British Association of Head and Neck Oncologists

Treatment options for HPV+ disease

Prof. Hisham Mehanna

Chair of Head and Neck Surgery

Director, Institute of Head & Neck Studies & Education

University of Birmingham

Queen Elizabeth Hospital Birmingham
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Escalating treatment for HPV+ disease

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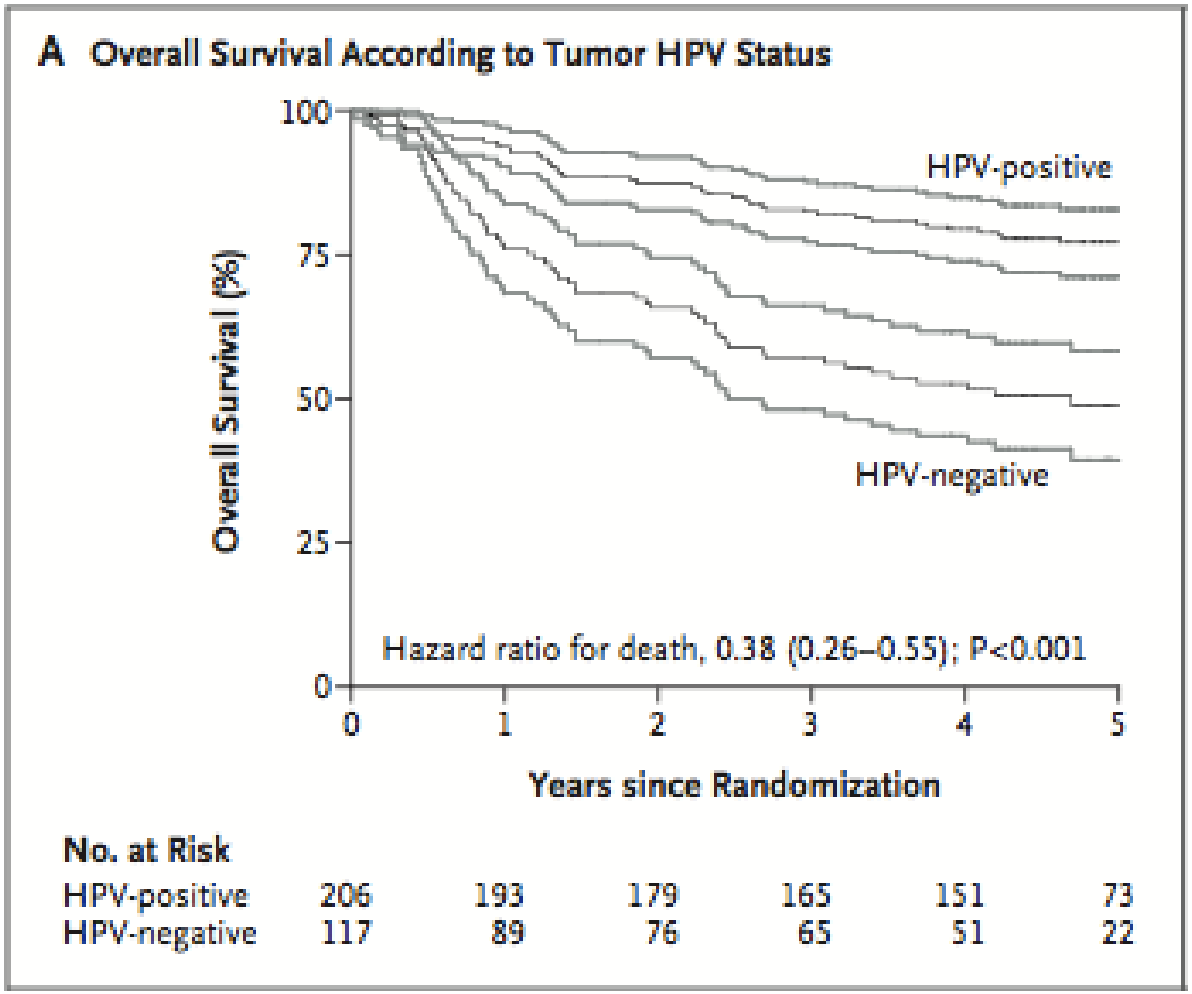
CRT and HPV

HR= 0.38
(0.26-0.55)



3 yr OS: HPV+ = 82.4% (95% CI, 77.2 to 87.6)
HPV- = 57.1% (95% CI, 48.1- 66.1)

Ang et al, NEJM, 2014

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Risk stratification in the new age

3 risk categories:

- Low risk: HPV+ / no or low smokers (50% patients)

