MACH-NC meta-analysis and ongoing trials (e.g., PATHOS, SIRS 2.0, KEYCHAIN) are redefining the role of IC and CRT in the immunotherapy era

Foundation for Tumor Boards & Trials: Mastery of these concepts empowers resjdents to actively contribute to multidisciplinary decisions, trial interpretation, and protocol planning

Section	Focus	Key Points
1. Organ Preservation	Concept & Rationale	Distinguish *functional* vs *anatomical* preser vation; importance in QOL; shift from radical surgery.
2. Induction Chemotherapy	Evolution & Evidence	Historical background, pivotal trials, present-day indications and controversies.
3. MACH-NC Meta-Analysis	Survival Benefit & Optimal Use	Pooled IPD evidence; superiority of concurrent chemoradiotherapy; subgroup insights.
4. Upcoming Trends & Trials	Future Directions	Immunotherapy integration, adaptive RT, novel systemic agents, next-gen preservation protocols.

SECTION I
ORGAN PRESERVATION TRIALS

SECTION II
INDUCTION CHEMOTHERAPY

SECTION III
MACH NC

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FUTURE TRENDS

Rationale for Organ Preservation

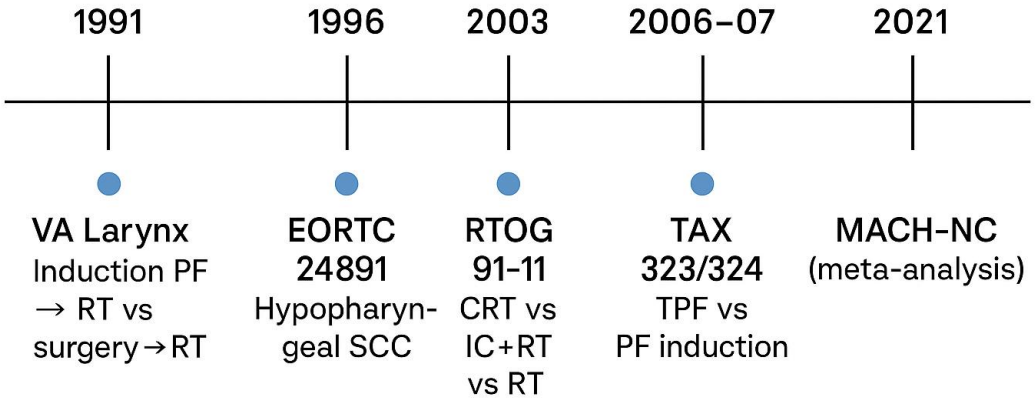
- Balance curative intent with quality of life
- Avoid permanent tracheostomy and aphonia
- Preserve normal appearance and swallowing function
- Prioritize patient-centered outcomes
- Reduce ICU stays and rehabilitation needs

Anatomical Preservation	Functional Preservation
Retention of physical structure *in situ* after treatment **Example:** Larynx remains intact after chemoradiotherapy (CRT) or partial laryngectomy.	**Retention of organ's physiological function — speech, swallowing, airway protection** **Example:** Patient can speak, swallow, and breathe without tracheostomy post-treatment
Goal: Avoid radical resection (e.g., total laryngectomy, total glossectomy) **Limitation:** Preserved anatomy may be non-functional due to fibrosis, neuropathy, or aspiration risk	**Goal:** Maintain quality of life by ensuring the organ works effectively **Importance:** Directly linked to patient-reported outcomes and functional quality of life

Modalities of Organ Preservation

- RT alone: effective in early-stage cancers
- CRT: cornerstone of non-surgical management
- Induction chemotherapy: downstages tumor, allows CRT
- Immuno-induction: emerging strategy, high response rates
- ART: RT plan modified based on tumor response

Key Organ Preservation Trials



VA Larynx Trial

Why:
Avoid tracheostomy and loss of voice via chemoselection

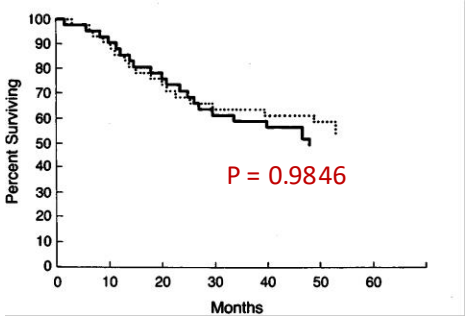
Hypothesis:
IC → RT = surgery + RT survival

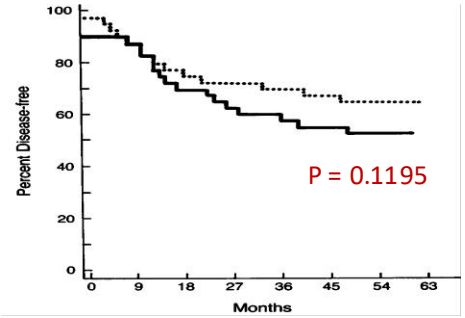
Design:
PF induction followed by RT in responders

↓

Results:
64% laryngeal preservation; OS ~54% in both arms

Significance:
Proved feasibility of organ preservation without OS compromise





Outcome	IC → RT Arm	Surgery + RT Arm
2-year OS	68%	68%
5-year OS	54%	55%
Larynx Preservation	64%	0%

ESMO ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

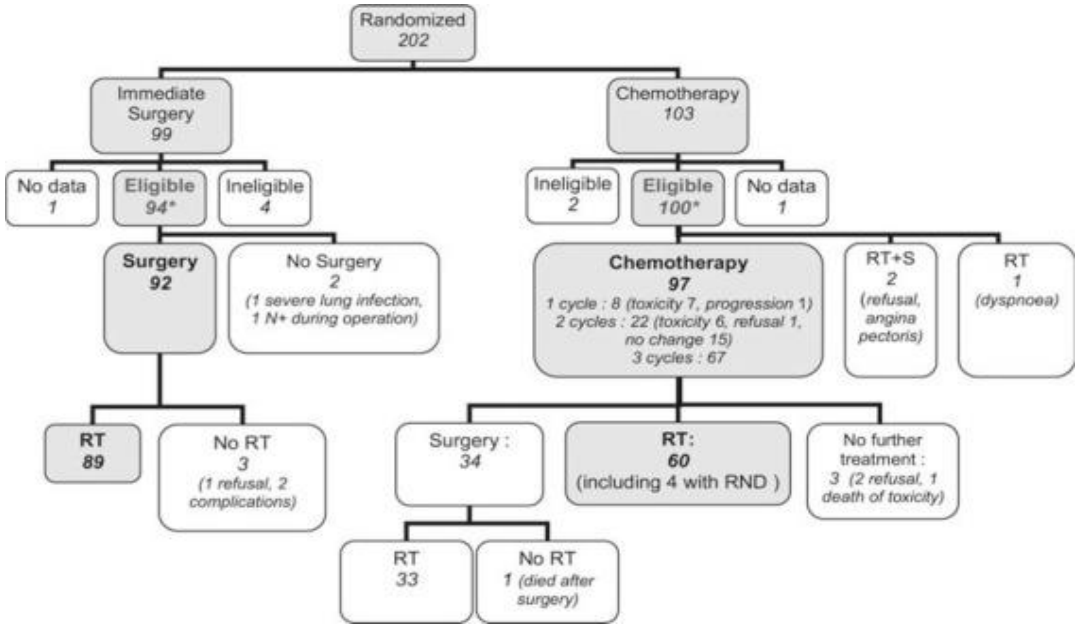
Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891

