Toxicity and synergy in combined treatment strategies for head and neck cancer

Rachel Galot, MD, PhD

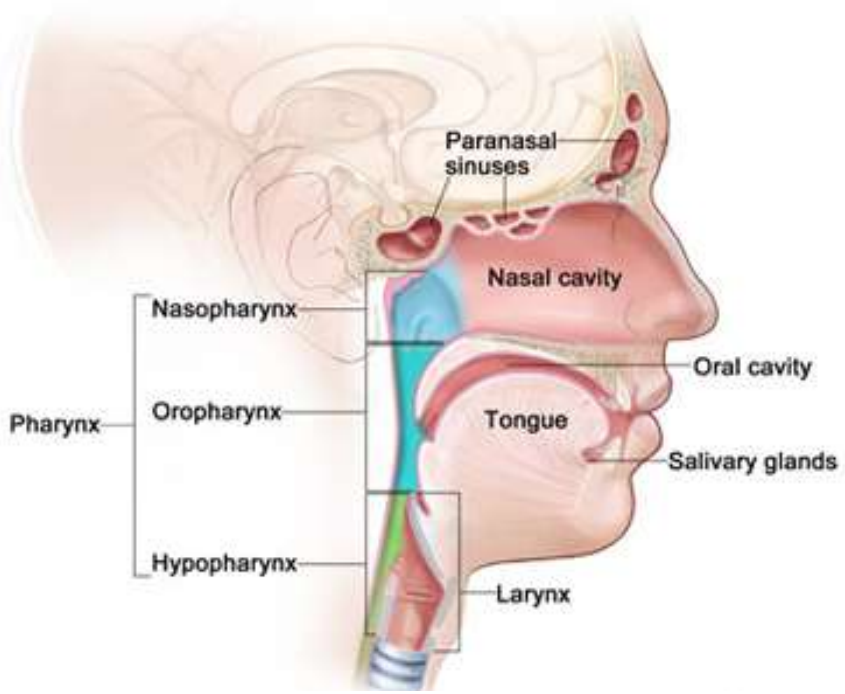
Cliniques Universitaires Saint-Luc, Brussels, Belgium

BeSTRO 2026



Introduction

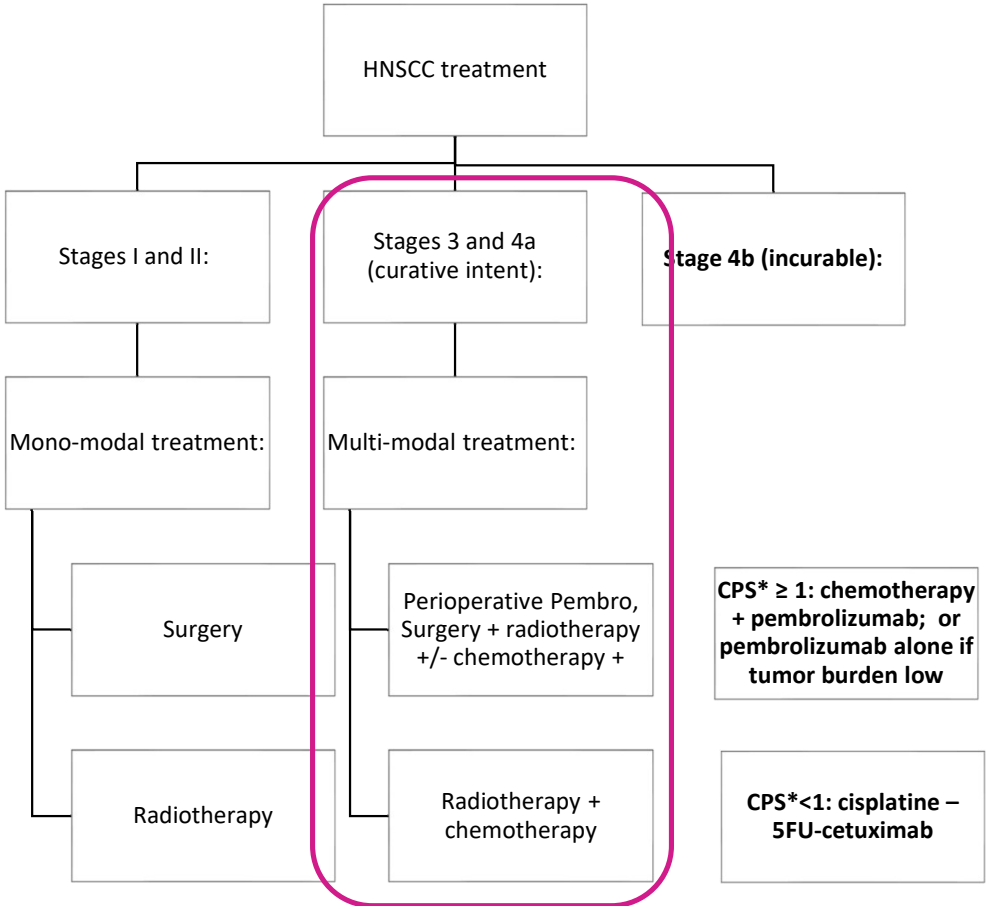
Head and neck squamous cell carcinoma (HNSCC)



- **Seventh most common malignancy**
- **Risk factors**
  - Alcohol & tobacco
    (oral cavity, larynx and pharynx)
  - Human Papillomavirus (HPV+)
    (oropharynx)

Introduction

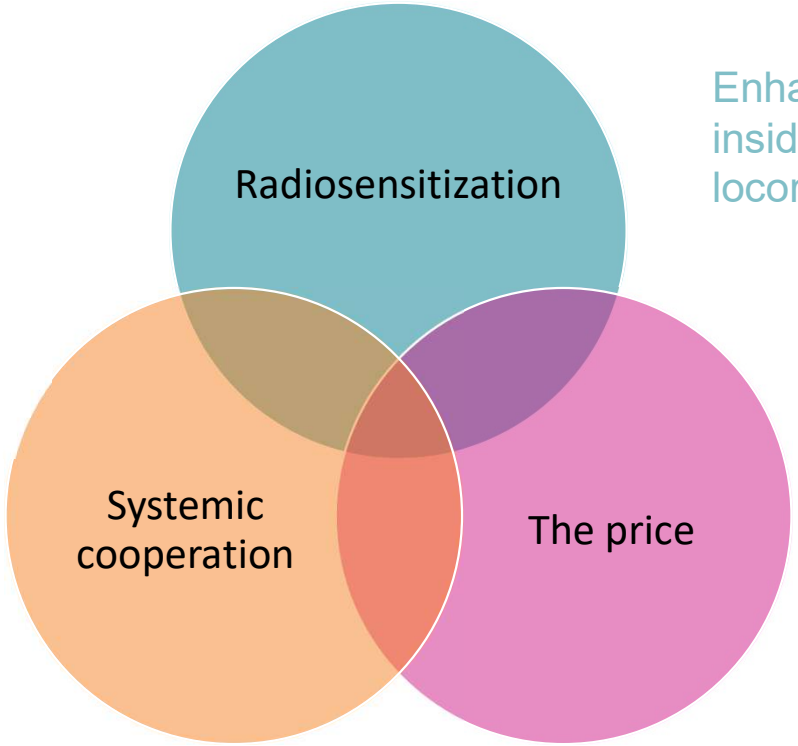
Treatment algorithm of HNSCC



Why combine RT and systemic R/?

Every combination is a bet on the therapeutic ratio





Enhance tumor cell kill inside the field to improve locoregional control.

Treat micrometastatic disease outside the field to reduce distant relapse.

Overlapping acute and late toxicities that can compromise RT delivery and long-term function.

