

Radiotherapy Plus Cytotoxic Therapy in Head and Neck cancer

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Head and Neck Cancer

Curative Treatment

- Surgery
- Radiotherapy

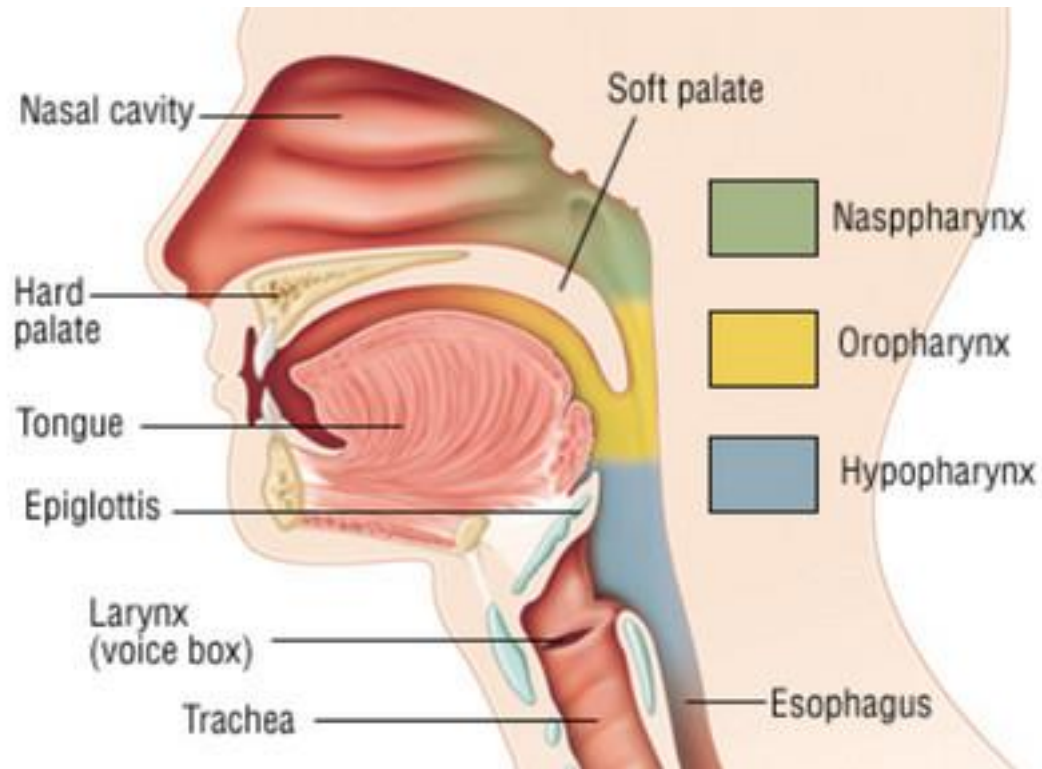


Head and Neck Cancer

Radiotherapy

Organ Preservation

- Oropharynx
- Larynx/Hypopharynx
- Nasopharynx



Head and Neck Cancer

Radiotherapy

Adjuvant Treatment

- Oral cavity
- Paranasal sinuses



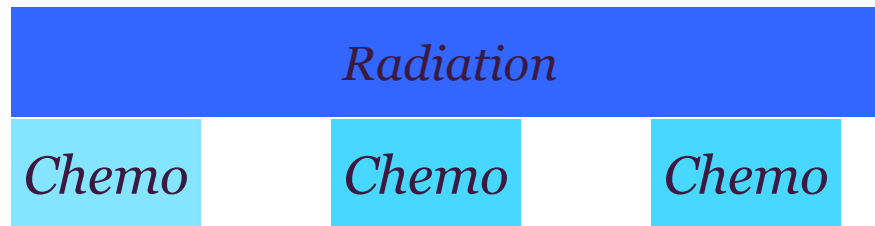
Head and Neck Cancer

Radiotherapy + chemotherapy

Induction