J.-L. Lefebvre[1] jl-lefebvre@o-lambret.fr · G. Andry[2] · D. Chevalier[3] · ... · D. de Raucourt[7] · J.A. Langendijk[8] · for the EORTC Head and Neck Cancer Group

ORIGINAL ARTICLES | HEAD AND NECK CANCER
Volume 23, Issue 10 P2708-2714 October 2012

Aimed to replicate VA Larynx strategy in a poorer prognosis subsite

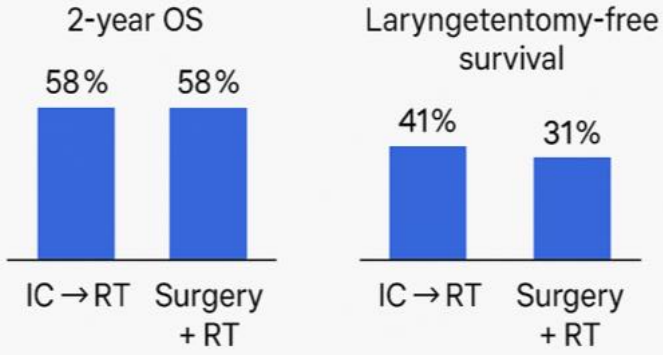
Hypothesis: PF-based IC followed by RT = surgery + RT for OS



EORTC 24891 Trial – Results Summary

Purpose: Determine if IC → RT non-inferior to Surgery + RT

Key Outcomes:



Conclusion: IC → RT non-inferior in overall survival

EORTC 24891
Criticism & Limitations

1. **Limited OS (~30%) despite preservation attempts**
2. **Poor documentation of function/QoL outcomes**
3. **Lack of modern toxicity and PRO reporting**
4. **No biomarker or immuno-era relevance**
5. **Historical importance, but outdated in 2025 context**

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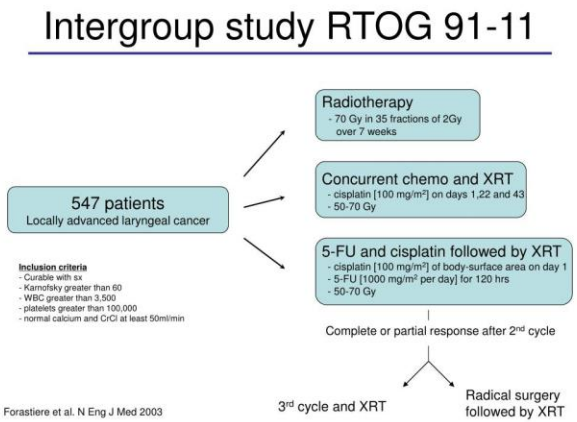
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer

Arlene A. Forastiere, Qiang Zhang, Randal S. Weber, Moshe H. Maor, Helmuth Goepfert, Thomas F. Pajak, William Morrison, Bonnie Glisson, Andy Trotti, John A. Ridge, Wade Thorstad, Henry Wagner, John F. Ensley, and Jay S. Cooper



1. First Phase III Trial Comparing All Non-Surgical Strategies
2. Established Concurrent CRT as Standard
3. Changed the Definition of "Success"
4. Late Toxicities Raised New Questions
5. 10-Year Follow-Up Showed Long-Term Tradeoffs
6. Largest U.S. Cooperative Trial in Larynx Preservation
7. Inspired Numerous Subsequent Trials
8. Anatomic vs Functional Preservation Debate
9. Cisplatin Dose Was Classic 100 mg/m^2 q3Weeks
10. Survival Benefit Was Modest – But Organ Preservation Was Dramatic

Feature	VA Larynx Trial (NEJM 1991)	EORTC 24891 (NEJM 1996)	RTOG 91-11 (JCO 2012)
Population	Stage III–IV Laryngeal Cancer	Stage II–IV Hypopharyngeal Cancer	Stage III–IV Laryngeal Cancer
Hypothesis	IC + RT = Surgery + RT in OS	IC + RT = Surgery + RT in OS	CRT > IC+RT or RT alone for preservation
Arms	PF→RT vs Surgery + RT	PF→RT vs Surgery + RT	CRT vs IC+RT vs RT Alone
Design	Chemoselection with responders to RT	Chemoselection model applied to poorer site	Direct comparison of 3 strategies
5-yr Larynx Preservation	64%	~40%	84% (CRT arm)
10-yr OS	~54% (both arms)	~30% (both arms)	CRT: 27.5%; IC+RT: 28.9%
Key Contribution	First proof of organ preservation w/o OS loss	Extended concept to hypopharynx	CRT became standard for larynx preservation
Limitations	RT alone arm missing; small cohort	Low OS; limited QoL data	Late toxicity higher with CRT

Take Home: Organ Preservation Trials

- **Proof of Concept:** Organ preservation feasible without compromising overall survival
  Early trials (e.g., **VA Larynx Trial, 1991**) established induction chemotherapy followed by RT as an alternative to laryngectomy
- **Functional Preservation vs. Anatomic Preservation**
- **Concurrent Chemoradiation Supersedes Induction + RT:** **RTOG 91-11 (2013 update, 10-year results)**
  This trial defined **concurrent CRT as the gold standard** for organ preservation
- **Overall Survival Maintained:** Across trials, no significant survival disadvantage
- **Patient Selection is Key**
- **Evolving Trends:** reducing toxicity: altered fractionation, better RT techniques (IMRT, proton therapy), and now **immunotherapy-based organ preservation trials**

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Evolution of Induction Chemotherapy

1991 — **VA Larynx Trial** NEJM 191
First organ preservation trial using PF induction in laryngeal cancer

1996 — **EORTC 24891** NEJM 196
Extended organ preservation to hypopharyngeal cancers withPF