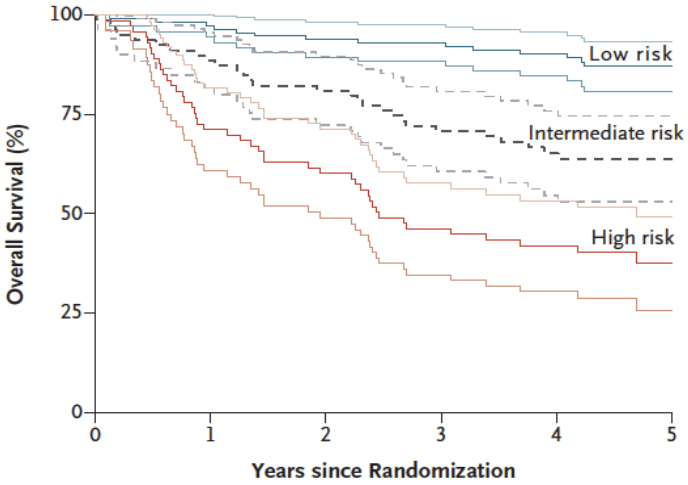
  OS 3 yr 93%

- Intermediate: HPV+ + smokers+N2b-N3 and HPV- + low-no smoker + T2-3

  OS 3yr 70.8%

- High: HPV- /high smokers or low smoker+T4

  OS 3yr 46.3%



No. at Risk						
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

Ang, NEJM, 2010

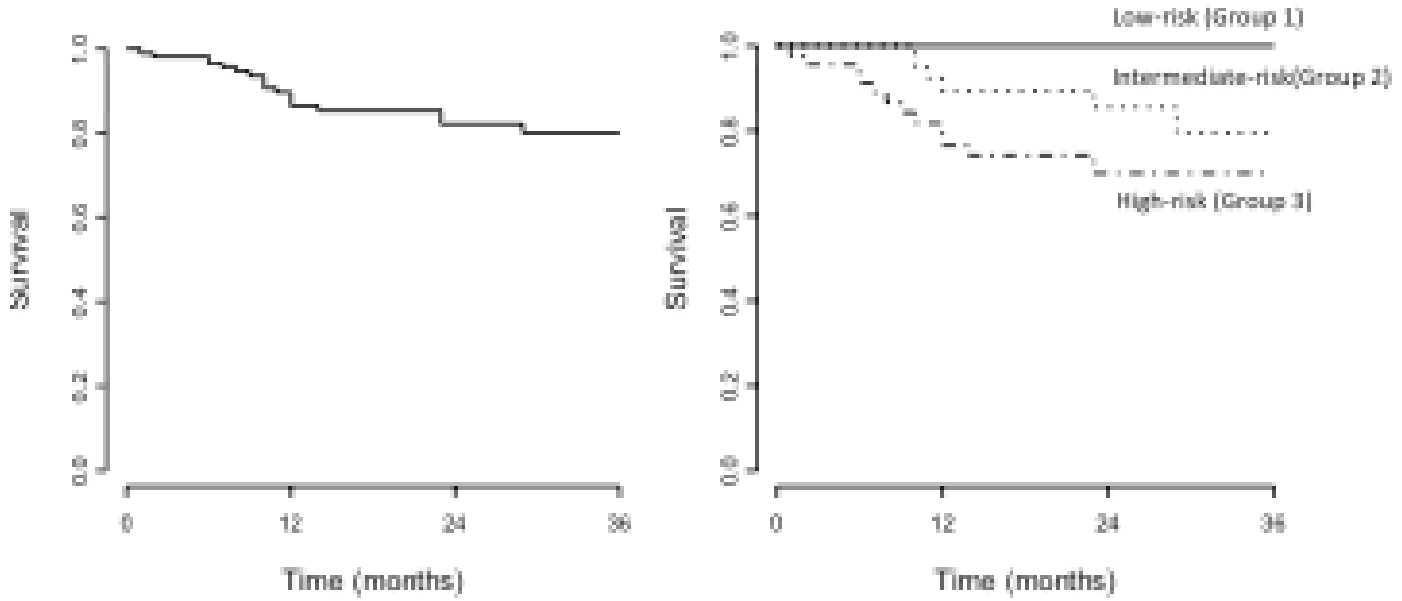
Annals of Oncology Advance Access published November 24, 2011

original article

Annals of Oncology
doi:10.1093/annonc/mdr544

Tumor stage, human papillomavirus and smoking status affect the survival of patients with oropharyngeal cancer: an Italian validation study

R. Granata[1], R. Miceli[2], E. Orlandi[3], F. Perrone[4], B. Cortelazzi[4], M. Franceschini[3], L. D. Locati[1], P. Bossi[1], C. Bergamini[1], A. Mirabile[1], L. Mariani[2], P. Olmi[3], G. Scaramellini[5], P. Potepan[6], P. Quattrone[7], K. K. Ang[8] & L. Licitra[1]*



120 OPC patients

www.inhanse.org

Prognostic Factors and Survival Unique to Surgically Treated p16+ Oropharyngeal Cancer

Bruce H. Haughey, MBChB, FRACS, FACS; Parul Sinha, MBBS, MS

Multivariate Cox Proportional Hazard Ratios for Disease-Free Survival in Models Based on Clinical T Stage.

Variables	HR (95% CI)	*P* Value
cT stage (T3-4 vs. T1-2)	3.03 (1.10-8.34)	.032
Smoker (ever vs. never)	4.19 (1.22-14.42)	.023
No. of nodes (0-1 vs. ≥2)	6.36 (1.72-23.47)	.005
No. of nodes (1-2 vs. ≥3)	7.06 (1.97-25.27)	.003*
pN stage (N2a+ vs. N0-2a)	3.8 (1.1-13.30)	.032
Adjuvant Rx (any vs. none)	0.21 (0.06-0.71)	.012†
cT stage (T4 tonsil vs. T1-3 tonsil)	4.93 (1.46-16.65)	.010
cT stage (T4 tonsil vs. T1-3 tongue base)	8.26 (2.27-29.99)	.001

*Significance observed in models that excluded patients with no involved neck nodes (n = 153).

†Lost its significance in models with T stage.

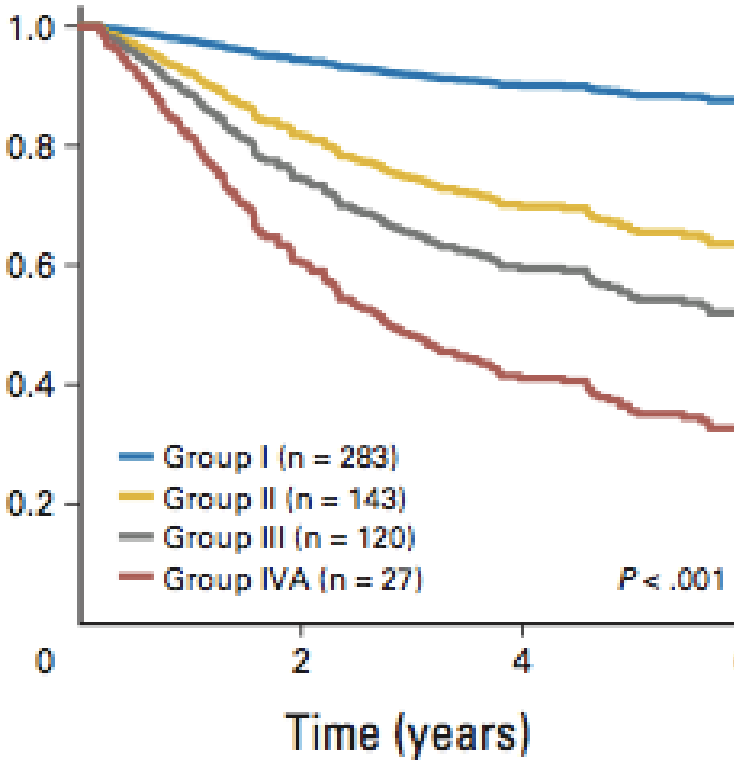
HR = hazard ratio; CI = confidence interval; cT = clinical T stage; pN = pathological N stage, Rx = Therapy.