Concomitant



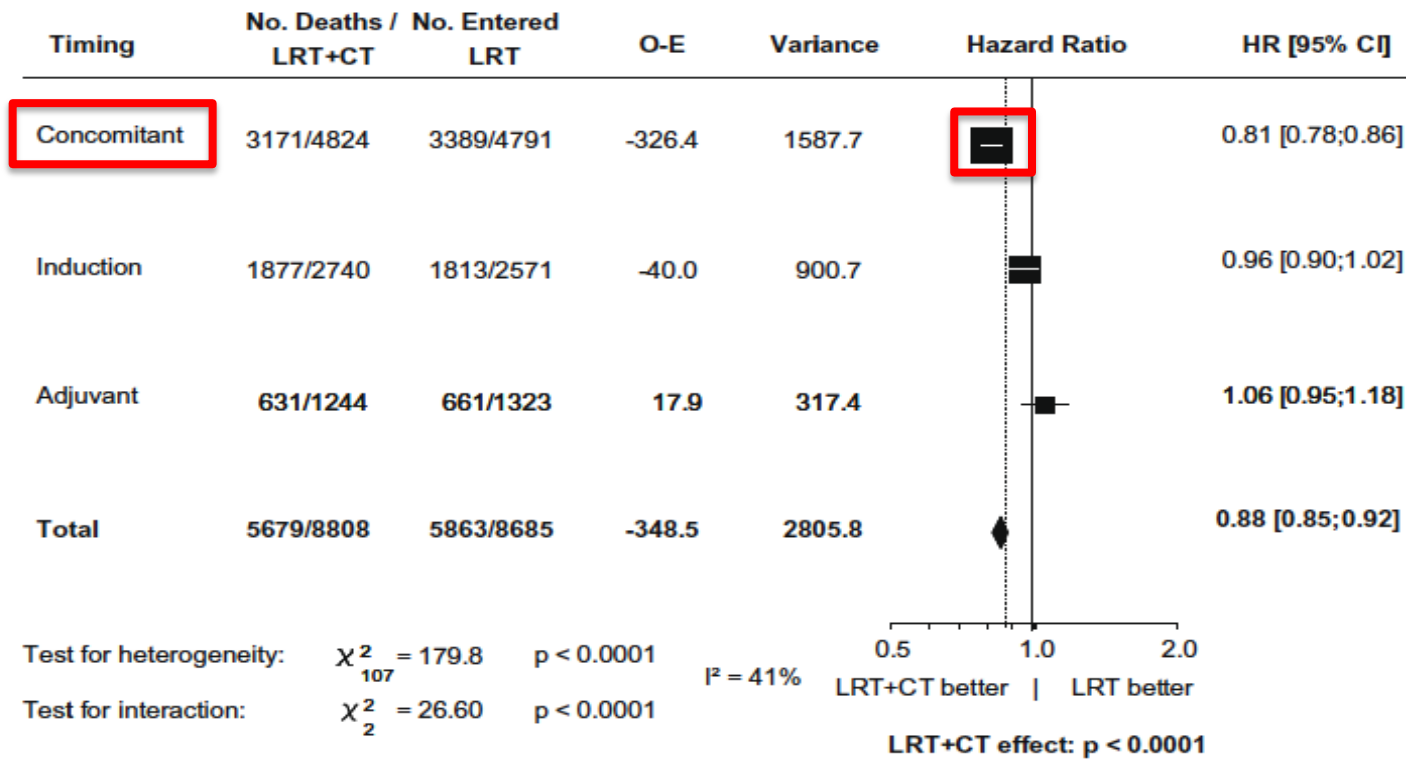
Adjuvant



Head and Neck Cancer

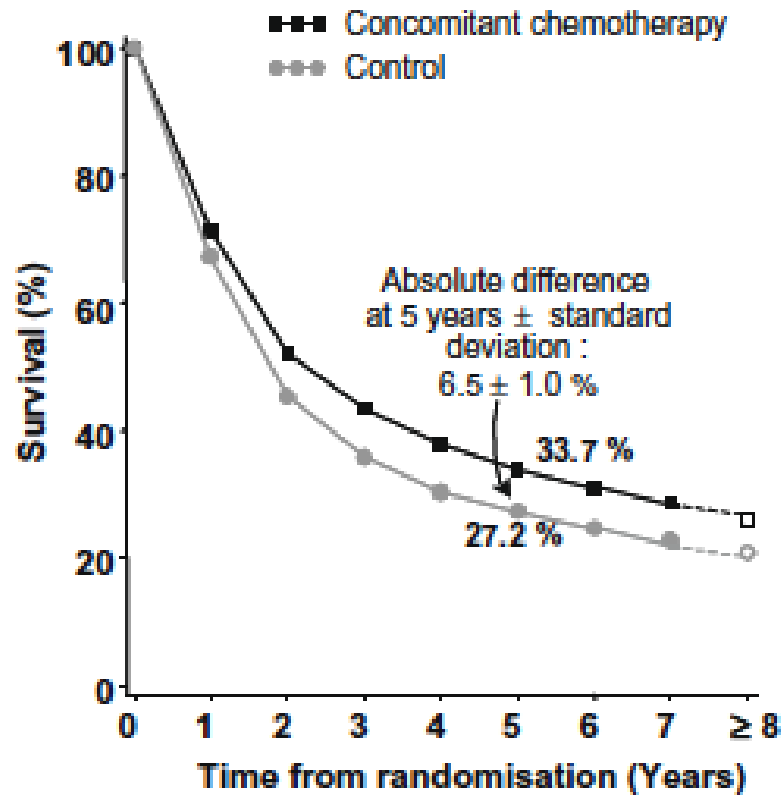
Radiotherapy + chemotherapy

(a) Hazard ratio of death.



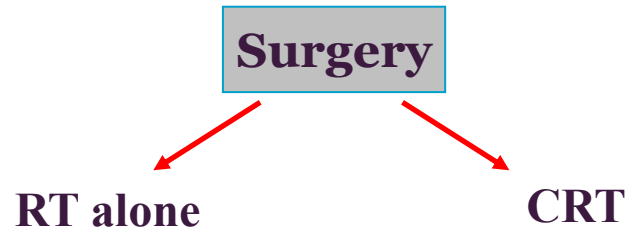
Head and Neck Cancer

Radiotherapy + Concomitant chemotherapy



Head and Neck Cancer

Adjuvant Chemo-Radiotherapy



RTOG 9501

Cooper et al NEJM 2004

- **L-R control HR = 0.61 (95% 0.41-0.91)**
- **2-year L-R control 82% C-RT vs 72% RT**
- **DFS HR = 0.78 (95% 0.61-0.99)**
- **OS HR = 0.84 (95% 0.65-1.09)**