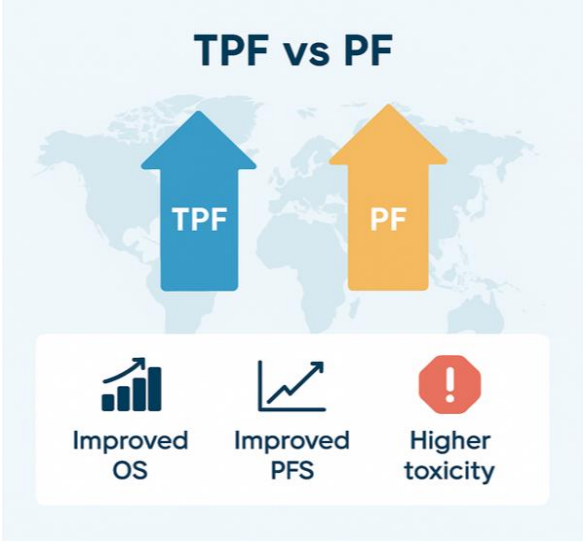
2000 — **MACH-NC** Lancet 2000
Meta-analysis: CRT > RT:
IC has modest OS benefit

2007 — **TAX 323** JCO 2007
TPF > PF in unresectable HNSCC.
Improved PFS, better QoL

2007 — **TAX 324** NEJM 2007
TPF > PF in resectable HNSCC.
Improved OS (71 vs 30 mo)

Ongoing — **Ongoing**
PATHOS, COMPARE, EORTC-1420, NRG-HN005
Aim to refine de-intensification and organ preservation strategies

TPF vs PF



The TAX trials were specifically designed to evaluate docetaxel-based induction chemotherapy in combination with cisplatin and 5-FU

Term	Meaning
TAX	Docetaxel-based chemotherapy trials
323	Trial number in European cooperative groups (EORTC)
324	Trial number used in American cooperative groups (RTOG/ECOG)

Approach	Timing	Key Rationale	Key Trials
Induction Chemotherapy	Before RT/CRT	- Reduces tumor bulk (downstaging) - Targets micrometastases early - Enables **chemoselection** - Improves RT dosimetry	VA Larynx (1991) TAX 323/324 (2007)
Concurrent Chemoradiotherapy	During RT	- Acts as **radiosensitizer** - Enhances local-regional control - Most effective for OS benefit	RTOG 91-11 MACH-NC (2009)
Adjuvant Chemotherapy	After surgery/RT	- Theoretical benefit in clearing residual microscopic disease - High toxicity; poor compliance - **No proven OS benefit** in MACH-NC	MACH-NC (2009)

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TAX 323/ EORTC 24971

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

ORIGINAL ARTICLE

Cisplatin, Fluorouracil, and Docetaxel in Unresectable Head and Neck Cancer

Authors: Jan B. Vermorken, M.D., Ph.D., Eva Remenar, M.D., Carla van Herpen, M.D., Ph.D., Thierry Gorlia, M.Sc., Ricard Mesia, M.D., Marian Degardin, M.D., John S. Stewart, M.D., +11 , for the EORTC 24971/TAX 323 Study Group* Author Info & Affiliations

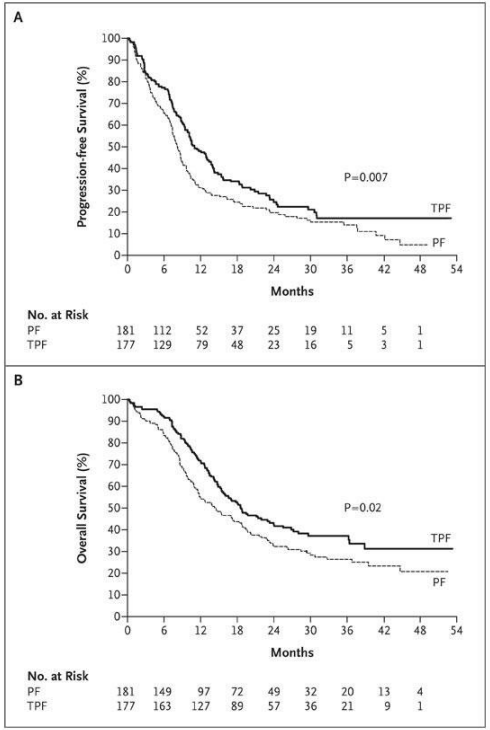
Published October 25, 2007 | N Engl J Med 2007;357:1695-1704 | DOI: 10.1056/NEJMoa071028 | VOL. 357 NO. 17

Trial Design: TAX 323/ EORTC 24971

- **Name:** TAX 323 = *Taxane trial no. 323*; run under **EORTC protocol 24971**.
- "TAX" prefix was used in Sanofi-Aventis–sponsored studies testing **docetaxel**.
- **Publication:** Vermorken JB et al., *NEJM* 2007; 357:1695–1704.
- **Population:** 358 pts with **unresectable stage III/IV HNSCC**.
- **Arms:**
  - **TPF** (docetaxel + cisplatin + 5-FU) × 4 → RT
  - **PF** (cisplatin + 5-FU) × 4 → RT
- **Endpoint:** Progression-free survival (primary), OS, response, toxicity

Results: TAX 323/ EORTC 24971

- **PFS:** Median 11.0 mo (TPF) vs 8.2 mo (PF); **HR 0.72, p=0.007**.
- **OS:** Median 18.8 vs 14.5 mo; **27% ↓ risk of death, p=0.02**.
- **3-yr OS:** 27% vs 21% in favor of TPF.
- **Response rate:** 68% (TPF) vs 54% (PF).
- **Toxicity:**
  - Higher **grade 3–4 neutropenia** with TPF (76% vs 61%).
  - PF arm had more **stomatitis and hearing loss**.



Effects of TPF and PF Therapy on Progression-free Survival (Panel A) and Overall Survival (Panel B)

Criticism: TAX 323/ EORTC 24971

- RT given **alone after IC** (no concurrent CRT) → **not contemporary comparator**.
- Results showed benefit **vs PF**, not vs CRT — limits present-day relevance
- Long-term OS curves converge; survival benefit less striking beyond 3 years

- **Conclusion:** Established **TPF > PF** as IC; did not prove IC better than CRT

Long Term Follow Up of TAX 323/ EORTC 24971

- **Publication & Follow-up:**
  - Long-term follow-up conducted by Szturz et al., published 2021 in *European Journal of Cancer*
  - Included **all 358 patients** randomized between 1999–2002, with a **median follow-up of 8.6 years**

- **Persistence of Benefit (TPF vs PF):**
  - **PFS:** TPF retained advantage → **adjusted HR 0.70; 95% CI 0.56–0.88; p = 0.002**
  - **OS:** Survival benefit sustained → **adjusted HR 0.75; 95% CI 0.60–0.95; p = 0.015**