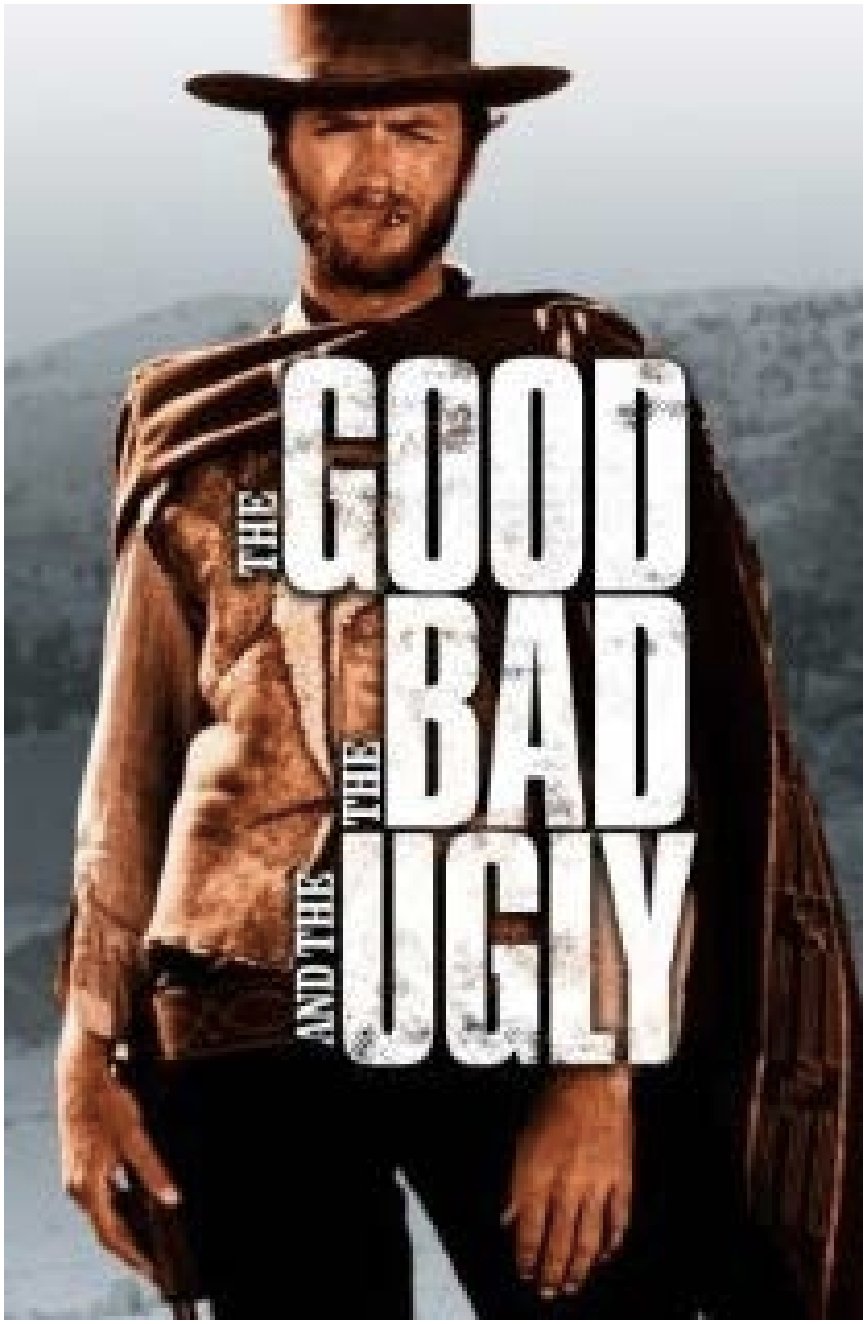
Other risk stratification – HPV+ only

5yr OS

- Group I: T1-3 N0-N2c smoker<20py : 89%
- Group II: T1-3 N0-N2c smoker>20py : 64%
- Group III: T4 or N3, <70yrs old : 57%
- Group IV: T4 or N3, >70yrs old : 40%

