Management of HPV-associated oropharyngeal cancer

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Disclosure Slide

I have no conflict of interest to disclose

Learning Objectives

After reading and reviewing this material, the participant should be able to:

- Understand the epidemiology and prognostic classification of HPV-associated oropharyngeal cancers (OPC)
- Present the standard of care treatment and ongoing clinical trials for HPV^+ OPC
- Summarize data on HPV-targeted therapies
- Present novel approaches for HPV^+ OPC

Outline

- Epidemiology
- Prognostic classification
- Current standard of care
- Clinical trials of treatment deintensification
- HPV-targeted therapies
- Novel agents

Epidemic of HPV-associated OPC*

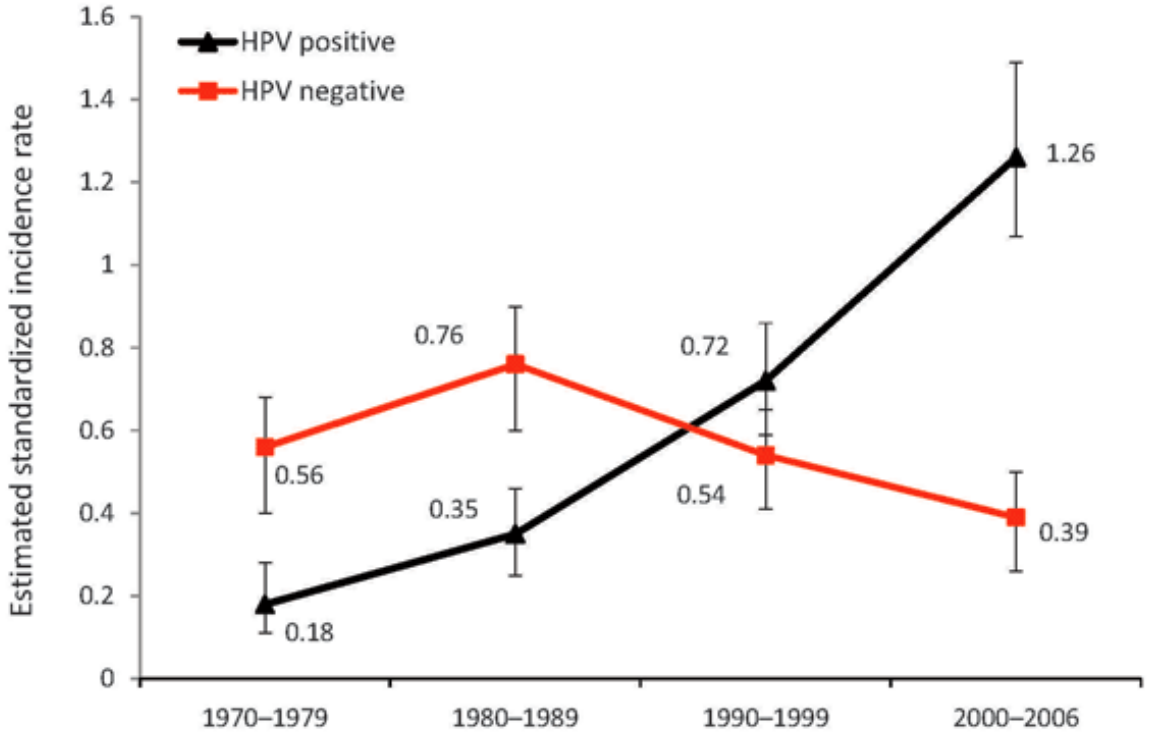
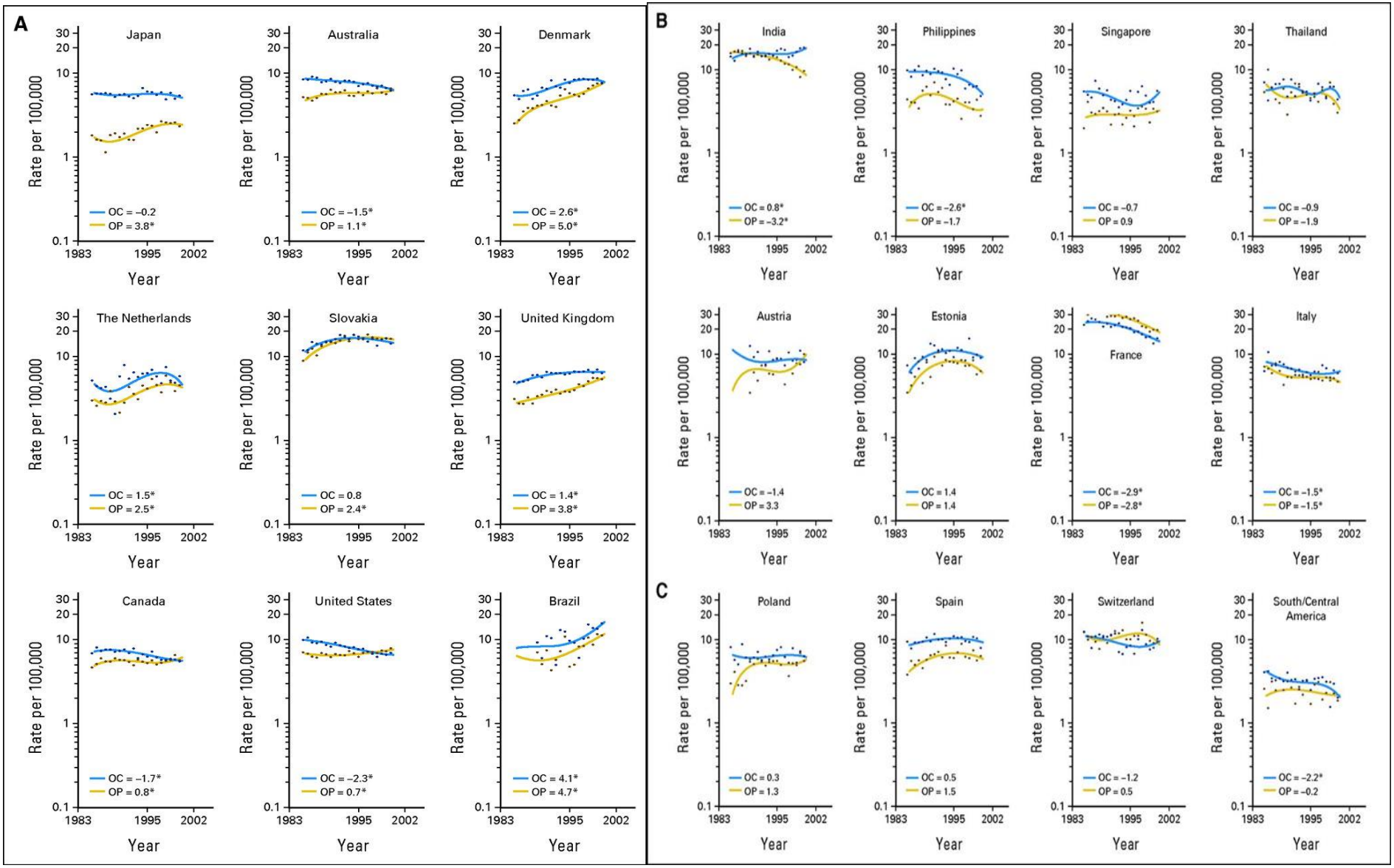
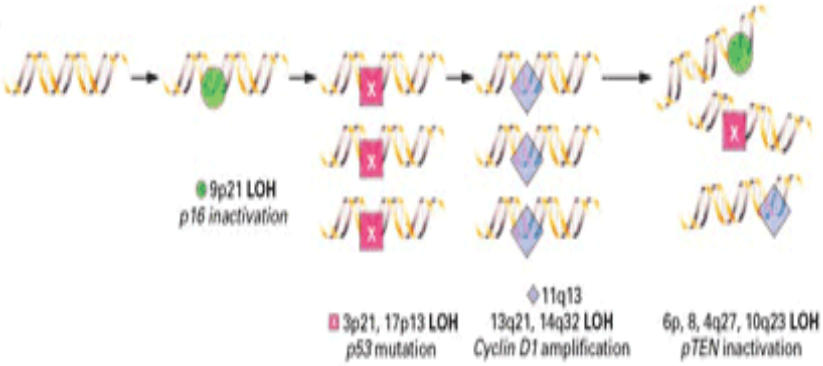