- **Long-Term Toxicity & Morbidity:**
  - **Tracheostomy rates:** 7% for TPF vs 5% for PF.
  - **Feeding tube dependency:** 3% (TPF) vs 6% (PF).
  - **Gastrostomy use:** 11% in both arms.
  - **Second malignancies:** More frequent with TPF (8% vs 3%)

TAX 324

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer

Authors: Marshall R. Posner, M.D., Diane M. Hershock, M.D., Ph.D., Cesar R. Blajman, M.D., Elizabeth Mickiewicz, M.D., Eric Winquist, M.D., Vera Gorbounova, M.D., Sergei Tjulandin, M.D., +22 , for the TAX 324 Study Group* Author Info & Affiliations

Published October 25, 2007 | N Engl J Med 2007;357:1705-1715 | DOI: 10.1056/NEJMoa070956 | VOL. 357 NO. 17

TAX 324: Trial Design

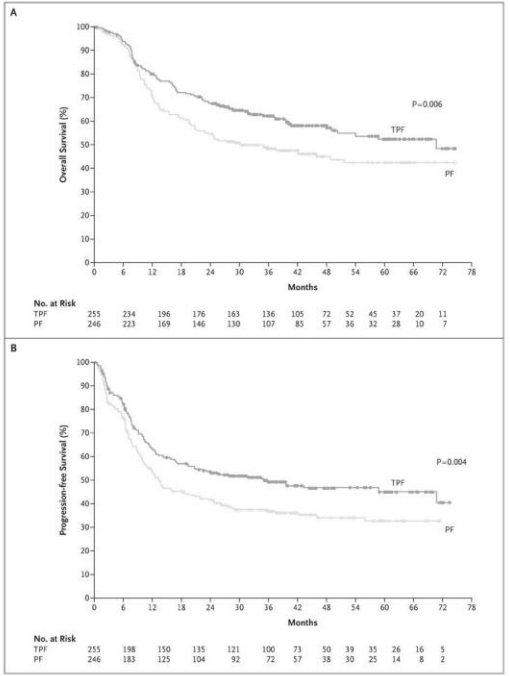
- **Population:** 501 pts, stage III/IV LA-HNSCC (resectable + unresectable)
- **Arms:**
  - **TPF × 3 → CRT (weekly carboplatin AUC 1.5, 70 Gy)**
  - **PF × 3 → same CRT**

- **Primary endpoint:** Overall survival (OS)
- Secondary: PFS, locoregional control, toxicity

TAX 324: Results

- **Median OS:** 71 mo (TPF) vs 30 mo (PF); **HR 0.70, p=0.006**
- **3-yr OS:** 62% vs 48%
- **PFS:** HR 0.71, p=0.004
- **Locoregional control:** Better with TPF (HR 0.65)

- **Toxicity:**
  - More **grade 3–4 neutropenia** (83% vs 56%)
  - More febrile neutropenia with TPF
  - Treatment-related deaths: ~2% in both arms



Overall Survival and
Progression-free Survival

TAX 324: Criticism

- **CRT backbone weak:** weekly carboplatin, not high-dose cisplatin → **underestimates control arm outcomes**.
- **Population heterogeneity:** included both **resectable** and **unresectable** patients, making results harder to generalize.
- Survival in PF+CRT arm (30 mo median) **much lower** than contemporary CRT trials with cisplatin — inflating relative benefit of TPF.
- High toxicity, cost, and logistics → **limited uptake outside trials**.
- **Conclusion:** Proved TPF > PF if induction used; but **did not establish induction > upfront CRT**

TAX 324: Long Term Results

Publication: **Posner MR et al., *JCO* 2013;31(7): 744–751**

Design: **Phase III**; 501 patients with unresectable, locally advanced HNSCC
Arms: **TPF** (Docetaxel, Cisplatin, 5-FU) → concurrent CRT (carboplatin + RT) vs **PF** (Cisplatin, 5-FU) → same CRT

Results (Median follow-up ~6 years)

- **Overall Survival (OS)**: TPF: **70.6 months** vs PF: **34.8 months** (HR 0.74; $p = 0.014$)
- **5-year OS**: **52% (TPF)** vs **42% (PF)**
- **Progression-Free Survival (PFS)**: Median: 36 months (TPF) vs 13 months (PF)
- **Locoregional Control**: improved with TPF arm
- **Toxicity**: Higher neutropenia/febrile neutropenia in TPF; but manageable

Key Takeaways

- **TPF induction → sustained long-term survival advantage** vs PF
- **Benefit maintained across subgroups**, esp. oropharynx & good PS
- **Set TPF + CRT as reference regimen** for induction in LA-HNSCC

Feature	Trial ID & Region	Patient Type	Design	Regimen Details	Primary Endpoint	Key Results	Clinical Relevance
TAX 323	**EORTC 24971** (Europe)	**Unresectable** Stage III–IV HNSCC (n= 358)	TPF vs PF → **RT alone**	TPF: Docetaxel 75 + Cisplatin 75 + 5-FU 750 (×5d) every 3 wks ×4 PF: same w/o docetaxel	**Progression-Free Survival (PFS)**	**PFS**: 11.0 vs 8.2 mo **OS**: 18.8 vs 14.5 mo **HR**: 0.73 (PFS) Similar toxicity profile	Showed **TPF superior** to PF for **unresectable** disease, with good tolerability
TAX 324	**US Intergroup** (USA/ Canada)	**Resectable** Stage III–IV HNSCC	TPF vs PF → **CRT with weekly carboplatin**	TPF: Docetaxel 75 + Cisplatin 100 + 5-FU 1000 (×4d) every 3 wks ×3 PF: same w/o docetaxel	**Overall Survival (OS)**	**OS**: 71 vs 30 mo **Improved LRC** Better compliance Reduced toxic deaths in TPF arm	Validated **TPF** a s standard IC in **resectable** cases; supported CRT backbone post-IC

Negative RCTs vs CRT-Alone (1): PARADIGM (Lancet Oncol 2013)

- **Design:** TPF→CRT (docetaxel or carbo) **vs** CRT (cisplatin) alone
- **Accrual:** stopped early; **145 pts**
- **Outcome: No OS benefit** (3-yr OS 73% vs 78%; **HR 1.09**, p=0.77);

  ↑febrile neutropenia with IC
- **Conclusion:** Underpowered; no survival advantage demonstrated

Negative RCTs vs CRT-Alone (2): DeCIDE (JCO 2014) & TTCC (Ann Oncol 2014)

- **DeCIDE:** N2/N3; **IC (TPF) → DFHX CRT** vs **DFHX CRT alone → No OS benefit**; ↑serious AEs with IC (47% vs 28%)
- **Spanish TTCC 2503:** **TPF→CRT** or **PF→CRT** vs **CRT alone** in unresectable LA-HNSCC → **No PFS/OS advantage** for IC arms