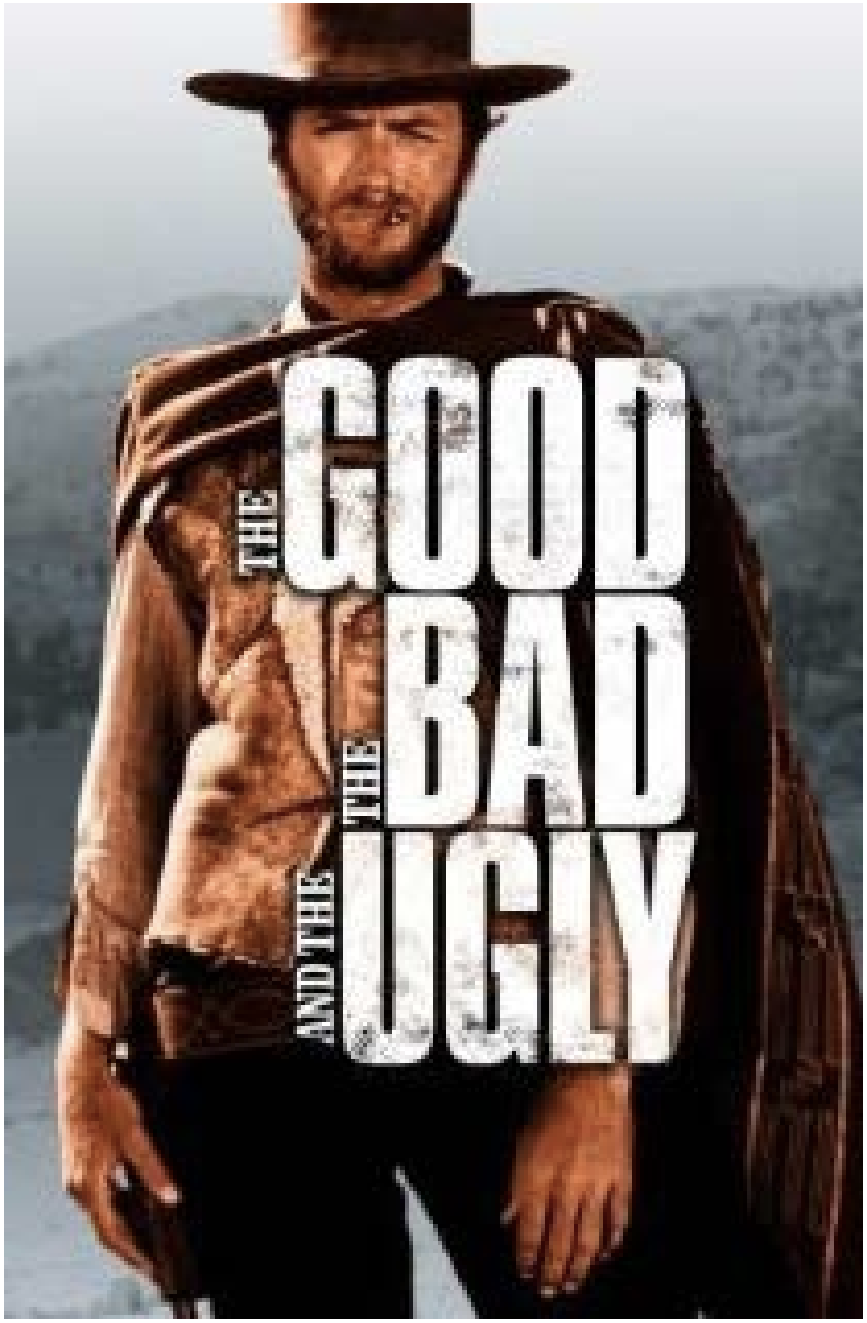
Huang, JCO, 2015





	3yr OS
Low	93%
Intermediate	70.8%
High	46.3%

Low



3yr OS

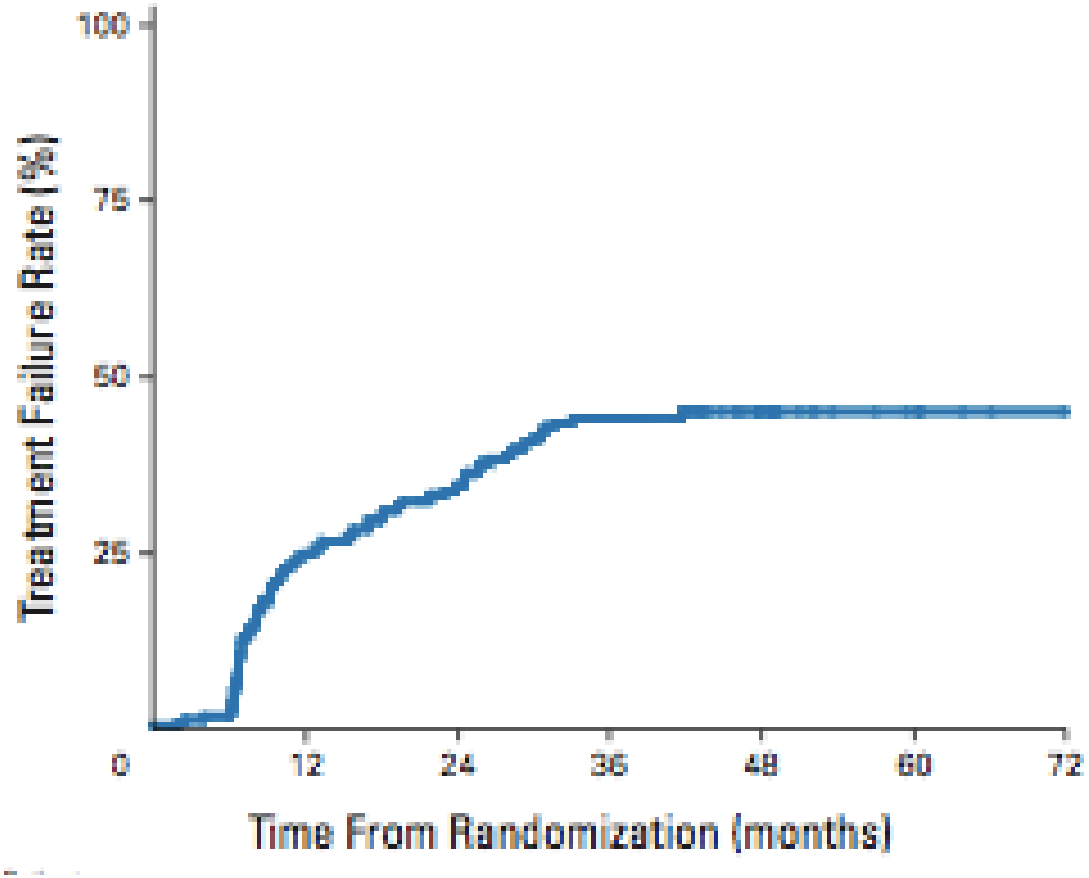
93%

Bad news


FIRST THE GOOD NEWS... TECHNICALLY THE OPERATION WAS A COMPLETE SUCCESS.....

CRT - toxicity

Higher survival rates in younger patients = living longer with morbidity



Machtay, JCO, 2008

Are we over-treating?

Are there any alternative treatment regimens with similar survival but less toxicity?

De-intensification options

- Less toxic chemotherapy agent

  De-Escalate / RTOG 1016
- Less radiotherapy

  ECOG 1308
- Do surgery and reduce RT

  ECOG 3311 / Pathos
- Remove chemotherapy agent – RT alone

  NRG HN002

De-ESCALaTE HPV

Determination of EGFR-inhibitor versus Standard CRT early And Late Toxicity Events in HPV – positive Oropharyngeal SCC

De-ESCALaTE HPV

CI: Hisham Mehanna

www.inhanse.org

Screen 910 biopsies from T3-T4NO, T1-4,N1-2 oropharynx SCC

HPV+ on PCR AND

p16+ on immunohistochemistry

(Central MHRA-approved Laboratory)

Randomise 304 patients 1:1

Stratified by Centre, Tumour site, T & N stage, Smoking status

Control

Concomitant Cisplatin

+ Radiotherapy (70 Gy in 35 F)

Study

Concomitant Cetuximab

+ Radiotherapy (70 Gy in 35 F)

10% Lost to follow up (n=17)

10% Lost to follow-up (n=17)

Analysed (n= 148)

Analysed (n= 148)

***Follow-up**:* 2 years

***Primary outcomes*:**

Severe Toxicity (Acute and Late) : using CTCAE grading, including *skin rashes*, mucositis

Secondary outcomes:

Health economics using EQ-5D, Early toxicity, Quality of life: using EORTC general and head neck specific modules, Swallowing: using MDADI questionnaire and gastrostomy - dependency rates, Mortality (cause of death), disease free survival, recurrence, metastases.

www.inhanse.org

RTOG 1016: A Randomized Phase III Trial of Chemoradiotherapy With Cisplatinum or Cetuximab in p16 Positive Oropharynx Cancer