Synergy only matters if it survives the toxicity

Combined treatments in HNSCC

Conventional radiosensitizers

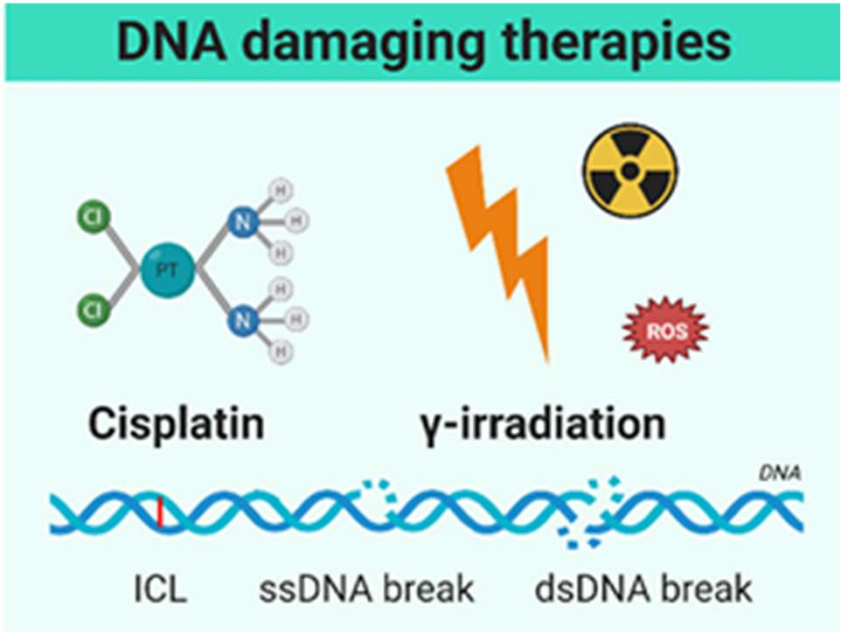
- Chemoradiation
- Radiotherapy plus cetuximab

Immunotherapy

Novel radiosensitizers

Conventional radiosensitizers

Cisplatin: inhibiting the repair of DNA damage



Repair blocked

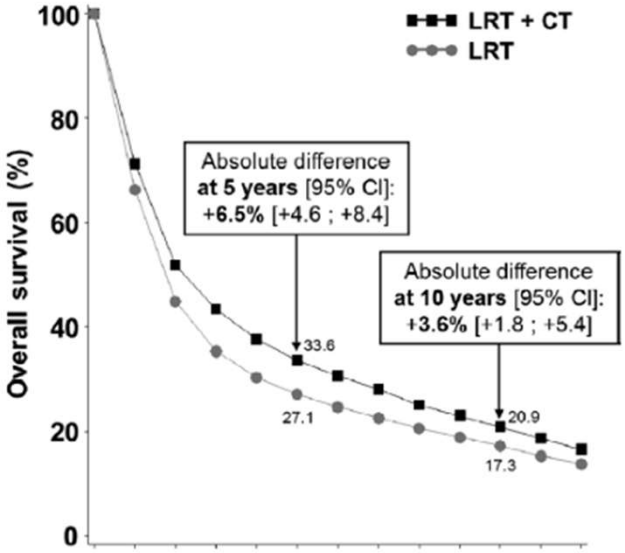
Adducts impair repair of radiation damage between fractions (non-homologous end joining)
Active in hypoxic cells

Lethal damage

More tumor cell kill per Gy

Conventional radiosensitizers

Radiotherapy + chemotherapy



Number of deaths / person-years

	Years [0;2[	Years [2;5[	Years [5;10[	Years 10+
LRT + CT	2454 / 7420	851 / 5629	407 / 4315	171 / 1513
LRT	2819 / 6981	800 / 4520	316 / 3507	126 / 1116

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC):
An update on 107 randomized trials and 19,805 patients

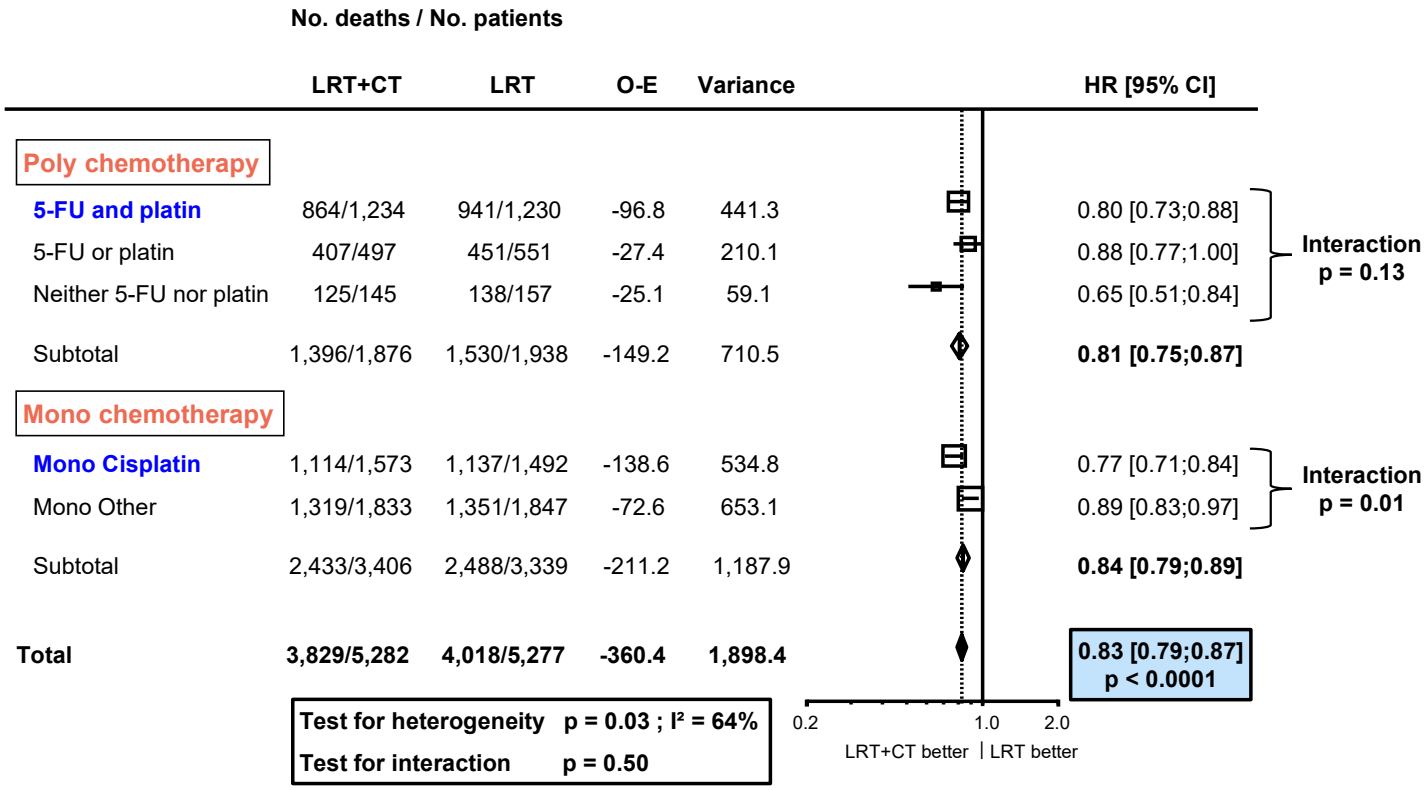
+6.5%

absolute 5-year overall survival gain with concurrent chemotherapy (MACH-NC)

2021, Radiotherapy and Oncology

Conventional radiosensitizers

Which chemotherapy ?