Trial	Design & Population	Arms	Primary Endpoint	Results	Criticism
TAX 324(Posner, NEJM 2007; JCO 2013)	501 pts, stage III–IV, resectable & unresectable	**TPF ×3 → CRT (weekly carbo + RT)** vs **PF ×3 → CRT**	OS	**Median OS:** 71 vs 30 mo (HR 0.70, p=0.006) **5-yr OS:** 52% vs 42%	CRT backbone weak (weekly carbo, not cisplatin); heterogenous population; toxicity high
PARADIGM(Haddad, Lancet Oncol 2013)	Planned 300 pts, only 145 accrued (stopped early)	**TPF ×3 → CRT (cisplatin +RT)** vs **CRT alone**	OS	**3-yr OS:** 73% vs 78% (NS); HR 1.09, p=0.77 No survival benefit	**Underpowered** due to poor accrual; ↑ febrile neutropenia with TPF; CRT control very strong
DeCIDE(Cohen, JCO 2014)	285 pts, bulky N2/N3, high distant risk	**TPF ×3 → CRT (DFHX)** vs **CRT alone (DFHX)**	OS	**3-yr OS:** 52% vs 48% (NS) No OS benefit; slight ↓DM not statistically significant	Higher grade 3–4 toxicity with TPF; underpowered for OS; intensified CRT control arm already highly effective

Present-Day Use (narrow, selected scenarios)

- **Routine upfront IC not standard** vs high-quality **concurrent CRT** for most LA-HNSCC
- **When considered:**
    - **Bulky N2c/N3, matted nodes / high distant risk** (aim: ↓DM)
    - **Borderline unresectable** disease to test chemosensitivity / enable definitive CRT or surgery
    - **Larynx-preservation protocols:** TPF improves **larynx preservation** & **larynx dysfunction-free survival** in GORTEC 2000-01 long-term data (strategy-specific)
- **Always** weigh center experience, support (nutrition, dental, rehab), and patient fitness

Take-Home Message

- **If you choose IC, use TPF (not PF)** — strongest induction evidence
- **But** vs contemporary **CRT-alone**, randomized trials & meta-analyses show **no OS advantage** for routine IC
- **Standard of care remains concurrent CRT;** consider IC **only in carefully selected, high-risk or strategy-specific situations** (e.g., larynx-preservation programs).

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MACH NC Meta Analyses

- **1980s–1990s**: trials on chemotherapy in head and neck cancer gave **conflicting results** — some positive, others negative
- **Jean-Pierre Pignon** and colleagues realized each trial was like a **piece of a jigsaw puzzle**: alone it gave a fragment, but together they could reveal the whole picture
- They collected **individual patient data (IPD)** from dozens of randomized trials and performed the **first MACH-NC meta-analysis (2000)**
- With subsequent updates in **2009** and **2021**, MACH-NC became a **lighthouse in oncology**, guiding treatment and policy worldwide.

Jean-Pierre Pignon

Lead Biostatistician at Institut Gustave-Roussy (Villejuif, France)

Spearheaded the landmark MACH-NC individual patient data meta-analysis,

Influential in promoting evidence-based oncology

META ANALYSIS

The statistical analysis of a large collection of results from individual studies for the purpose of integrating the findings

Why it's done:

- To **increase sample size** and statistical power
- To detect **small effects** that single studies may miss
- To resolve **conflicting results** from different trials
- To generate **stronger evidence** for guidelines and practice

How it works:

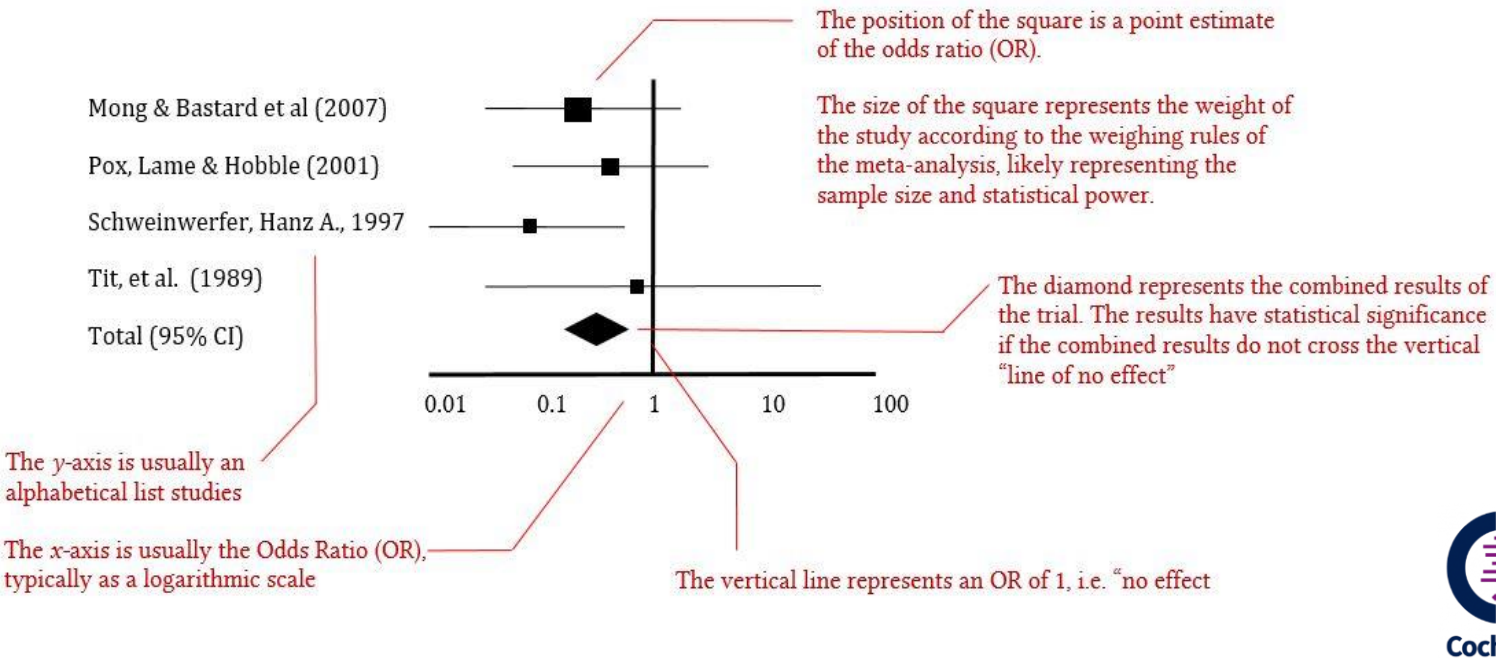
- Select relevant studies (RCTs, observational)
- Extract common outcomes (e.g., overall survival, response rates)
- Apply statistical models (e.g., fixed or random effects)
- Generate a **summary result** (like pooled hazard ratio or odds ratio)

Visual Output: Often shown as a **forest plot**, where each study's effect is represented by a line and box, and the pooled estimate is a diamond.