Stratify: HPV, Smoking, Stage

ELIGIBILITY

Stage

III, IVA, B

Resectable

P16+

Oropharynx

Cancer

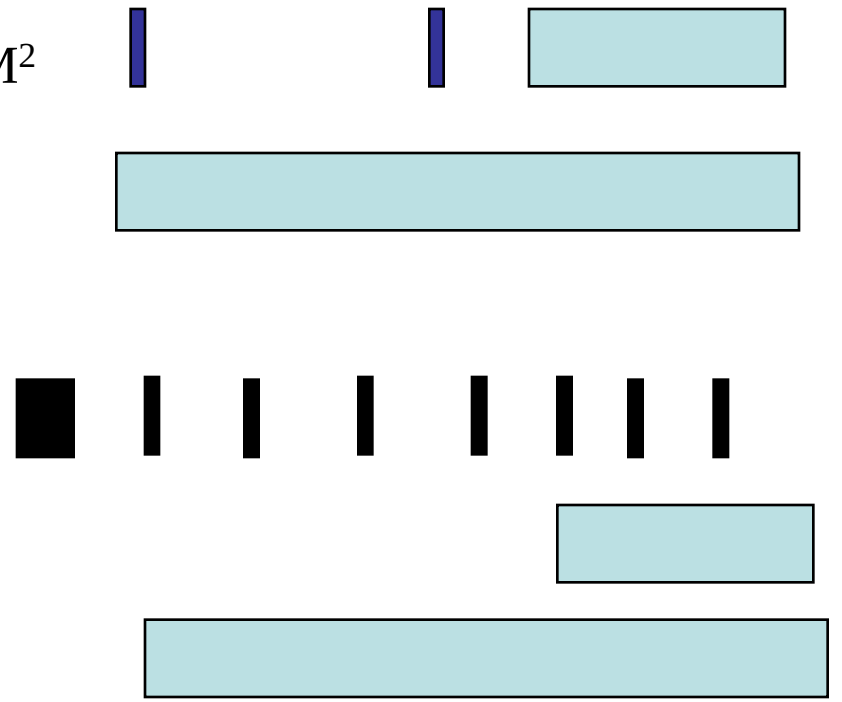
RANDOMIZE

P - 100 mg/M^2

XRT

C225 400/250 mg

XRT



70 Gy in 35 Fxs

LOW and INT RISK OPC

CI: Trotti, Gillison

www.inhanse.org

Low

3yr OS

ONLY 20% OPSCC patients in most countries Outside North America

Vast majority of patients in most countries
Outside North America

Aim of management: better survival
→ Need to escalate treatment

Interm… 60%

…gh 46.3% 20%

Failure mainly locoregional

- Data from RTOG 0129.
- Differences in survival between the low, intermediate and high-risk groups:
  - mainly due to differences in 3 years LRC
  - Low risk: 90.4%,
  - Intermediate risk: 80.9%
  - High risk: 57.3%

Options for improving locoregional control

- Add induction chemotherapy
- Add more RT – intensification of RT?
- Add surgery
- Other regimens?

Options for improving locoregional control

- **Add induction chemotherapy**
- Add more RT – intensification of RT?
- Add surgery
- Other regimens?

Induction chemotherapy before concomitant CRT

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

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., Svetislav Jelic, M.D., Jan Betka, M.D., Joachim H. Preiss, M.D., Ph.D., Danielle van den Weyngaert, M.D., Ahmad Awada, M.D., Ph.D., Didier Cupissol, M.D., Heinz R. Kienzer, M.D., Augustin Rey, M.D., Isabelle Desaunois, M.Sc., Jacques Bernier, M.D., Ph.D., and Jean-Louis Lefebvre, M.D., for the EORTC 24971/TAX 323 Study Group*

N ENGL J MED 357;17 WWW.NEJM.ORG OCTOBER 25, 2007

DeCIDE

- 280 pt, LAHNC, N2/N3 patients
- All sites
- Unconventional regimen:
  CRT (D, F, hydroxyurea) + split hyperfractionated RT
  vs TPF+CRT
- Same outcomes
- ? No HPV analysis

PARADIGM

- 145 pts – slow to recruit so stopped
- All tumour sites- 50% OPC
- TPF followed by carbo+RT or docetaxel+RT vs CRT
- Same outcomes: 3 YR OS 73% vs 78%
  - Outcomes were much better than expected – suggests that there is a large proportion of HPV+ patients
- No HPV analysis or adjustment

Conclusion

The question of whether the addition of induction chemotherapy to concurrent chemoradiotherapy improved survival over concurrent chemoradiotherapy alone remains unfortunately unanswered and it might not be answered soon. Both treatment modalities are effective in the treatment of head and neck cancer. A cost-benefit and quality-of-life analysis might prove beneficial in addressing the true value of induction chemotherapy while integrating stratification on HPV status in this disease.

Haddad et al, Lancet Oncol, 2013

Ghi et al ASCO, 2014

- TPF followed by:
  - CRT
  - Cetuximab + RT
- 421 LAHNSCC pts, stage III/IV

	3yr PFS	3yr OS	HR
CRT	36.7%	45.7%	
Induction+CRT	46.8%	57.6%	0.72 (p=0.025)

Add induction?

- No definitive data on whether TPF+ standard CRT is effective in intermediate and high risk disease

Options for improving locoregional control

- Add induction chemotherapy
- **Add more RT – intensification of RT**
- Add surgery
- Other regimens?

Increase RT dose

- OPC

- 62.5 Gy in 25 daily fractions over 5 weeks + Cetuximab
- Only 1 patients missed last fraction of RT
- 85% completed all 6 doses of cetuximab
- 4 year follow-up
- 3 yr OS =75.5%
- 3 yr DSS= 85.2%

Thomson IJROBP 2014 S

Increase RT dose

- OPC

- Toxicity
  - 4% needed PEG after 1 year
  - LATE TOXICITY
    - Grade 3 pain 8%
    - Anorexia 8%
    - Weight loss 4%
    - Dental problems 8%

Thomson IJROBP 2014 S

Increase RT dose

- OPC- Archimedes
  - phase I dose-escalation pilot
  - RT regimen: 64Gy in 25F
  - 15 patients
  - Intermediate and high risk OPC
  - Outcomes : toxicity

Sanghera et al, 2015

Increase RT dose

Results

- All patients completed minimum 3 months follow up required for the primary end point.
- All 15 patients completed the full intended dose of radiotherapy
  - median overall treatment time of 32 days (31-35).
- Grade 3 mucositis was absent in all patients at three months.

Increase RT dose

Feeding at 3 months

- 1/15 patients required supplementary tube feeding at 3 months (metastatic disease)
- 14/15 tube independent (includes any use)
- 9/15 Normal diet

Increase RT dose

May be an option for treatment escalation in intermediate and high risk OPSCC

Options for improving locoregional control

- Add induction chemotherapy
- Add more RT – intensification of RT?
- **Add surgery**
- Other regimens?