EORTC

Bernier et al NEJM 2004

- **5 year PFS = 47% C-RT vs 36% RT**
- **OS HR = 0.70 (95% 0.52-0.95)**
- **5-year OS = 53% C-RT vs 40% RT**



Head and Neck Cancer

Chemo-Radiotherapy

Agents used

- Cisplatin
- Carboplatin
- Taxanes
- 5-FU



Radiotherapy Toxicity

Toxicity	Incidence (%) - Grade 3	Duration post-RT
Mucositis	40%	6-8 weeks
Feeding tube	40-60%	6-8 weeks
Taste Alteration	80-90%	Up to 6 months
Dermatitis	30-50%	2-3 weeks
Salivary toxicity	80%	Up to 6 weeks
Fatigue	70-80%	Up to 12 months
Weight loss	40-50%	6-8 months



Chemo-radiation Toxicity

Relative risk of acute toxicity

Side-effect	RR
N +V	80
Mucositis	3
Dermatitis	1.43
Delays in RT	3
Myelosuppression	15
Overall	2



Chemotherapy Toxicity

Specific Agents

Cisplatin

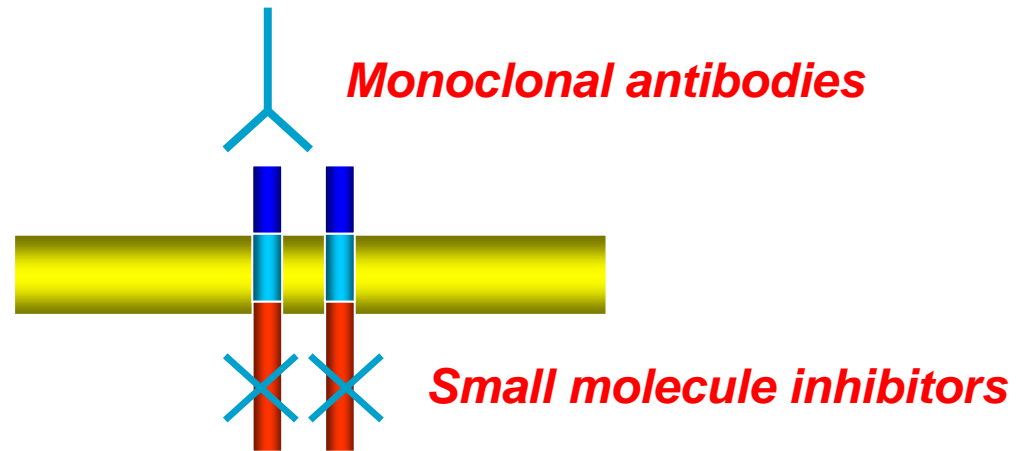
- Ototoxicity
- Nephrotoxicity

Carboplatin

- Delayed myelosuppression



EGFR-inhibitors



NO DOWNSTREAM SIGNALING

VEGF
angiogenesis



JAK-STAT
pathway
regulating gene
transcription



Pro-proliferative
RAS-MAPK
pathway



MMP9
invasion

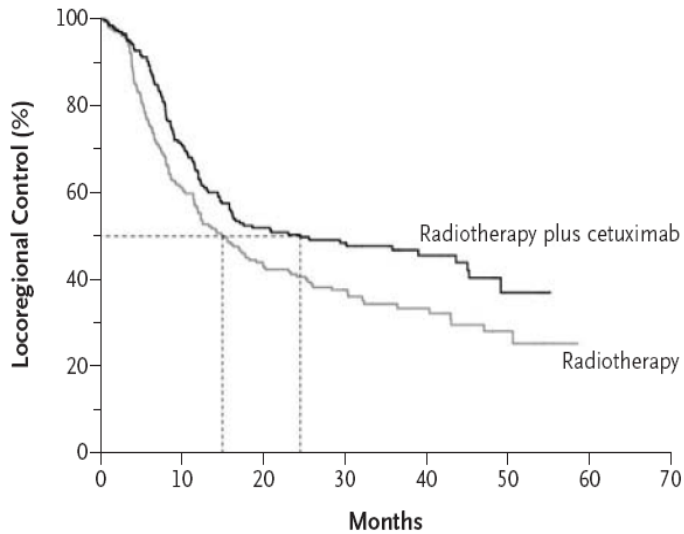
DNA-repair



PI3K-AKT
survival
pathway



Cetuximab Plus RT

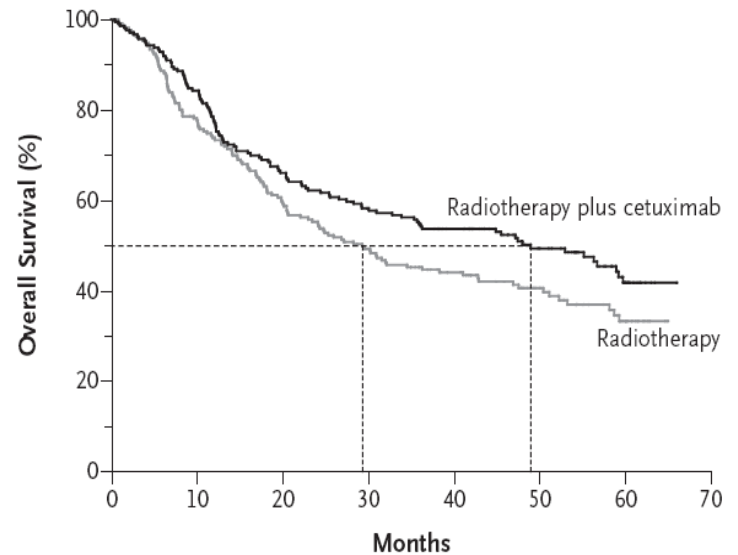


No. at Risk

Radiotherapy	213	122	80	51	30	10
Radiotherapy plus cetuximab	211	143	101	66	35	9