Cisplatin

Standard of care

- Radiotherapy 70Gy with high dose cisplatin 100mg/m2 Q3W
- Weekly 40 mg/m^2 is an option; weekly 30 is not.
- Aim for a cumulative dose ≥ 200 mg/m^2

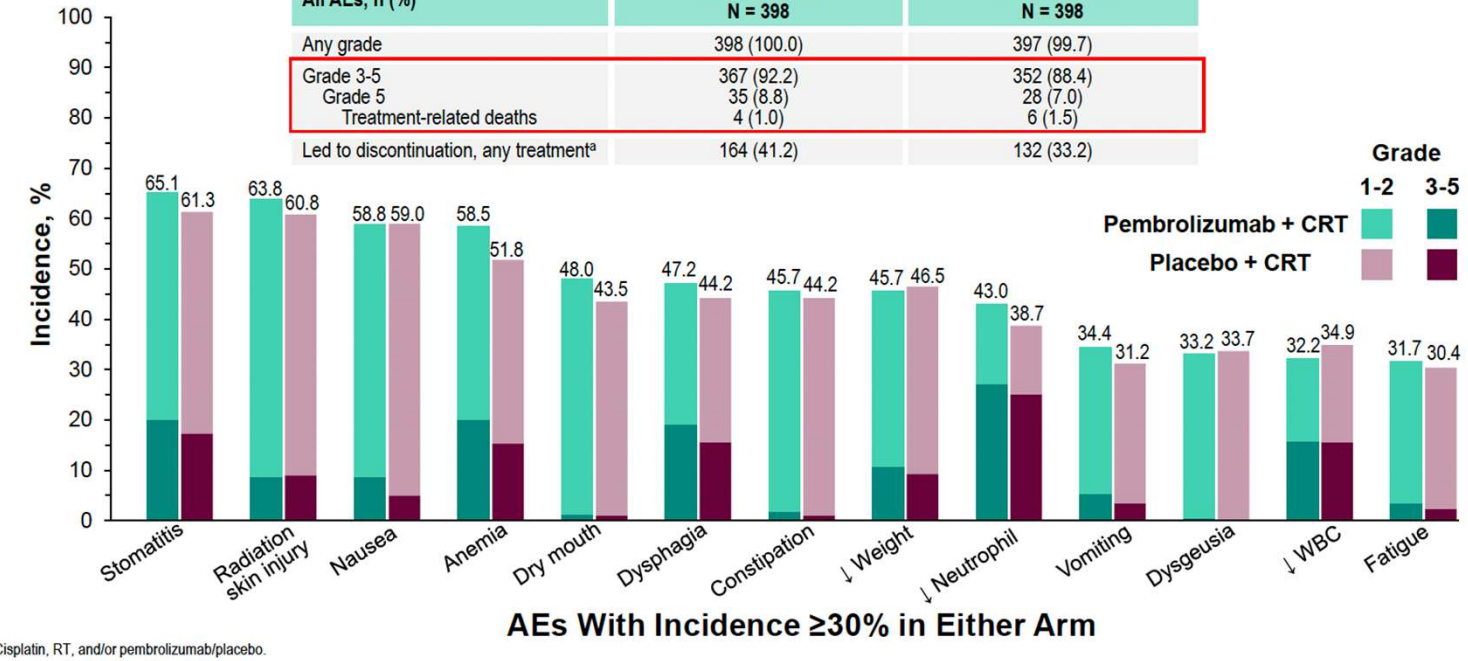
• Bourhis J et al ESMO 2016

Conventional radiosensitizers

Chemoradiation: Toxicity

Control arm CRT of KN 412

All AEs, n (%)	Pembro + CRT N = 398	Placebo + CRT N = 398
Any grade	398 (100.0)	397 (99.7)
Grade 3-5	367 (92.2)	352 (88.4)
Grade 5	35 (8.8)	28 (7.0)
Treatment-related deaths	4 (1.0)	6 (1.5)
Led to discontinuation, any treatment[a]	164 (41.2)	132 (33.2)



cisplatin, RT, and/or pembrolizumab/placebo.
ata cutoff date: May 31, 2022.

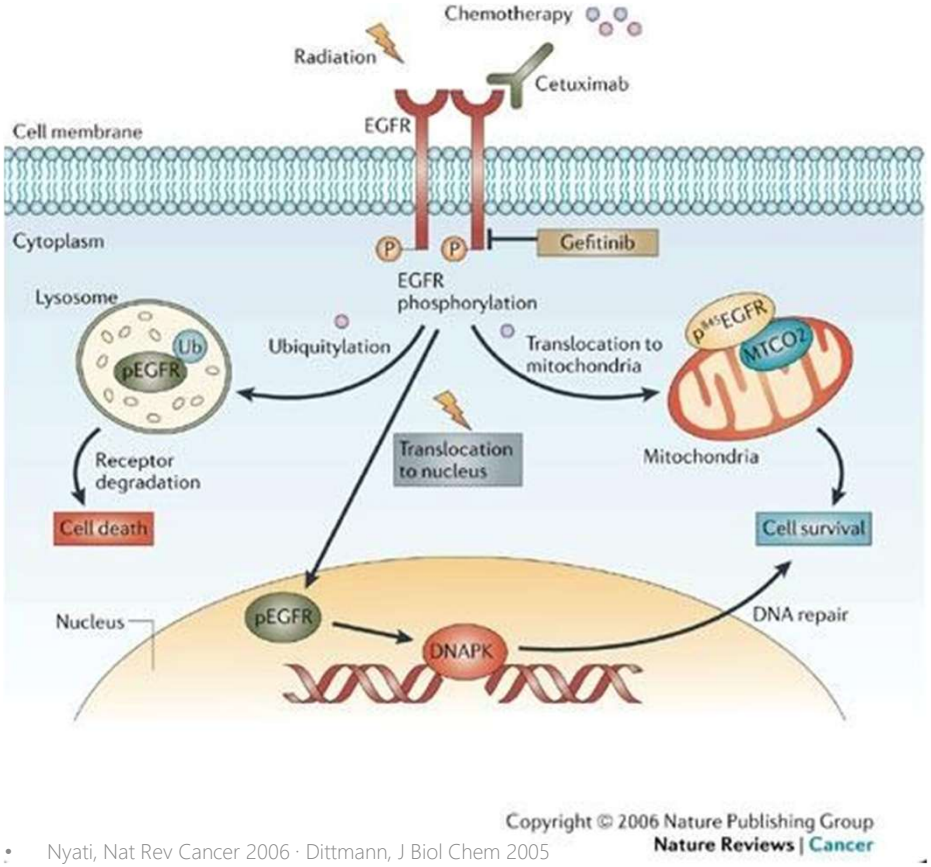
Acute: mucositis, emesis, nephrotoxicity, ototoxicity, neuropathy

Late: dysphagia, feeding-tube dependence; excess non-cancer deaths with long follow-up of concurrent CRT (RTOG 91-11)

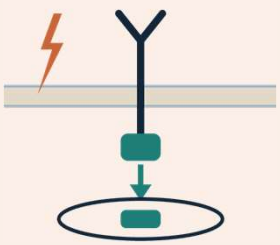
- KN 412, ESMO 2023

Conventional radiosensitizers

EGFR blockade: preventing repopulation and repair

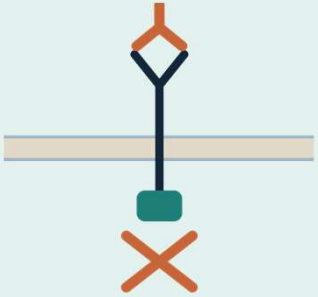


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What radiation does

Activates EGFR, which moves to the nucleus, binds DNA-PK and promotes DNA repair; EGFR signaling fuels repopulation.