Open Surgery +/- RT

Surgery +/-RT

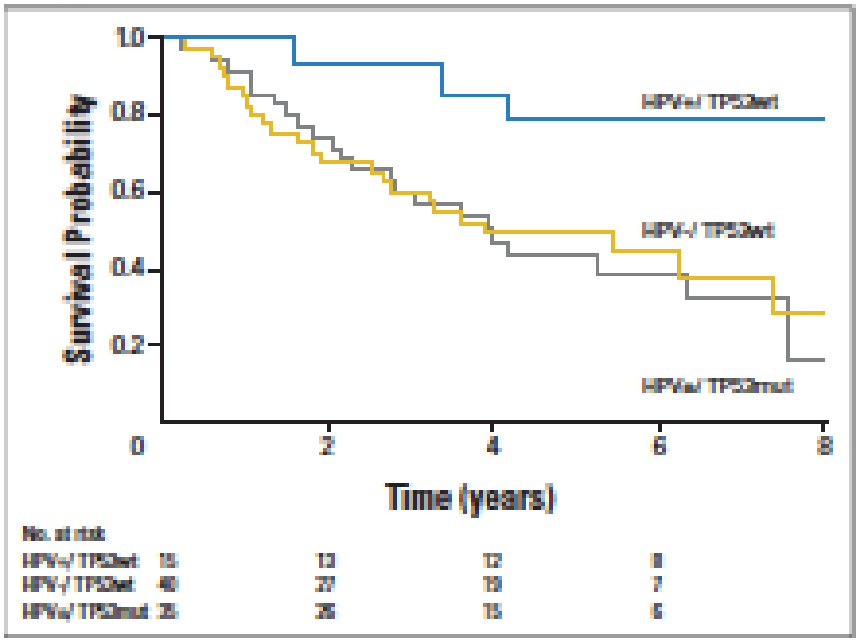
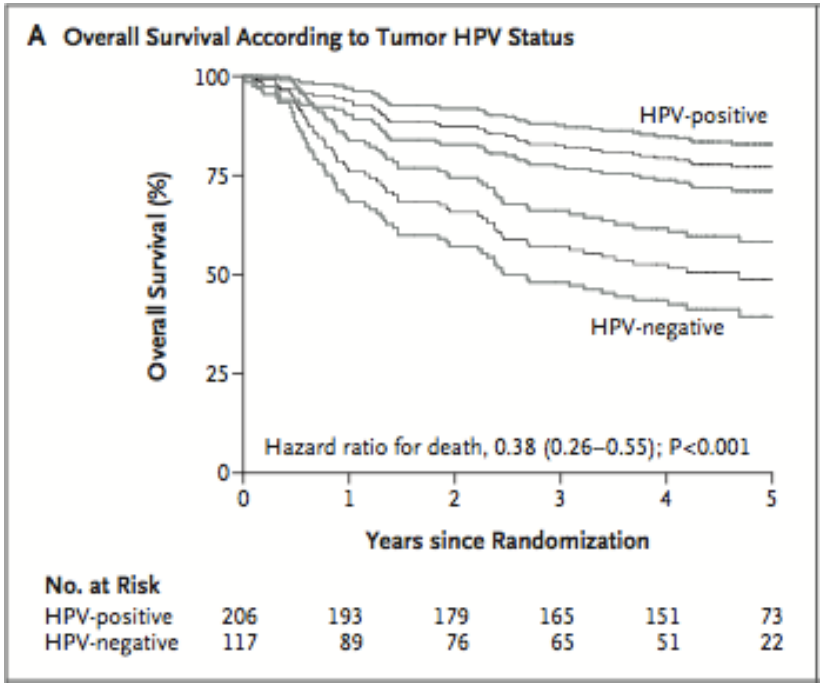


Fig 1. Overall survival according to human papillomavirus (HPV)/TP53 status. mut, mutated; wt, wild type.

HPV+ 2yr OS 92%
HPV- 2 yr OS 75%

Licitra et al,JCO,2006

CRT



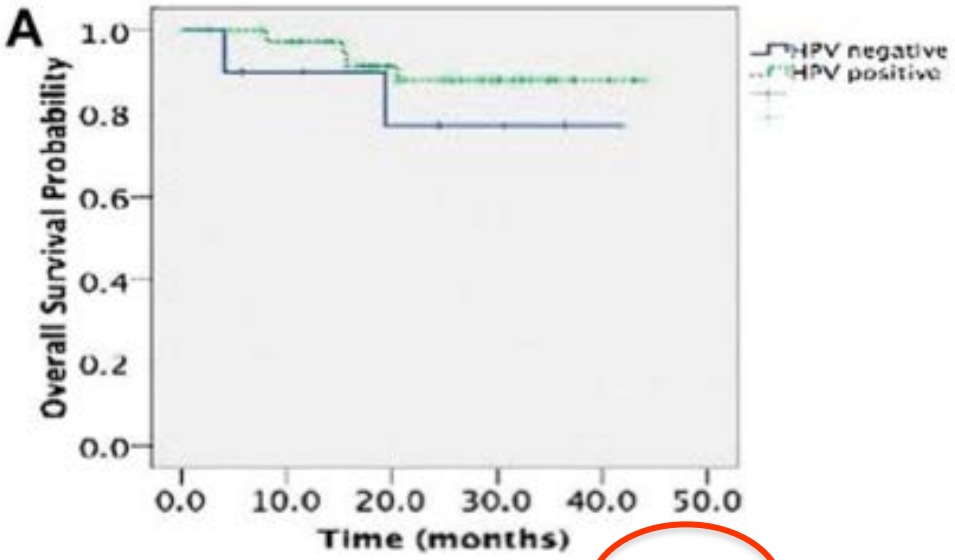
HPV+ 2yr OS 93%
HPV- 2yr OS 62%

Ang, NEJM,2010

TRANSORAL ROBOTIC SURGERY AND HUMAN PAPILLOMAVIRUS STATUS: ONCOLOGIC RESULTS

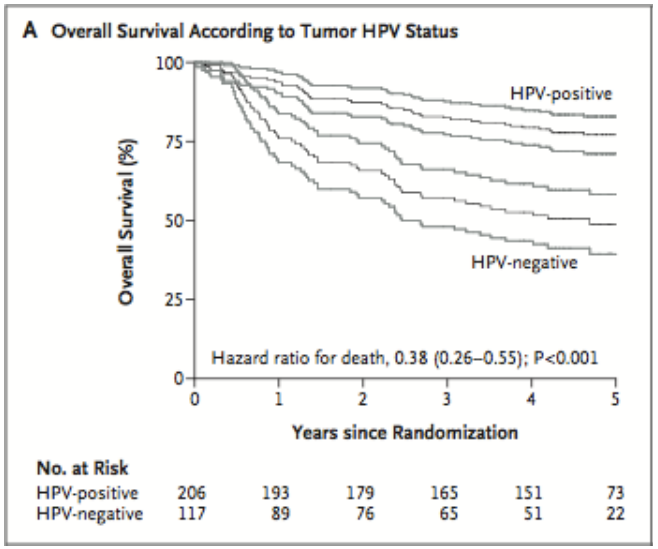
Marc A. Cohen, MD,[1] Gregory S. Weinstein, MD,[1] Bert W. O'Malley, Jr, MD,[1]
Michael Feldman, MD,[2] Harry Quon, MD[1,3]