Gene V Glass

1976
Presidential address to the American Educational Research Association.

Forest Plot


The position of the square is a point estimate of the odds ratio (OR).
The size of the square represents the weight of the study according to the weighing rules of the meta-analysis, likely representing the sample size and statistical power.
Mong & Bastard et al (2007)
Pox, Lame & Hobble (2001)
Schweinwerfer, Hanz A., 1997
Tit, et al. (1989)
Total (95% CI)
0.01
0.1
1
10
100
The diamond represents the combined results of the trial. The results have statistical significance if the combined results do not cross the vertical "line of no effect"
The y-axis is usually an alphabetical list studies
The x-axis is usually the Odds Ratio (OR), typically as a logarithmic scale
The vertical line represents an OR of 1, i.e. "no effect

IPD vs Aggregate Data

Feature	IPD (Individual Patient Data)	Aggregate Data
Level of detail	Data for **each patient**	Summary statistics from each trial
Analyses possible	Advanced, flexible (e.g., time-to-event, subgroups)	Limited to what is reported
Subgroup analysis	Yes, patient-level subgrouping (age, stage, etc.)	Often not possible
Data collection effort	High (requires trial data from investigators)	Lower
Statistical accuracy	Higher	Lower
Preferred for meta-analysis?	**Yes** — Gold standard	Less preferred

MACH-NC Meta-Analysis:
A Landmark in Head and Neck Cancer Evidence

- **MACH-NC** stands for **Meta-Analysis of Chemotherapy in Head and Neck Cancer**
- Conducted by the **Meta-Analysis Group in Cancer**
- Largest **individual patient data (IPD)** meta-analysis in oncology, focused on **locally advanced head and neck squamous cell carcinoma (LA-HNSCC)**
- Aim: Evaluate the **survival benefit of chemotherapy** when added to locoregional treatment (surgery/radiotherapy)

Why MACH NC Metanalysis

Inconsistent Trial Results	RCTs on chemotherapy in HNSCC showed conflicting outcomes — some positive, some negative
Need for Quantified Benefit	Required clear evidence on survival benefit and timing (induction, concurrent, adjuvant)
Subgroup Clarification	Needed to identify which patients (by age, subsite, PS) benefit most
Compare Chemo Timing Strategies	Clarify which approach (induction vs concurrent vs adjuvant) is most effective
Improve Statistical Power	Pooled data from thousands of patients enhances reliability and statistical validity
Individual Patient Data (IPD)	Enables standardized re-analysis across trials with flexible subgroup and time-to-event analyses
Lack of Existing Meta-Analyses	No previous IPD meta-analysis specific to HNSCC treatment strategies
Guide Clinical Practice	Inform international guidelines and create consensus for standard treatment

Publication (Yr)	Journal	Patients (Trials)	Focus / Additions	Key Findings	Notes
Pignon J-P et al., 2000	Lancet	~10,741 (63 RCTs)	First large-scale individual patient data (IPD) meta-analysis	Addition of chemotherapy → **4% absolute OS benefit at 5 years**; greatest with **concurrent CT-RT**	Established CT as meaningful adjunct in LA-HNSCC
Pignon J-P et al., 2009	Radiother Oncol	~17,346 (93 RCTs)	Update; longer follow-up; subgroup analysis	**5-yr OS benefit 6.5% with concurrent chemo**; induction (PF-based) weaker; adjuvant no OS gain	Showed **concurrent chemo-RT as standard**; quantified modest benefit
Blanchard P, Bourhis J, Pignon J-P et al., 2021	Lancet Oncol	~19,805 (100+ RCTs)	Extended update; included newer agents/trials	Confirmed **concurrent cisplatin-based CT-RT superior**; no added benefit for IC/Adj CT	Cemented concurrent cisplatin as **benchmark**; highlighted **limited role of ICT/ACT**

Journal Pre-proofs

Original Article

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19805 patients, on behalf of MACH-NC group

PII: S0167-8140(21)00013-X
DOI: https://doi.org/10.1016/j.radonc.2021.01.013
Reference: RADION 8695

To appear in: *Radiotherapy and Oncology*

Received Date: 15 October 2020
Revised Date: 22 December 2020
Accepted Date: 8 January 2021

The MACH-NC meta-analysis is the distilled voice of thousands of patients across decades, speaking in unison to tell us when chemotherapy truly changes the fate of head and neck cancer

MACH NC 2021: Study Design

- **Trials included:** 107 randomized controlled trials
- **Patients:** 19,805 (IPD available for ~80%)

  Trials involving untreated HNSCC(oral cavity, oropharynx, hypopharynx and larynx) Those which compared:

  1. Curative LRT with LRT+CT
  2. Induction chemotherapy + RT and CRT
- **Time frame:** 1965–2016
- **Treatment strategies evaluated:**

  Concurrent chemoradiotherapy (CRT)
  Induction chemotherapy
  Adjuvant chemotherapy
  Mixed/combination approaches

Data Acquisition

Individual patient data (IPD)
Patient and tumor characteristics
Dates of randomization
Failures and death
Treatment group allocation
Details of treatment received
Acute and late toxicities

Primary end point- Overall survival

Secondary end point- Event free survival, loco regional failure, distant failure, cancer and non cancer mortality

120 day mortality- proxy for deaths to treatment

MACH NC 2021 UPDATE: END POINTS

OS- Time from randomization till death from any cause

EFS- Time from randomization to first recurrence or progression or death from any cause

Non cancer mortality- deaths without previous failures and resulting from known causes other than treated HNC

Cancer mortality- death from any cause with previous failure and deaths from treated HNC

Deaths from unknown cause- without previous failure regarded as cancer mortality if they occurred within 5 years after randomization and non cancer mortality otherwise

MACH NC 2021 UPDATE: END POINTS

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Primary question- **Addition of chemotherapy to LRT**
Secondary question- **Induction vs. concomitant chemotherapy**

Concomitant Chemotherapy

- **Concurrent CRT** → clear survival benefit
- **5-year absolute OS gain:** +6.5% (across all patients)
- **Hazard ratio (HR):** ~0.83 vs RT alone
- Benefit **consistent across decades**, validating CRT as standard of care
- OS gain modest but **durable**

Primary question- Addition of chemotherapy to LRT
Secondary question- Induction vs. concomitant chemotherapy

Concomitant Chemotherapy

- Cisplatin-based regimens most effective
- CRT provides durable OS benefit
- Particularly strong in younger, fitter patients
- Remains the benchmark treatment in LA-HNSCC
- Supported by guideline bodies (NCCN, ESMO, ASCO)