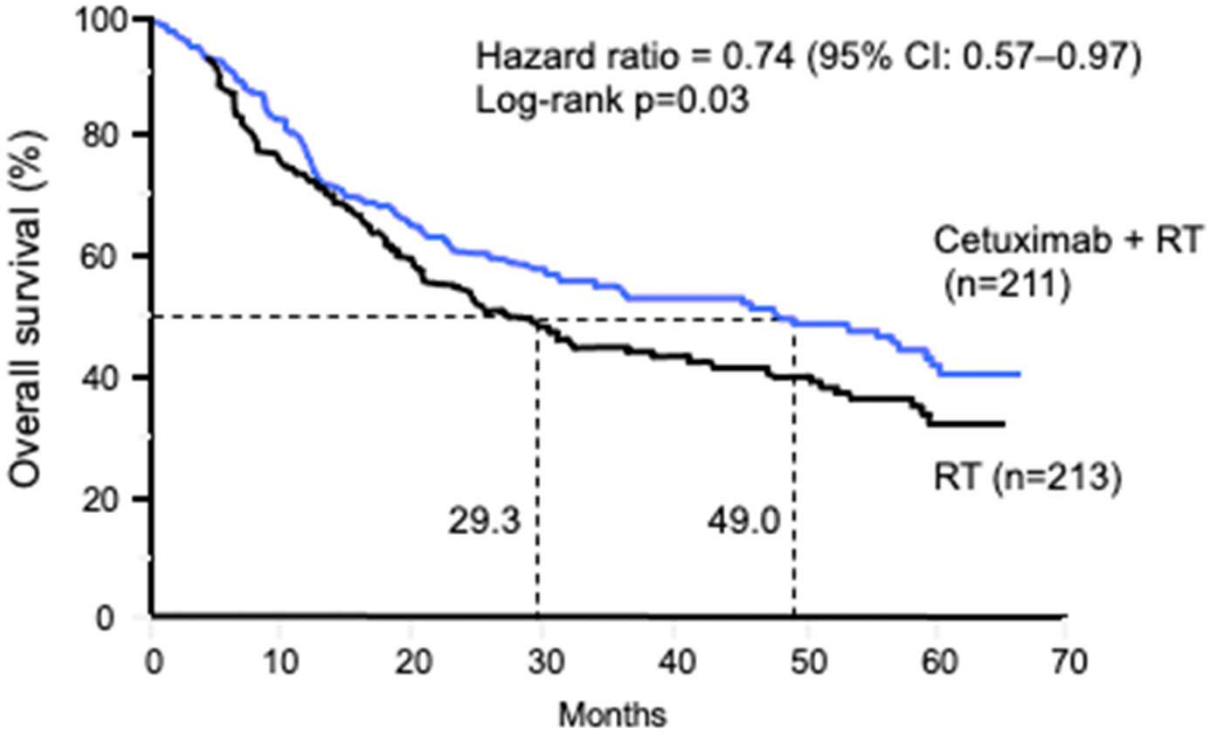
What cetuximab does

Blocks the receptor: less DNA-PK-dependent repair, less repopulation, G1 arrest, plus NK-cell cytotoxicity.

- Nyati, Nat Rev Cancer 2006 · Dittmann, J Biol Chem 2005

Conventional radiosensitizers

Radiotherapy + cetuximab



Versus RT alone

Bonner trial

RT + cetuximab improved 5-year OS

(45.6% vs 36.4%)

- Bonner, Lancet Oncology 2010

Conventional radiosensitizers

Cisplatin or cetuximab + RT for p16+ OPC

Study	Control arm	Population	OS (Chemotherapy vs cetuximab)
De-ESCALaTE Mehanna et al	Standard fractionation (70 Gy in 7 weeks) Cisplatin 100 mg/m2 Day 1, 22, 43	T1N1-T4N3 M0 T3-T4 N0 M0 Non-Smokers or < 10 pack-year	2-y OS rate: 97 vs 89%
NRG Oncology RTOG 1016 Gillison et al	Accelerated fractionation (70 Gy in 6 weeks) Cisplatin 100 mg/m2 Day 1, 22	T1-T2, N2a-N3 M0 T3-T4, N0-N3 M0 Smokers included	5-y OS rate: 85 vs 78 %
TROG 12.01 Rischin et al	Standard fractionation (70 Gy in 7 weeks) Cisplatin 40 mg/m2 weekly	T1-T2 N2 T3 N0-N2 Exclude N2b > 10 pack-year	3-y FFS rate 93 vs 80%

Versus RT + Cisplatin

inferior survival with cetuximab-RT, without an overall toxicity gain.

Conventional radiosensitizers

Radiotherapy + cetuximab is not a « gentle » option



⚠️

Specific Toxicity

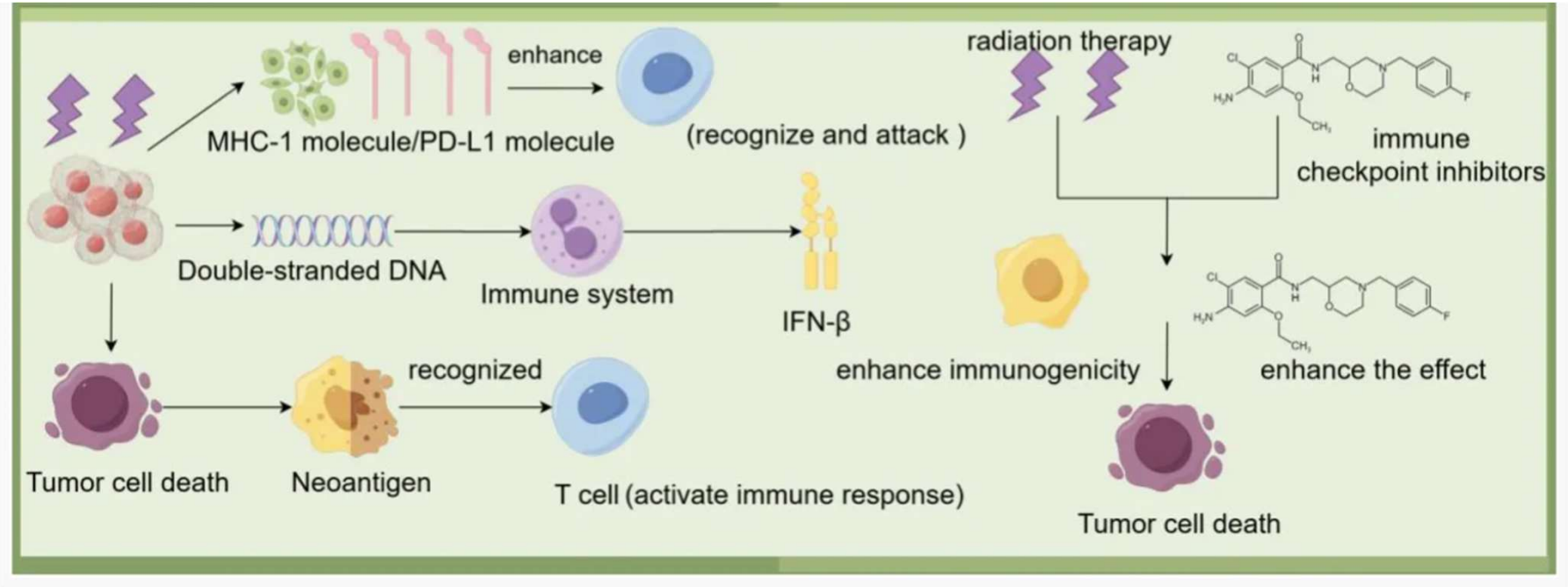
More severe radiation dermatitis, acneiform rash, infusion reactions, hypomagnesemia.



Radiation Oncology 2008; Annals of Oncology 2011

Immunotherapy

Radiotherapy + PD(L)1 blockade



Counterforces ?

Radiation-induced lymphopenia · irradiation of the draining nodes where priming occurs · hypoxic, immunosuppressive microenvironment

Immunotherapy

« Transformative » in R/M HNSCC

What could be the gain in LA HNSCC ?