TORS+/-CRT



HPV-ve 2yr OS 75%

CRT



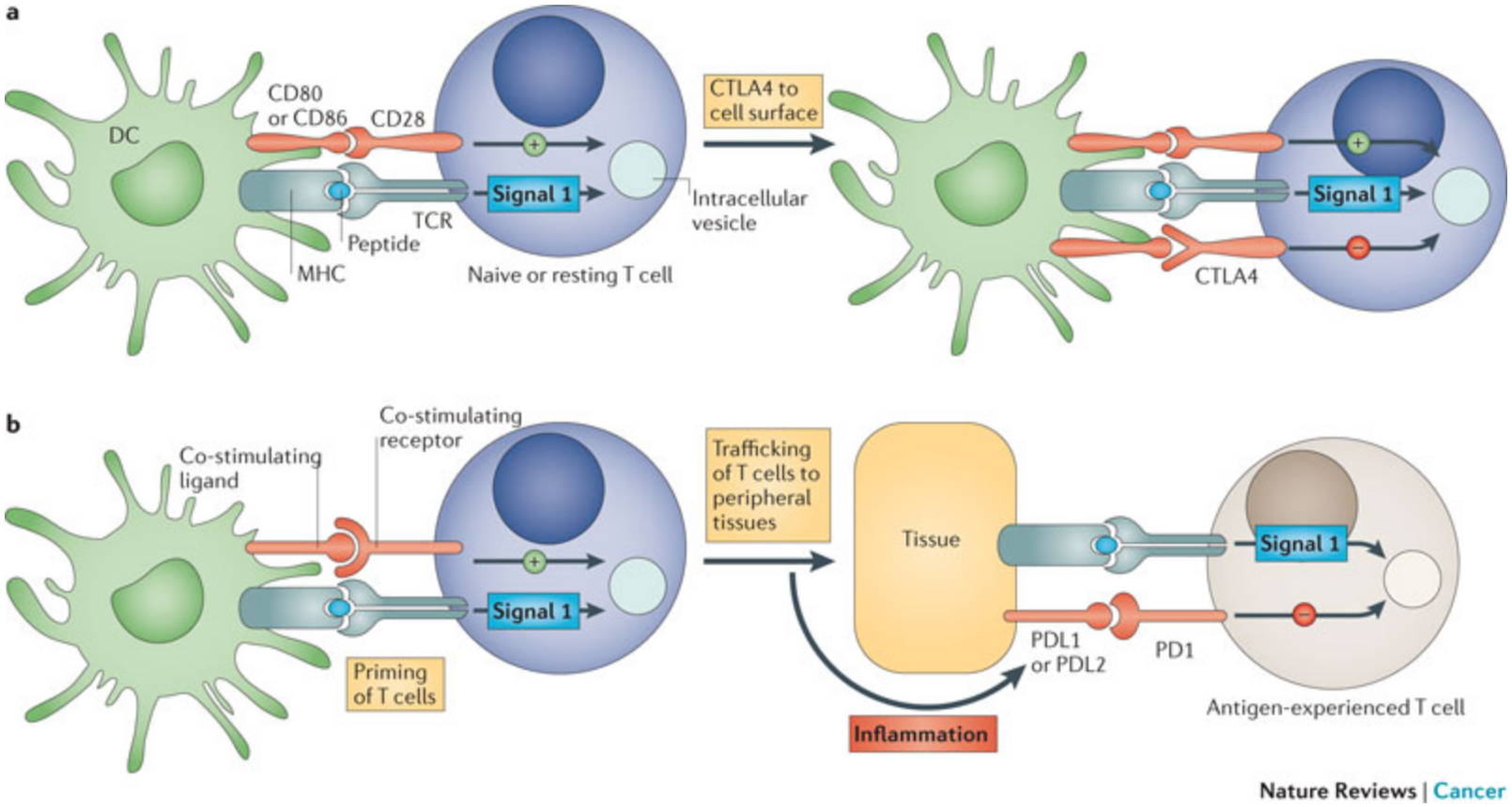
2yr OS 62%

Add surgery

- Surgery added to current standard CRT (not post-op dose)

Other treatments?

- Immunotherapy revolution!