Figure 1. Kaplan–Meier Estimates of Locoregional Control among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for locoregional progression or death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.68 (95 percent confidence interval, 0.52 to 0.89; $P=0.005$ by the log-rank test). The dotted lines indicate the median durations of locoregional control.



No. at Risk

Radiotherapy	213	162	122	97	73	47	22
Radiotherapy plus cetuximab	211	177	136	116	98	61	24

Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; $P=0.03$ by the log-rank test). The dotted lines indicate the median survival times.

Cetuximab Plus RT

SCCHN

Oro/Hypopharynx, Larynx R

T2N2-3, T3-4N(any)

n = 945

RTOG 0522

RT (6 weeks) + CDDP days 1 and 22

RT (6 weeks) + CDDP days 1 and 22
+ Cetuximab (7 weeks)

No difference in primary end-points



Cetuximab Plus RT

SCCHN

Oro/Hypopharynx, Larynx
T2N2-3, T3-4N(any)

R

*RT (7 weeks) + CDDP days 1,22, 43

*RT (67weeks) + CDDP days 1,22, 43
+ Panitumumab

Concert

No difference in 2 yr LC, PFS and OS



Cetuximab Plus RT

Current status

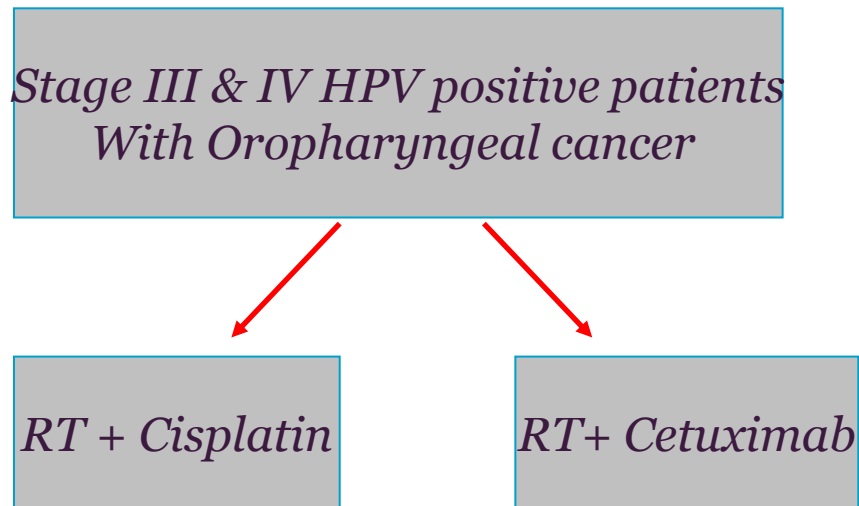
NICE guidelines

- Contraindication to platinum agents



Cetuximab Plus RT

Current status



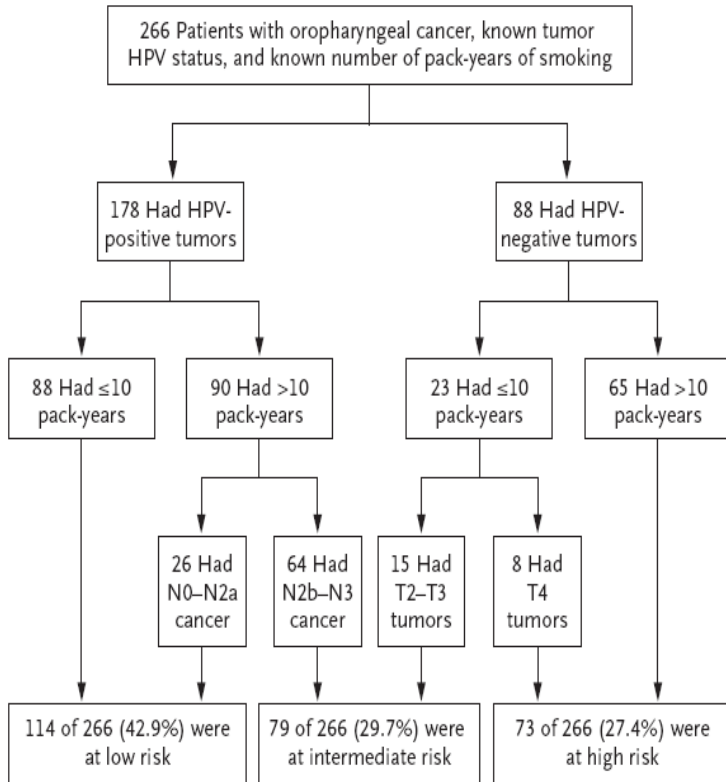
Current Trials:

- *RTOG 1016 – North America- Sample Size - 706*
- *TROG 12.01- Australia- Sample Size - 200*
- *De-Escalate- Uk- Sample Size - 304*