- Decrease toxicity in case of better prognosis (Stage I/II p16-positive oropharyngeal cancer) – **De-escalation ?**
- **Decrease the toxicity** of high-dose cisplatin-based chemoradiation (fit or unfit patients) ?
- Improve outcome in locally advanced head and neck cancer (Stage III/IV HNSCC disease) – **Treatment intensification ?**

Immunotherapy

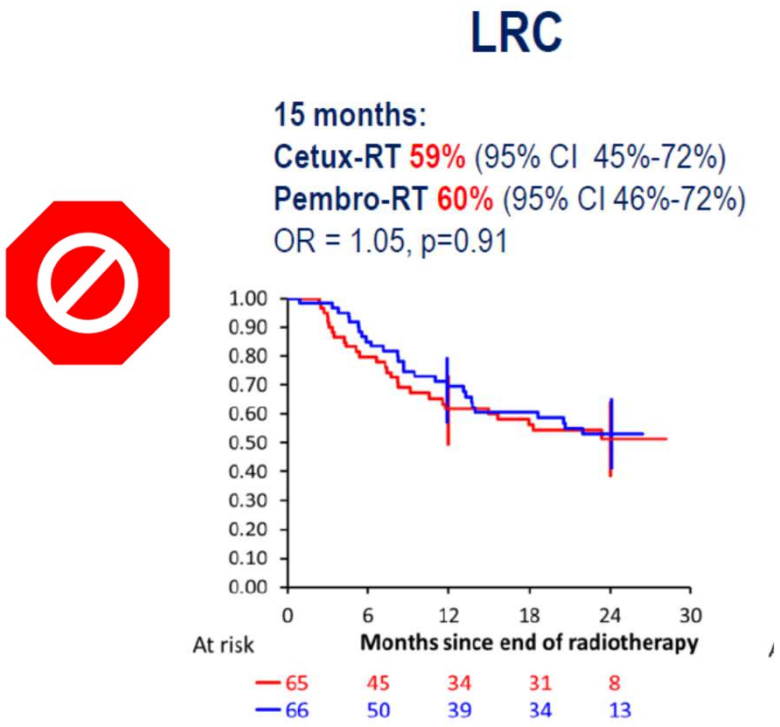
De-escalate: Replace cisplatin with anti-PD(L)1 in HPV + ?

	Design	Population	
NCT03952585 (HN005) Phase II/III (N=711)	Standard CRT (70 Gy) *versus* Reduced dose RT (60 Gy) + nivolumab *versus* Reduced dose RT (60 Gy) + CT	T1-2, N1 or T3, N0-N1 < 10 pack-year	Stopped for futility
NCT03799445 Phase II (N=180)	Nivolumab and ipilimumab with reduced-dose RT	T1 N2, T2 N1-N2, T3 N0-N2	
CCTG HN.9 --- EORTC1740 Phase II (N=180)	Standard CRT (70 Gy) *versus* RT + durvalumab (concomitant and adjuvant)	T1-2 N1 (smokers) T3 N0-N1 (smokers) T1-3 N2 (any smoking status)	Negative

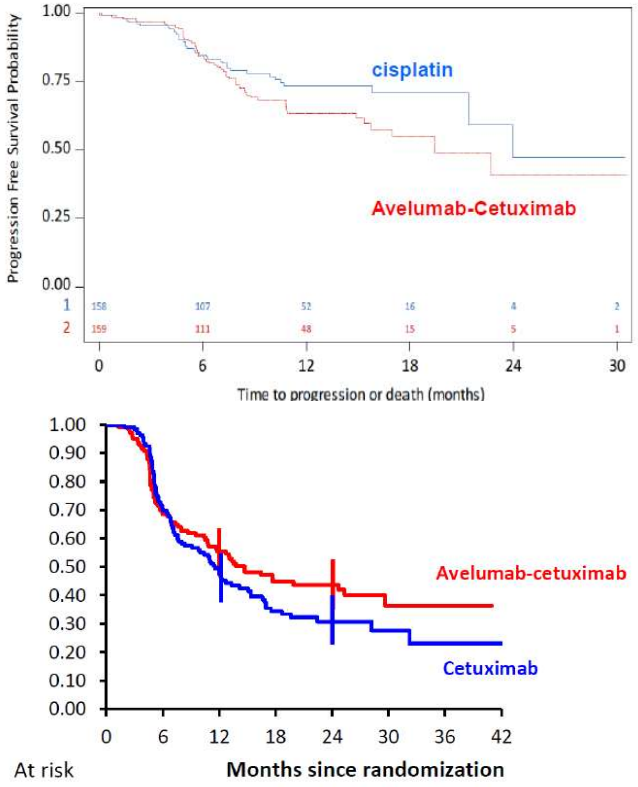
Immunotherapy

Decrease toxicity and improve/maintain efficacy?

GORTEC 2015-01: Pembro-RAD



GORTEC REACH (Fit/unfit)



Fit cohort
Stopped for Futility boundary

UnFit cohort

HR 0.84 for PFS, non significant
p 0.14

Immunotherapy

Improve outcome – treatment intensification ?

Study	Treatment	Outcome	N	
JAVELIN 100	Chemoradiation +/- Avelumab	PFS HR 1.21 (95% CI 0.93 – 1.57)	N= 697	negative
KEYNOTE 412	Chemoradiation +/- Pembrolizumab	EFS HR 0.83 (95% CI 0.68 – 1.03)	N = 804	Positive trend
IMVOKE 010	Primary treatment + adjuvant atezolizumab	EFS HR 0.94 (95% CI 0.7 – 1.26)	N = 406	negative

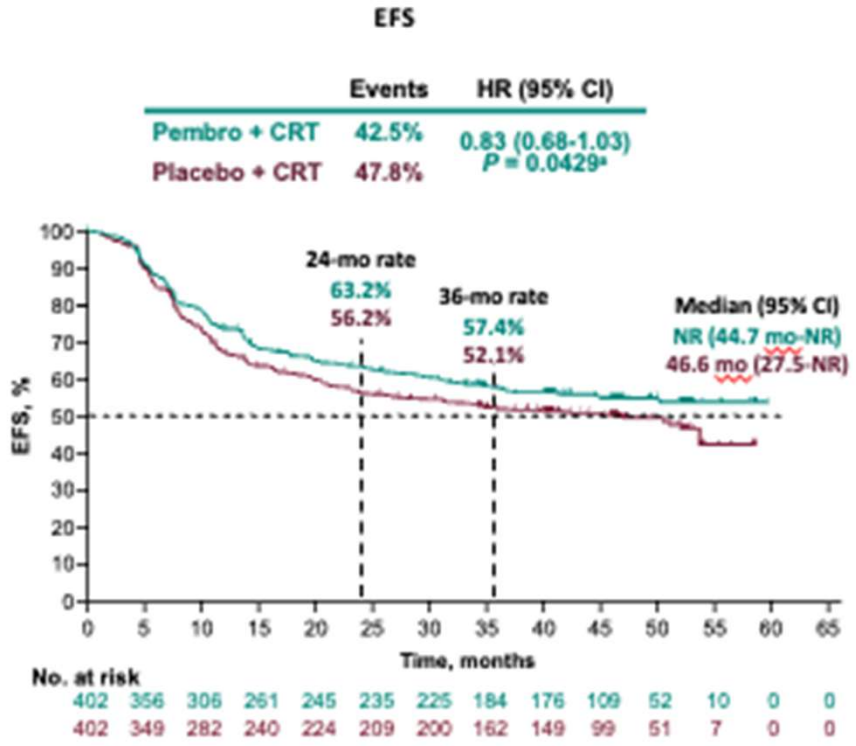
Toxicity
grade ≥3 events only slightly higher, mostly driven by CRT (KEYNOTE-412: 92% vs 88%).

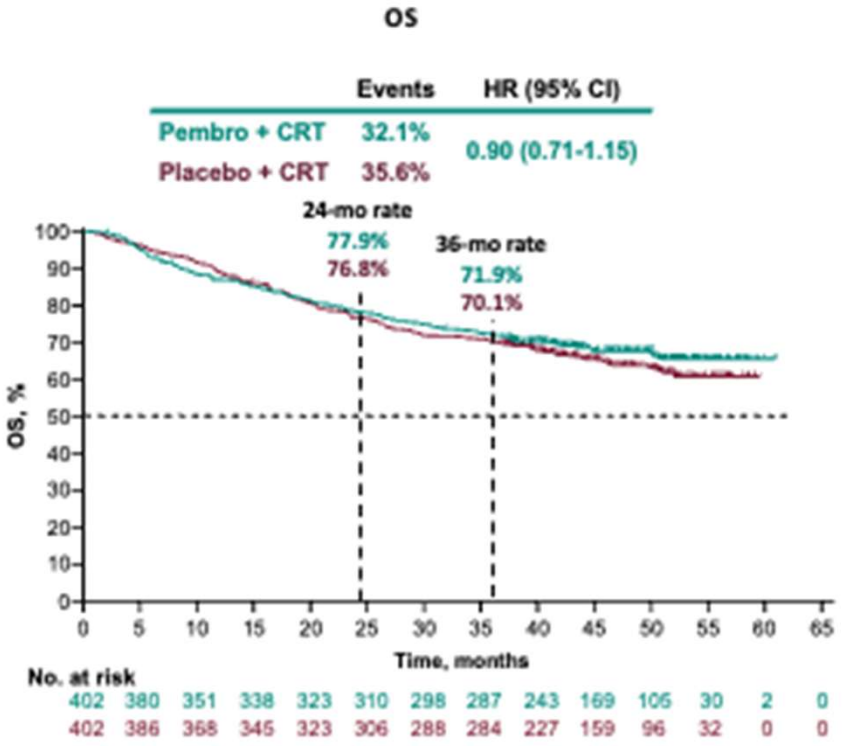
The problem was not toxicity, but the absence of added efficacy.