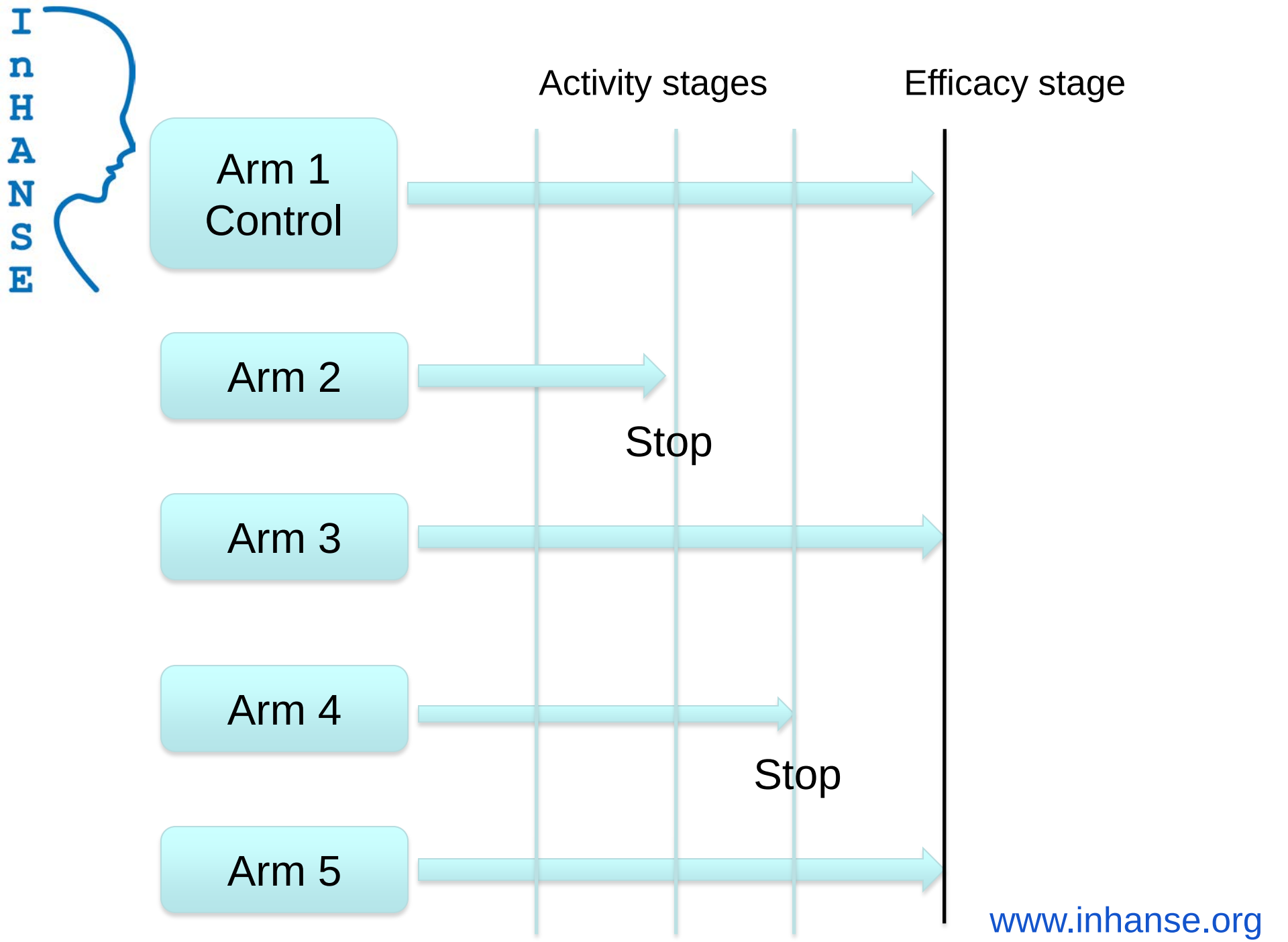
HPV+ high risk?

Phase III randomised controlled trial
Comparing **A**lternative **R**egimens for
Escalating treatment of intermediate and high-risk oropharyngeal cancer

CompARE

CI: Prof Hisham Mehanna

www.inhanse.org


Activity stages
Efficacy stage
Arm 1
Control
Arm 2
Stop
Arm 3
Arm 4
Stop
Arm 5

CompARE

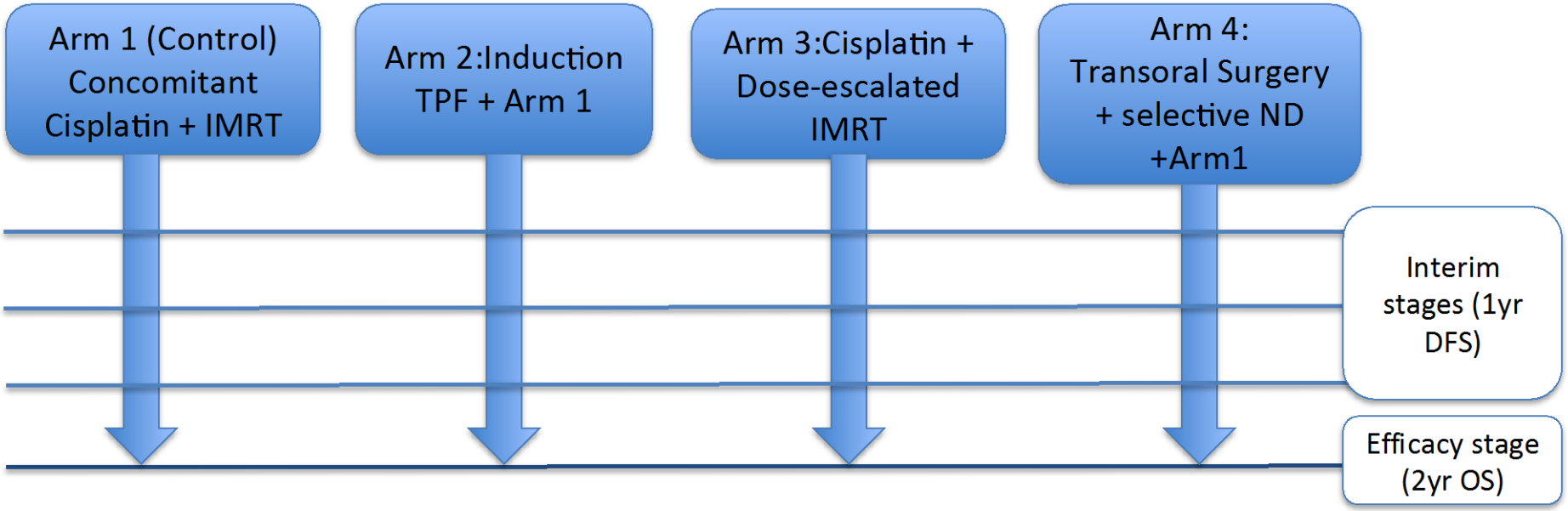
Population

Intermediate or high risk OPC, >18yrs, ECOG PS 0-1, Fit for surgery and chemotherapy.

RANDOMISE to ARMS 1-4 or ARMS 1-3 only

Stratify Intermediate vs High risk & Centre.

Adjust for Site (Tonsil vs Base of Tongue) and size (T1-3 vs T4) of tumour and nodes (N0-2A vs N2B-3)



Primary Outcome

Overall survival (2 years)

Secondary Outcomes

Disease free survival, Acute and Late severe toxicity using CTCAE,
QoL using EORTC QLQ-C30 & HN35, & MDADI (for Swallowing),
Cost-effectiveness using EQ-5D, Surgical complications, Molecular markers

Conclusions

- Low risk HPV+OPSCC different disease entity with very good prognosis
  - Need to study alternative treatments with less toxicity

- Intermediate and high risk HPV+ OPSCC → poor prognosis
  - Vast majority of patients outside N America
  - Need better treatments → treatment escalation

Do not change management of OPSCC patients without evidence

Enroll your patients into appropriate clinical trials

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Clinical trials and effectiveness

Experimental and translational medicine

Quality of life