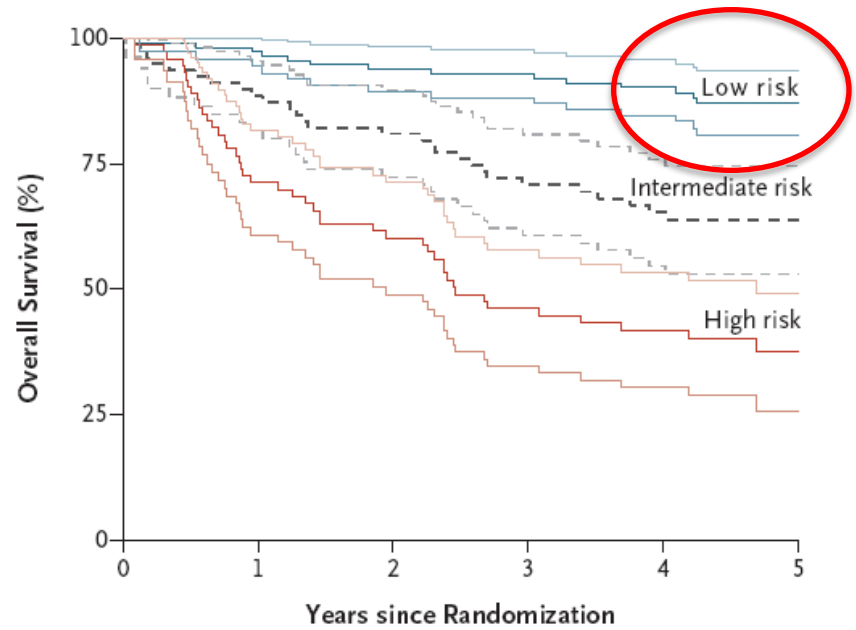


Delineation of Prognostic Groups

A



B



No. at Risk

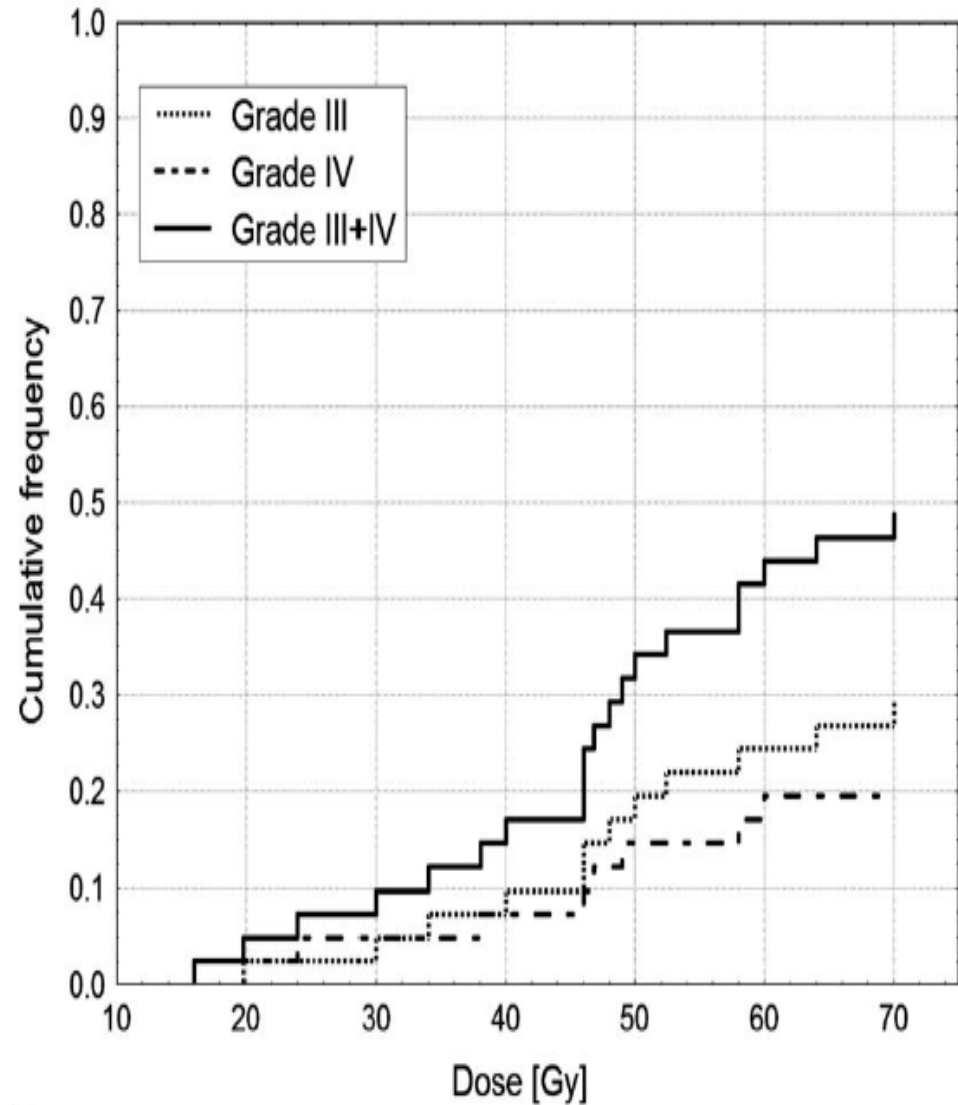
	0	1	2	3	4	5
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8