Immunotherapy

KN 412: EFS and OS in ITT population

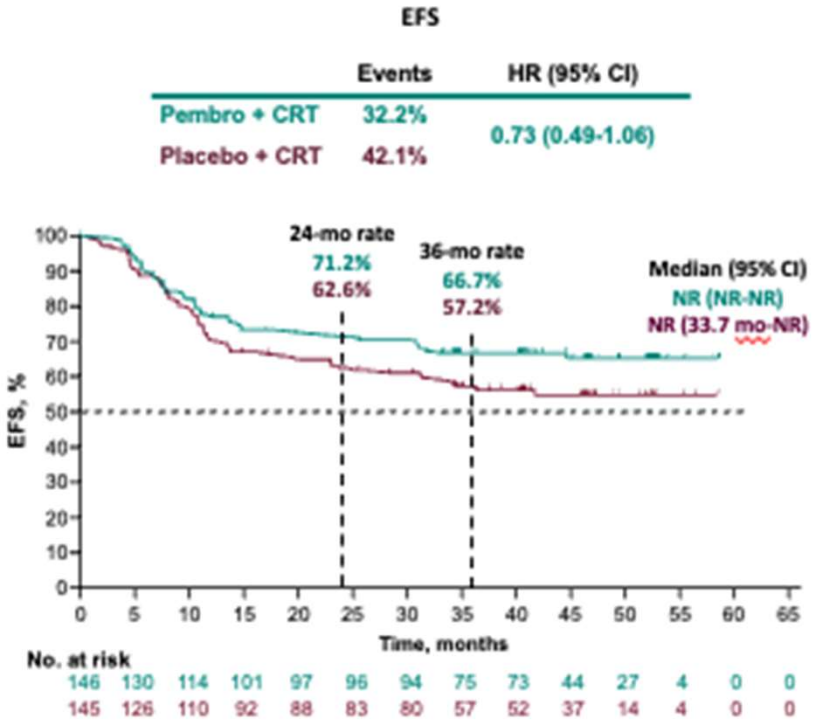


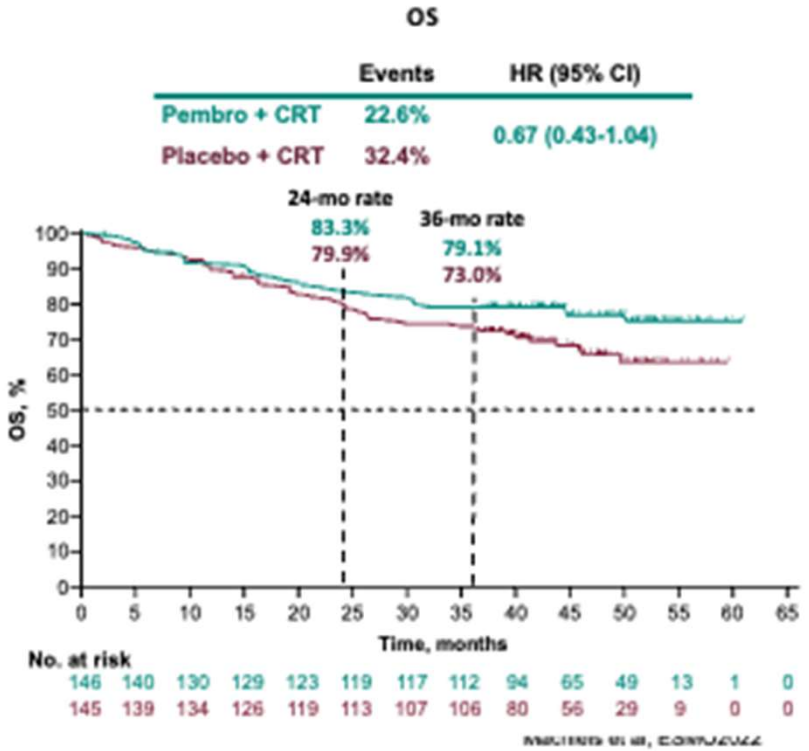


Machiels et al; ESMO2022

Immunotherapy

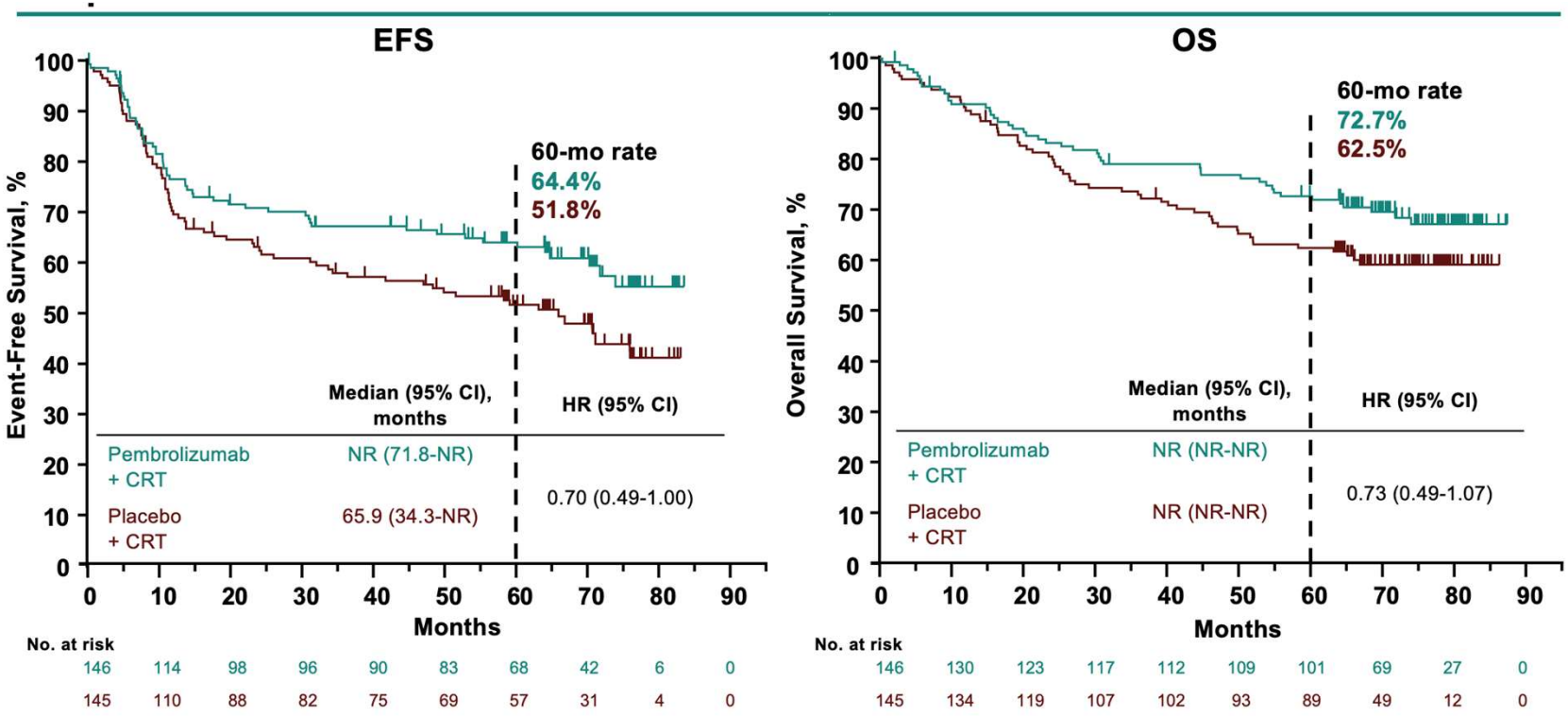
KN 412: EFS and OS in CPS ≧ 20 (post-hoc)