Primary question- **Addition of chemotherapy to LRT**
Secondary question- **Induction vs. concomitant chemotherapy**

Induction Chemotherapy

- Mostly **PF-based** induction regimens
- No significant OS improvement vs RT/CRT alone
- Did not translate into long-term survival benefit
- **TAX 323 & 324** suggested TPF > PF → but MACH-NC did not confirm OS advantage in pooled setting
- Role: **debatable, investigational** outside select bulky disease/organ preservation

Primary question- Addition of chemotherapy to LRT
Secondary question- Induction vs. concomitant chemotherapy

Adjuvant Chemotherapy

- Evaluated post-RT strategies
- No survival benefit
- Often associated with poor compliance and toxicity
- Confirmed to have no role in standard management

MACH NC 2021 UPDATE

Subgroup Insights

- **Age:**
  - <70 yrs → clear OS benefit
  - ≥70 yrs → minimal OS benefit; higher toxicity
- **Performance status:** ECOG 0–1 benefit most
- **Tumor site:** Oropharynx & larynx > hypopharynx
- **Nodal burden:** N0–N2 gain > N3 disease
- **HPV status:** Chemotherapy benefit observed regardless of HPV, though magnitude differs

Evolution Over Time

- Across **3 decades**, benefit remained stable
- No evidence of diminishing effect in modern RT era
- Even with IMRT, **cisplatin CRT = standard backbone**
- Targeted therapy and altered RT fractionation **did not improve OS beyond CRT**

MACH NC 2021 Update: Take Home

- **Concurrent cisplatin CRT** = standard for LA-HNSCC
- **Induction chemo**: reserved for organ preservation or trials
- **Adjuvant chemo**: abandoned
- **Elderly/frail patients**: individualized approach, often RT alone ± targeted/ IO
- MACH-NC update provides **definitive evidence base for guidelines**

SECTION I
ORGAN PRESERVATION TRIALS

SECTION II
INDUCTION CHEMOTHERAPY

SECTION III
MACH NC

SECTION IV
FUTURE TRENDS

Beyond MACH-NC: The Next Frontier in LA-HNSCC

From Chemoradiotherapy Benchmarks to Tailored, Biology-Guided Strategies

The Shift to De escalation: PATHOS Trial

- **Rationale:** HPV+ oropharyngeal SCC has excellent outcomes but suffers from long-term dysphagia due to aggressive adjuvant therapy
- **PATHOS (Phase II/III):** Risk-stratified, reduced-intensity adjuvant treatment post-transoral surgery in HPV+ OPSCC, results expected in 2028
- **Design:** Stratifies patients into low/intermediate/high risk → assigns no RT, reduced-dose RT, or RT vs CRT respectively
- **Goal:** Preserve swallowing function (via MDADI score) while maintaining disease-specific survival

SMART KEY Trial Overview

- **Trial Name: SMART-KEY (LACOG 0720)**
- **Type: Phase II, single-arm, multi-institutional trial**
- **Focus:** Organ preservation strategy in locally advanced larynx cancer

- **Treatment Sequence:**
  - **Induction chemo-immunotherapy** (details not fully disclosed—presumably TPF or similar plus pembrolizumab)
  - **Radioimmunotherapy** (likely combining RT with checkpoint inhibitor)
  - **Consolidation immunotherapy** (continued immunotherapy post-RT)

- **Primary Endpoint:** Laryngectomy-free survival—preserving the organ and its function
- **Sample Size:** 39 patients

SMART KEY: Significance & Rationale

Why SMART-KEY Matters:

- First-of-its-kind study integrating **chemo + immunotherapy + radiotherapy** to preserve the larynx without sacrificing oncologic outcomes
- Focuses on **functional recovery**, not just survival—aligning with modern quality-of-life-driven treatment paradigms

Key Aspirations:

- Achieve **durable tumor control** while avoiding total laryngectomy
- Leverage immunotherapy to enhance CRT efficacy and patient outcomes
- Establish a **template for future organ-preservation regimens** in HNSCC

Looking Ahead:

- If successful, SMART-KEY could **reshape organ preservation strategies**, promoting immuno-radiotherapy backbones
- Builds the foundation for future **biomarker-driven, de-escalated, yet effective treatments** in laryngeal HNSCC

KEYNOTE-412 Trial – Pembrolizumab + Chemoradiotherapy

Machiels JP et al., *Lancet Oncology*. May 2024;25(5):572–587. DOI: 10.1016/S1470-2045(24)00100-1

Design:

- Phase III, double-blind, randomized, global trial (NCT03040999)
- Enrolled 804 patients with high-risk, unresected locally advanced HNSCC
- Intervention: Pembrolizumab (200 mg Q3W) added to CRT, followed by maintenance for up to 17 cycles
- Comparator: Placebo plus same CRT regimen

Endpoints:

- Primary: Event-Free Survival (EFS)
- Secondary: Overall Survival (OS), safety

Results:

- Median follow-up ~47.7 months
- **Median EFS**: Not reached with Pembrolizumab vs 46.6 months with Placebo (HR 0.83; 95% CI 0.68–1.03; $p = 0.043$)—did not meet prespecified significance threshold of $p \leq 0.02$
- **Safety**: Higher rates of serious adverse events with Pembrolizumab (62% vs 49%)

CheckMate-141 Trial – Nivolumab in Recurrent/Metastatic HNSCC

Ferris RL et al., *NEJM*. 2016;375:1856–1867. DOI: 10.1056/NEJMoa1602252

Design:

- Phase III, open-label, randomized controlled trial (NCT02105636)
- 361 patients with recurrent/metastatic HNSCC progressing within 6 months post-platinum therapy
- Randomized 2:1 to **Nivolumab (3 mg/kg IV Q2W)** vs **investigator's choice** (methotrexate, docetaxel, or cetuximab)

Endpoints:

- Primary: Overall Survival (OS)
- Secondary: Progression-Free Survival (PFS), Objective Response Rate (ORR), safety, quality of life

Results:

- **Median OS**: 7.5 months with Nivolumab vs 5.1 months with investigator's choice (HR 0.70; p = 0.01)
- **1-year OS**: 36% vs 16.6%
- PFS similar between arms; ORR higher with Nivolumab (13.3% vs 5.8%)
- **Toxicity**: Fewer grade 3–4 adverse events with Nivolumab (13.1% vs 35.1%)
- Quality of life remained stable with Nivolumab but declined with investigator's choice therapy