Cetuximab Plus RT

Toxicity

- Dermatitis
- Infusion reaction



Cetuximab Plus RT

Dermatitis – Grade 2

Non- haemorrhagic

- Dry desquamation
- Moist desquamation



Cetuximab Plus RT

Dermatitis – Grade 3

Haemorrhagic

- Dry desquamation
- Moist desquamation



Cetuximab Plus RT

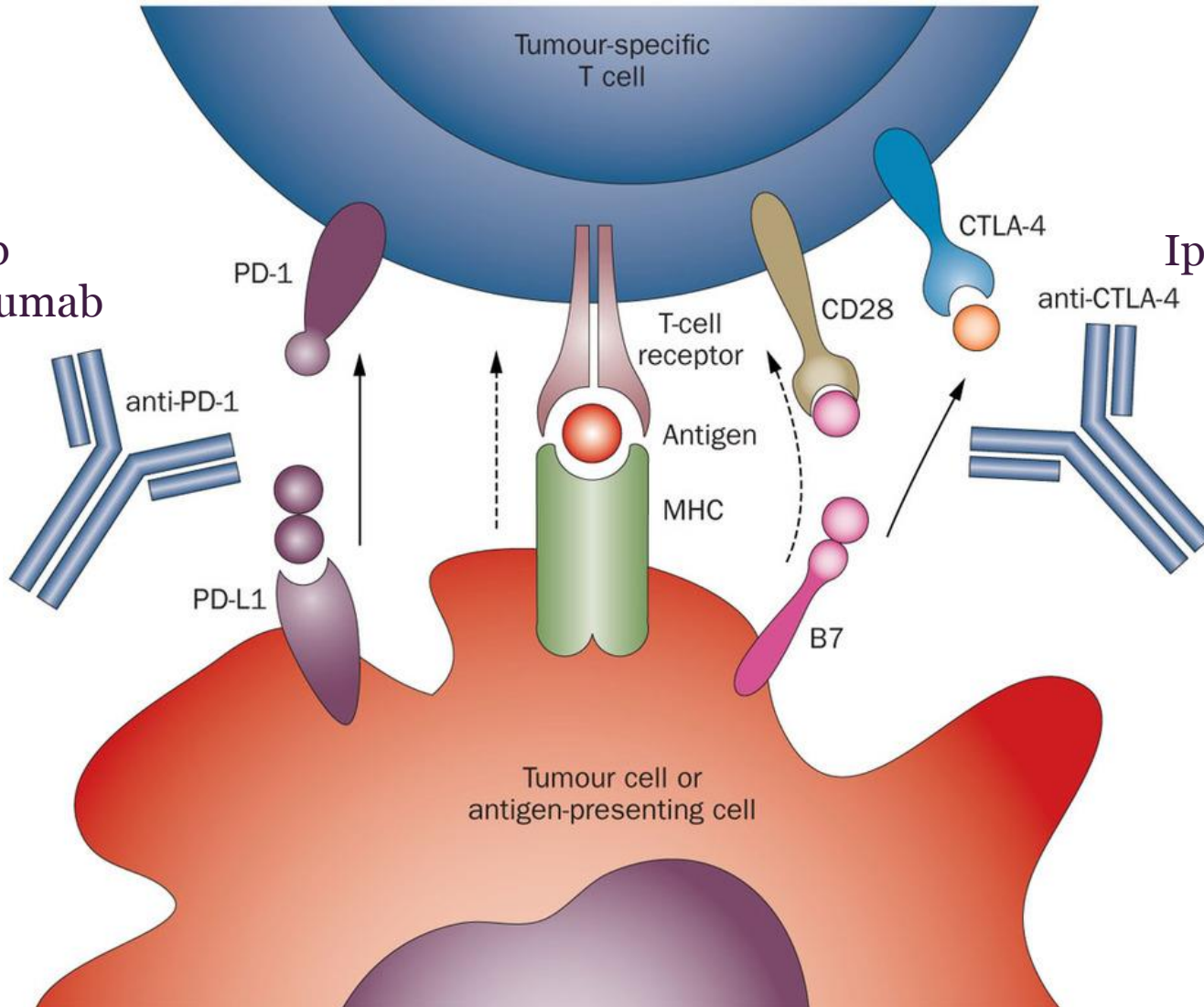
Dermatitis – Management

- Regular monitoring
- Topical Steroids (1-2 weeks)
- Topical Antimicrobials
- Systemic Antimicrobials