Immunotherapy

KN 412: Long-term EFS and OS in CPS ≧ 20 (post-hoc)



Immunotherapy

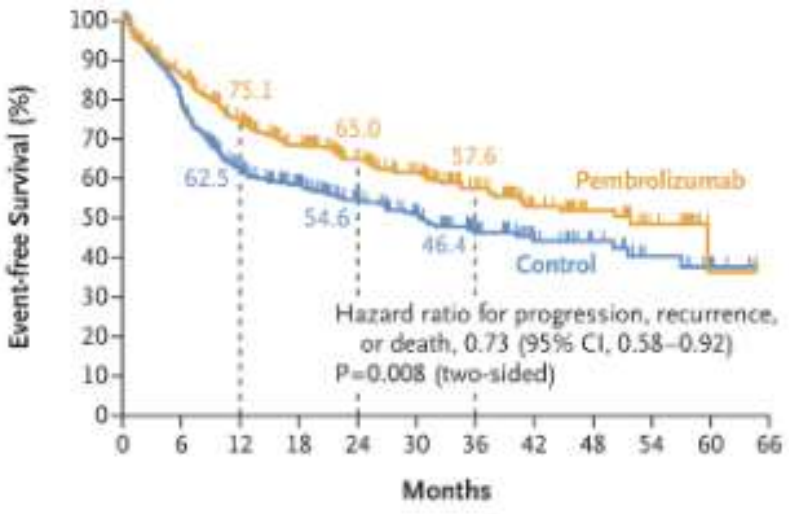
Gamechanger in operable HNSCC

Keynote-689

Neoadjuvant + adjuvant pembrolizumab with standard surgery and (C)RT.

Median EFS 51.8 vs 30.4 months.

Similar AE rates; surgery not compromised (about 90% proceeded in both arms).

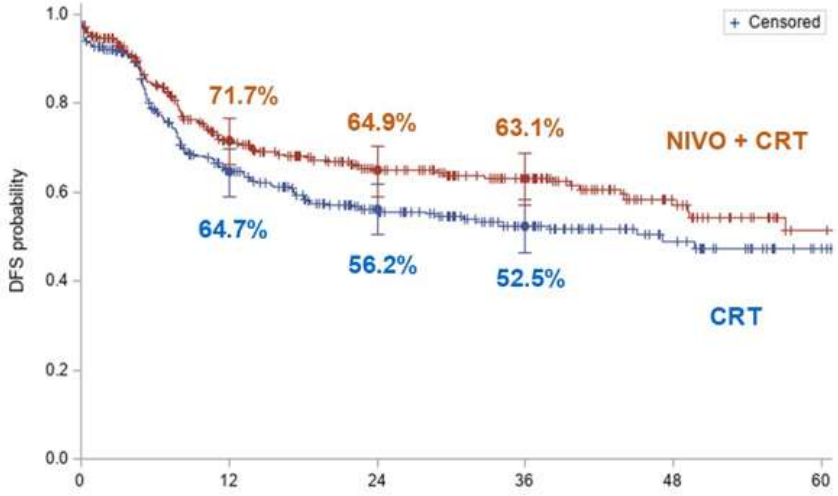


NIVOPOSTOP

Nivolumab added to postoperative cisplatin-RT in high-risk resected disease.

3-year DFS 63.1% vs 52.5% (HR 0.76).

Modest increase in grade 3–4 toxicity.



Uppaluri, NEJM 2025 · Bourhis, Lancet 2026

Immunotherapy

Why did concurrent immunotherapy fail ?

- **Timing/duration of priming ?**
  - PD-(L)1 blockade started just before CRT, when the draining nodes are irradiated and priming is impaired.

- **Sequencing ? Concurrent IO with CRT vs sequential IO**
  - RCT phase 2 in favor of sequential (JCO 2025) but IMVOKE010 is negative… JADE (sequential) ongoing

- **Lymphopenia ?**
  - Large fields and cisplatin deplete the lymphocytes IO relies on

- **Fields ?**
  - Elective irradiation of the nodal basins may remove the site of immune priming.

- **Selection?**
  - No biomarker enrichment… JADE (PD-L1 positive) ongoing

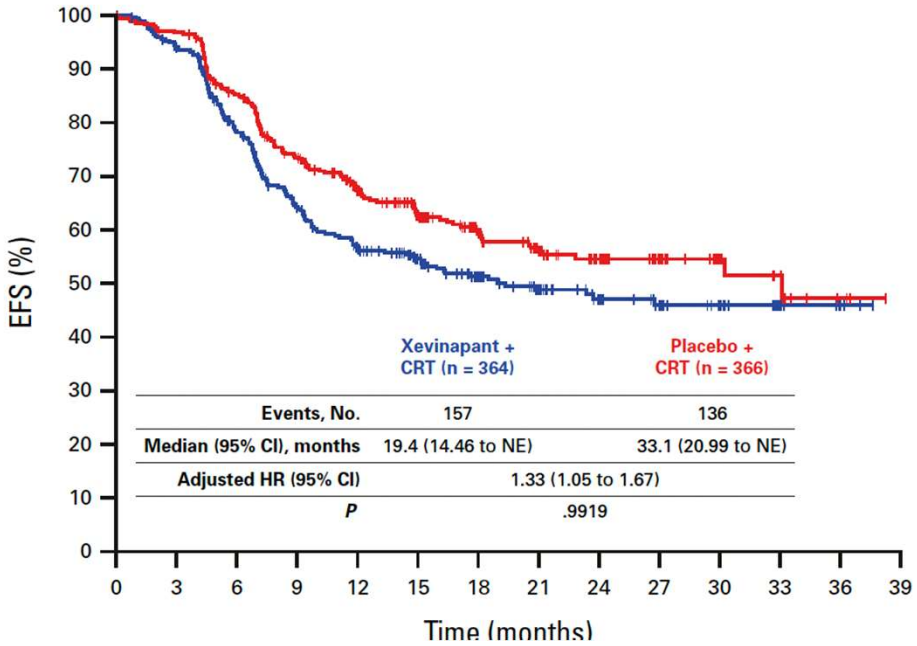
New radiosensitizers

Targeting how tumor cells survive radiation

Strategy	Mechanism	Example (stages)
DNA damage response inhibitors	Block repair of radiation-induced breaks or cell-cycle checkpoints	DNA-PK, ATR, WEE1 and PARP inhibitors with RT (phase I–II)
Apoptosis restoration	IAP inhibitors lower the threshold for radiation-induced apoptosis	Xevinapant (negative phase III)
Physical radioenhancers	High-Z nanoparticles increase the local dose deposited in the tumor	NBTXR3, hafnium oxide (phase III ongoing)
Hypoxia modification	Sensitize radioresistant hypoxic cells	Nimorazole (DAHANCA 5; not confirmed in later trials, stopped early)

New radiosensitizers

When toxicity erases synergy: Xevinapant



Trilynx study

Xevinapant + CRT vs placebo + CRT

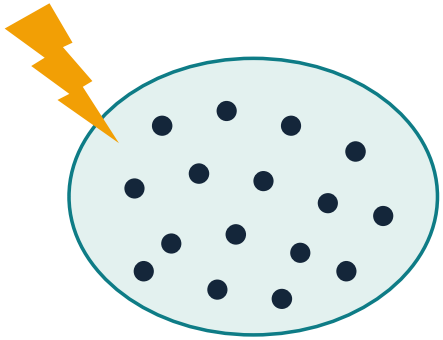
EFS HR 1.33
OS HR 1.39 in favor of placebo

Serious AEs 53% vs 36%

! a positive randomized phase 2 did not predict phase 3 benefit; added toxicity can translate into worse survival!