Criticism of KEYNOTE-412 and CheckMate-141

Aspect	KEYNOTE-412 (Pembrolizumab + CRT)	CheckMate-141 (Nivolumab in R/M HNSCC)
Efficacy	Missed statistical significance (OS trend only, p=0.043 vs 0.0242 required)	OS gain modest (7.5 vs 5.1 mo); PFS unchanged
Population	Heterogeneous HPV+ and HPV–, multiple sites → diluted benefit	No biomarker stratification at design (PD-L1, HPV)
Response	Event-free survival ↑ but OS benefit not definitive	ORR low (13% vs 6%), most patients progressed
Toxicity	Higher grade ≥3 AEs (62% vs 49%) with pembrolizumab	Acceptable safety, but not transformative
Take-Home	Suggests benefit but not practice-changing	Landmark trial, but benefit limited to subgroups

IO: Ongoing & Future

- **GORTEC REACH**: Atezolizumab/nivolumab ± CTLA-4 blockade with CRT; interim safety good
- **Other ongoing trials**: Durvalumab, nivolumab, and novel checkpoint/IO combinations
- **Current take-home**:
  - ICIs not yet standard with CRT.
  - Potential benefit in **biomarker-defined subsets (PD-L1+, HPV+)**.
  - Awaiting mature OS results—**next frontier after MACH-NC 2021**

Novel Immunomodulating Agents

News I Article I August 5, 2025 I onclive.com

FDA Outlines Next Steps for Development of Eftilagimod Alfa in PD-L1–Negative HNSCC

Author(s): Chris Ryan Fact checked by: Jax DiEugenio

Eftilagimod Alpha (Efti) in HNSCC

- **Mechanism**
  - Soluble **LAG-3 fusion protein**, activates APCs → boosts innate & adaptive immunity.
- **TACTI-003 (Phase IIb, HNSCC, PD-L1 CPS <1)**: **Efti + pembrolizumab** vs historical PD-1 monotherapy benchmarks.
- **Key Results**
  - **ORR:** ~27–36% (CRs up to 13%)
  - **DCR:** ~58%
  - **Median OS:** 17.6 mo (vs 7.9–11.3 mo historically).
- **Safety**: Well tolerated; no unexpected signals.
- **Regulatory Status**
  - **FDA Fast Track (2021)** for frontline R/M HNSCC.
  - Ongoing development toward registrational studies, esp. in **PD-L1–negative** patients

Aspect	Details	TORPEdO Trial
Full Title & Acronym	TORPEdO – *TOxicity Reduction using Proton bEam therapy for Oropharyngeal cancer*	
Purpose	Phase III randomized trial to determine if **Intensity-Modulated Proton Therapy (IMPT)** reduces long-term toxicity compared to standard **Intensity-Modulated Radiotherapy (IMRT)** in locally advanced oropharyngeal SCC patients receiving CRT	
Significance	UK's **first national proton therapy clinical trial**—a landmark in establishing IMPT as evidence-based practice	
Study Design	Patients randomized IMPT vs IMRT during CRT with mandatory **cisplatin**, followed via functional and quality-of-life metrics	

Future Directions & Resident Focus

Quality of Life Focus

– **DO-IMRT/DARS**: proven swallowing preservation benefit
– **Protons (TORPEdO trial)**: awaiting results for toxicity reduction

HPV+ Post-op De-intensification

– **PATHOS trial**: risk-adapted adjuvant RT/CRT, results expected ~2028

Immunotherapy Horizons

– Ongoing Phase III: **GORTEC REACH, KEYNOTE-689, peri-operative IO strategies**

Practical Compass for Residents

– Stick to **cisplatin-CRT as SOC**.
– Use **DO-IMRT now** where available
– Watch **PATHOS & TORPEdO** to shape next generation toxicity-minimization strategies

Feature	GORTEC REACH	KEYNOTE-689
Trial Phase / Year	Phase III, safety phase 2020; ESMO update 2021	Phase III, published *NEJM* 2025
Population	Locally advanced, **cisplatin-ineligible** SCCHN	Resectable, locally advanced HNSCC
Design	Randomized; **avelumab (PD-L1) + cetuximab + RT** vs **RT ± cetuximab**	Perioperative pembrolizumab: **2 cycles neoadjuvant → surgery → adjuvant RT ± cisplatin + pembrolizumab → pembrolizumab maintenance** vs **standard surgery + RT ± cisplatin**
Primary Endpoint	Progression-free survival (PFS)	Event-free survival (EFS)
Key Results	- No significant PFS improvement (HR 0.84; p=0.14) - Some reduction in distant metastasis (HR 0.31; p=0.007)	- EFS improved significantly (ITT HR 0.73, p=0.0041) - Major pathologic response ↑ (CPS ≥10: +13.7 pp, *p*<0.00001)
Safety	Acceptable; no major new toxicities	Similar grade ≥3 AE rates; immune AEs higher (~10% vs ~0.6%) but manageable
Conclusion	Safe but **negative**—did not change standard of care	**First positive perioperative immunotherapy trial** in HNSCC; potential practice-changing

Trial	Domain	Potential Impact
PATHOS (UK / EORTC; NCT02215265)	Post-op de-escalation in HPV+	May endorse TORS + less RT → better swallowing + equivalent survival
PRESERVE (European ERA PerMed Project)	Precision selection modelling (clinical, molecular and multi-omics data)	Enables biomarker-guided preservation strategies in LHSCC
FOPS trial (Functional Organ Preservation Surgery)	Surgery-based preservation	May validate functional preservation with surgery + limited adjuvant RT
ECOG/ORATOR/EORTC (De-escalation Platforms in HPV+ OPSCC)	De-escalation in HPV+ OPSCC	May refine adjuvant RT intensity based on risk/pathology
SMART-KEY etc. (Immune-Induction or Immuno-De-Escalation Trials)	Induction ICI ± chemo	May allow RT postponement/de-intensification or surgery avoidance trajectories

Take-Home Message

• **Organ Preservation in HNSCC:** From surgery vs RT debates → to induction chemotherapy & CRT → to modern functional outcomes focus

• **Induction Chemotherapy:** TAX 323/324 established **TPF → RT/CRT** as a backbone in selected patients, but **not universal SOC** due to toxicity and mixed benefit

• **MACH-NC Meta-analyses (2000, 2009, 2021):** >100 trials, >19,000 patients – show **clear OS gain with concurrent CRT**, marginal benefit for induction, and ongoing refinement of patient selection

Take-Home Message

• **Immunotherapy & Beyond:** Recent trials (KEYNOTE-689, CheckMate-141, TORPEdO, REACH, SMART, PATHOS, PRESERVE, FOPS) mark the shift toward **perioperative IO, de-escalation, precision RT, and multimodal integration**

• **Future of HNSCC:** **Personalized therapy** balancing cure with function—guided by biology, immunotherapy, and adaptive radiotherapy

Søren Kierkegaard

(1813-1855)

Danish theologian and philosopher

There are two ways to be fooled. One is to believe what isn't true; the other is to refuse to believe what is true.