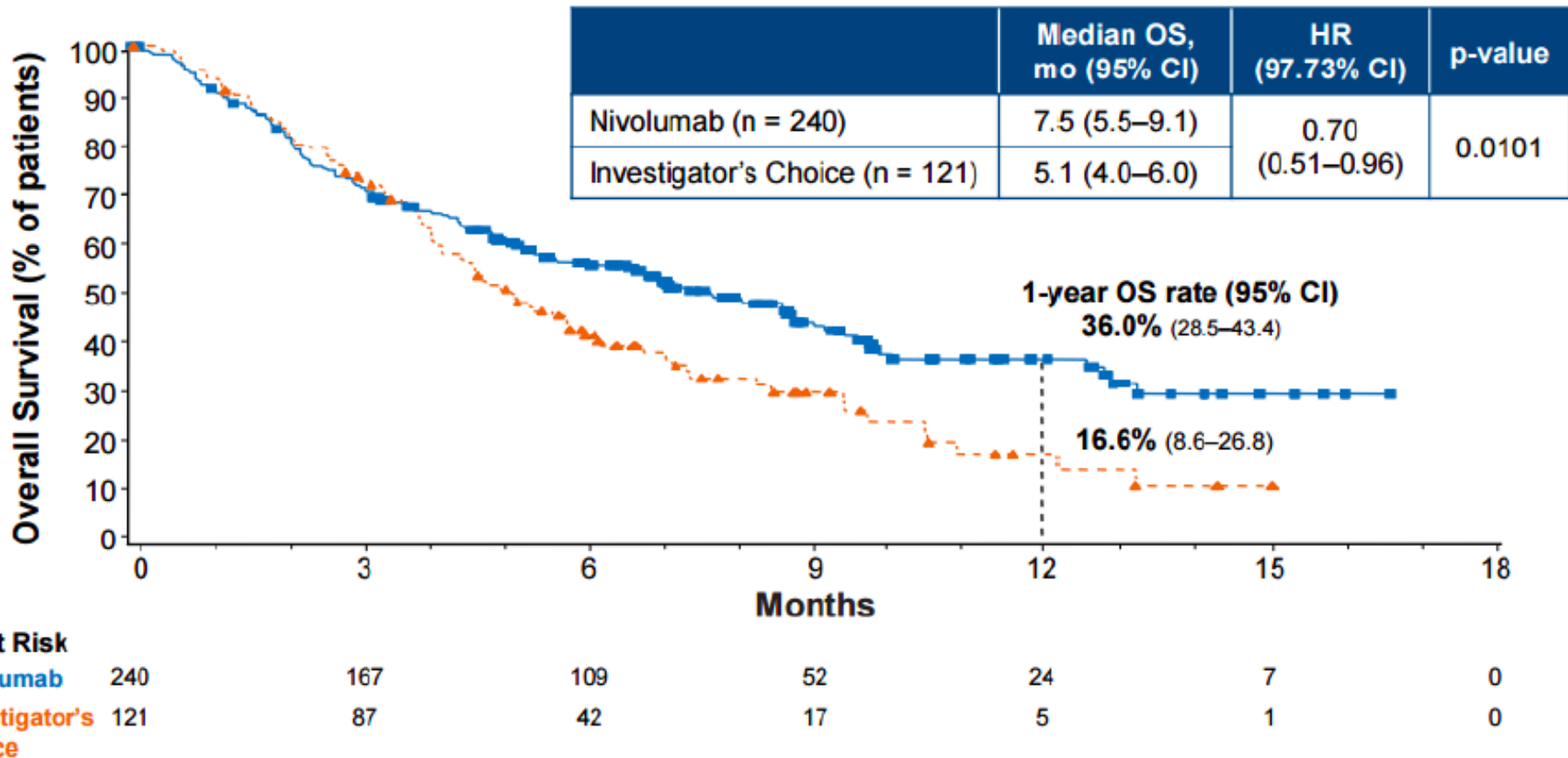
Immune Checkpoint Modulators

Nivolumab
Pembrolizumab



Immune Checkpoint Modulators

Checkmate -141 : Metastatic HNSCC



Immune Checkpoint Modulators

Radical Therapy

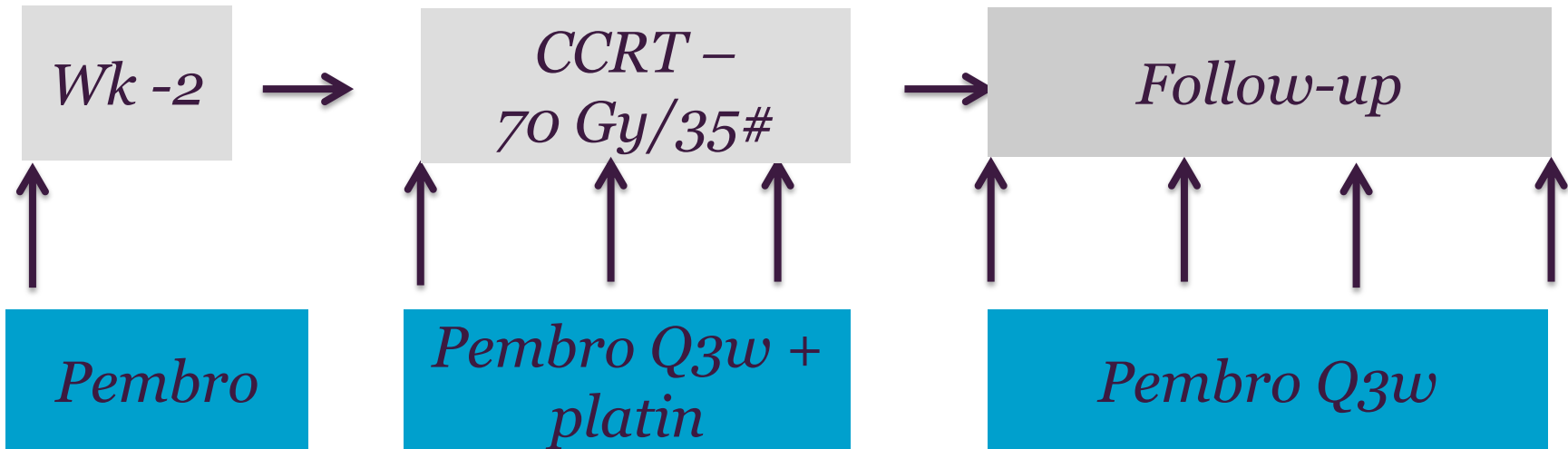
PEACH - Phase I dose-escalation study of Pembrolizumab (MK3475) Anti-PD1 immune checkpoint inhibitor combined with radical Chemoradiotherapy in patients with stage IV squamous cell carcinoma of the Head and neck