New radiosensitizers

NBTXR3 (hafnium oxide): a physical radioenhancer



Hafnium oxide nanoparticles (Z = 72) injected into the tumor

One injection

Intratumoral, before RT. Inert until irradiated.

Activated by RT

High electron density: absorbs X-rays and emits many more electrons than tissue.

More dose in the tumor

ROS and DNA damage; healthy tissue spared

Phase 1 expansion, cisplatin- and cetuximab-ineligible (N = 56, median age 72)

Injected lesion: ORR 82%, complete response 64%. Median PFS 11.4 mo, OS 18.1 mo. Grade ≥ 3 related AEs 11%.

Phase 3 NANORAY-312 ongoing

RT ± cetuximab, with or without NBTXR3, in elderly platinum-ineligible LA-HNSCC. Proof of concept in sarcoma: pCR 16% vs 8%.

- Le Tourneau, JAMA Otolaryngol Head Neck Surg 2026 · Bonvalot, Lancet Oncol 2019

Future directions

Next generation of combinations

Sequencing

Immunotherapy before RT, while nodes are intact: neoadjuvant and window-of-opportunity designs

Volumes and dose

Reduced elective nodal volumes, hypofractionation and lymphocyte-sparing techniques, including protons

Designing the next generation of combinations

Selection

PD-L1 CPS and ctDNA-based minimal residual disease to intensify only where needed.

Eg. JADE trial, MIRAGE-HN

New partners

Bispecific EGFR antibodies with RT: early-phase trials.

Eg. Petosemtamab,...

Conclusion

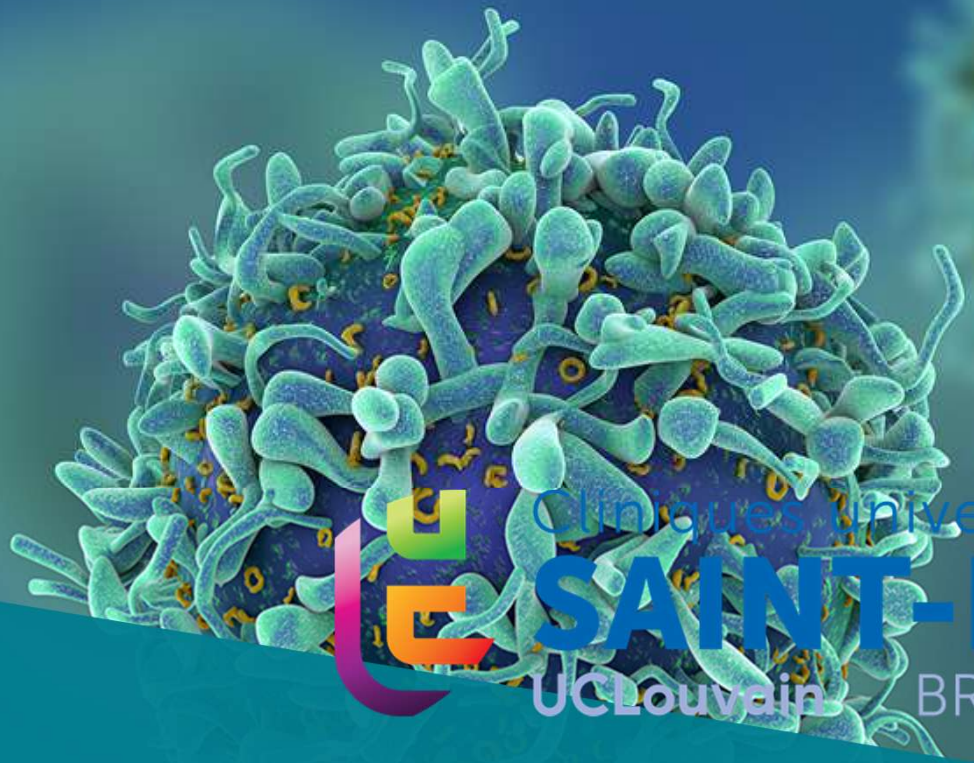
Take-home messages

- Cisplatin –RT remains the benchmark
  - De-intensification has so far cost efficacy

- Concurrent PD-(L)1 blockade with definitive CRT adds little toxicity but no benefit in unselected patients
  - Results awaited for biomarker-driven trials (eg JADE)

- Immunotherapy works in peri-operative setting (KN-689)
  - Do timing and nodes matters ?

- Toxicity can erase synergy
  - protect RT delivery and manage overlapping toxicities together



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Thank you!

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Conventional radiosensitizers

Cisplatin: weekly or high-dose ?

Study	Setting	N	Cisplatin
Noronha JCO 2018	Mostly post-operative (93%)	300	Weekly 30 mg/m² vs 100 mg/m² q3w
JCOG1008 Kiyota, JCO 2022	Post-operative, high risk	261	Weekly 40 mg/m² vs 100 mg/m² q3w
ConCERT Sharma, ASCO 2022	Definitive CRT	266	Weekly 40 mg/m² vs 100 mg/m² q3w
NRG-HN009	Definitive CRT	Ongoing	Weekly 40 mg/m² vs 100 mg/m² q3w

Dose matters

Weekly 40 mg/m² is an option; weekly 30 is not. Aim for a cumulative dose ≥ 200 mg/m².

- Noronha, JCO 2018 · Kiyota, JCO 2022 · Sharma, ASCO 2022

Conventional radiosensitizers

Cisplatin-ineligible: RT + docetaxel

	RT + docetaxel (n = 180)	RT alone (n = 176)	
2-year DFS	42.0%	30.3%	HR 0.67, p = 0.002
2-year OS	50.8%	41.7%	HR 0.75, p = 0.035
Grade ≥ 3 mucositis	49.7%	22.2%	p < 0.001
Grade ≥ 3 odynophagia	52.5%	33.5%	p < 0.001
Grade ≥ 3 dysphagia	49.7%	33.0%	p = 0.002

Phase III, Tata Memorial (N = 356)

Docetaxel 15 mg/m² weekly × 7. Survival gain, at the price of doubled grade ≥ 3 mucositis.

- Patil et al, JCO 2023

Toxicity

Overlapping toxicities

Toxicity	Radiotherapy	Cisplatin	Cetuximab	Anti-PD-1
Mucositis, dysphagia	+++	++	+	rare
Dermatitis, rash	++	–	++ (in-field increase)	+
Pneumonitis	+ (in field)	–	rare	+ (any lobe)
Hypothyroidism	++ (late)	–	–	+ (early)
Nephro- / ototoxicity	–	+++	–	rare
Lymphopenia	++	+	–	–

Multimodality management in expert team

Before treatment

Baseline TSH and free T4, renal function, audiometry for cisplatin, dental assessment, nutrition, history of autoimmune disease.

During and after

Irradiated field? Outside the field? pneumonitis, dermatitis, colitis. TSH every 6 weeks. Steroids according to guidelines.

Organization

Shared multidisciplinary pathway, one point of contact for the patient, early involvement of dietitian and speech therapist.

Avoid radiotherapy interruptions

Immunotherapy

Radiotherapy + PD(L)1 blockade



Dose per fraction

Moderate hypofractionation (8 Gy × 3) activates cGAS–STING; very high single doses induce TREX1, which blunts the response.



PD-L1 upregulation

RT increases tumor PD-L1 through interferon-γ: a direct rationale for PD-(L)1 blockade.



Timing

PD-L1 blockade worked when given during fractionated RT, not after it.



Draining lymph nodes

Elective nodal irradiation reduced the efficacy of RT + immunotherapy: the nodes are where priming happens.

- Preclinical (mouse) data · Vanpouille-Box, Nat Commun 2017 · Dovedi, Cancer Res 2014 · Marciscano, Clin Cancer Res 2018