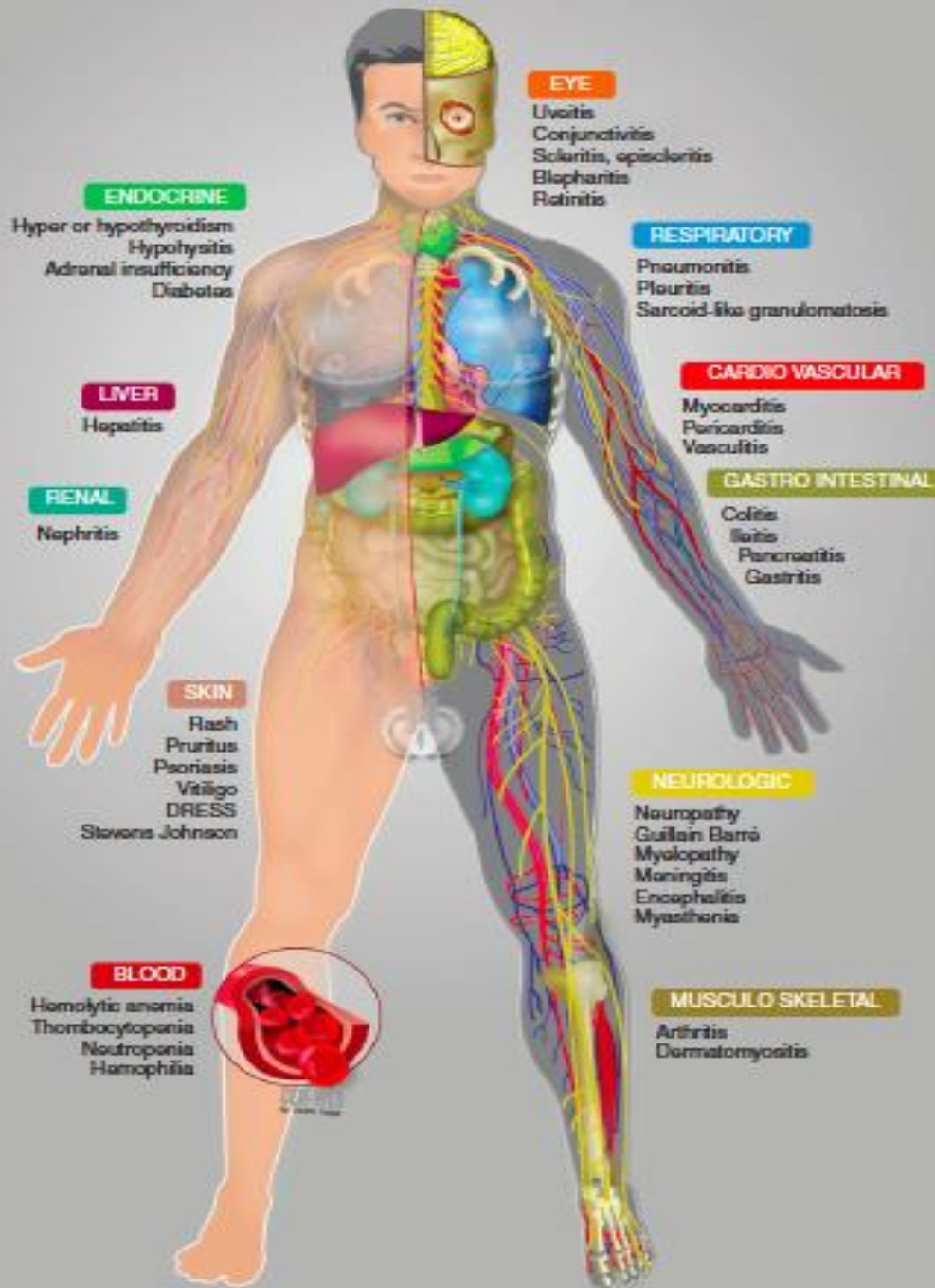


Immune Checkpoint Modulators

PEACH: Trail Schema

Pembrolizumab : 100 mg





Immune Checkpoint Modulators

Toxicity: Common >10%

- Pruritis
- Rash
- Fatigue
- Diarrhoea
- Arthralgia
- Endocrine deficiencies



Immune Checkpoint Modulators

Toxicity: Rare <10% : life-threatening

- Colitis
- Pneumonitis
- Infusion reaction
- Diabetic ketoacidosis
- Severe dermatitis
- Myocarditis
- Neurological toxicity
- Nephritis
- Acute adrenal toxicity



Conclusion

- Concomitant platinum – Std. of care

- Targeted therapies
 - EGFR inhibitors
 - Immune checkpoint modulators

- Targeted therapies
 - Different toxicity profile