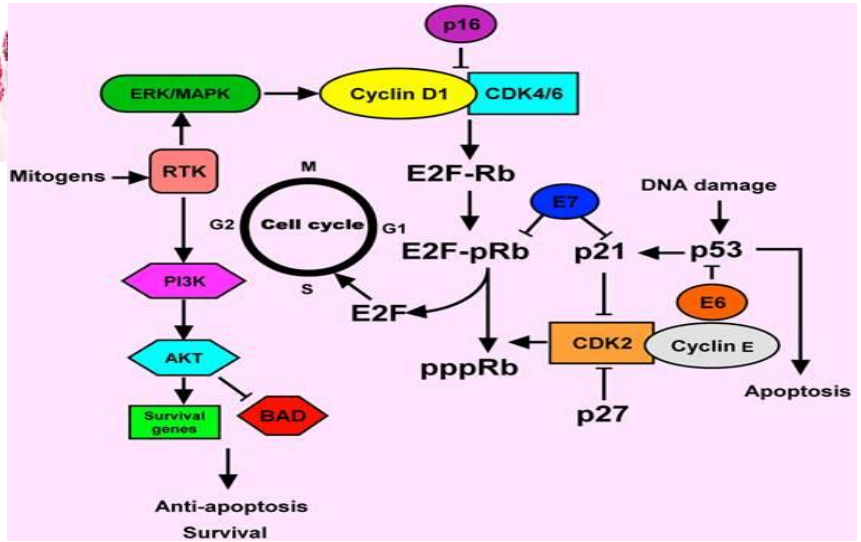
Figure 3. Estimated age-standardized incidence of human papillomavirus (HPV)–positive and HPV-negative tonsillar cancer squamous cell carcinoma cases per 100,000 person-years, Stockholm, Sweden, 1970–2006. Error bars indicate 95% confidence intervals. Data from Näsman et al. (*13*), with permission of John Wiley and Sons (www.interscience.wiley.com).

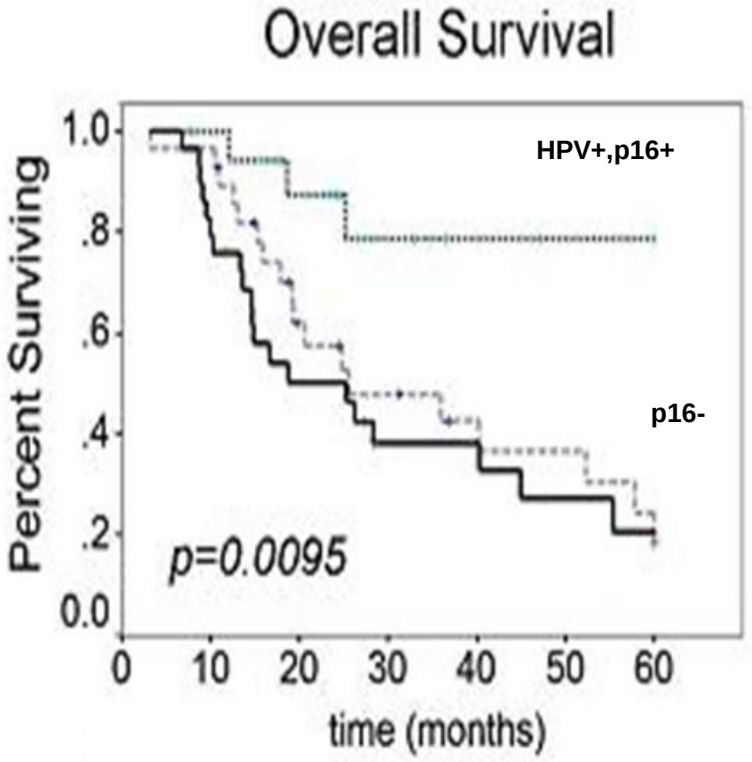


Anil K. Chaturvedi et al. JCO 2013;31:4550-4559

Oropharyngeal Cancer Disease Variants: Tobacco-related, HPV-related and mixed







Weinberger PM, Psyrri JCO 2006

HNSCC: two disease entities

	HPV positive	HPV negative
Tumor site	Tonsil/BOT	All sites
Histology	Basaloid	keratinized
Age	Younger	Older
SE status	High	Low
Risk Factors	Sexual	ETOH/tobacco
Survival	Improved	Dismal
Incidence	increasing	decreasing

OS by HPV status in prospective clinical trials

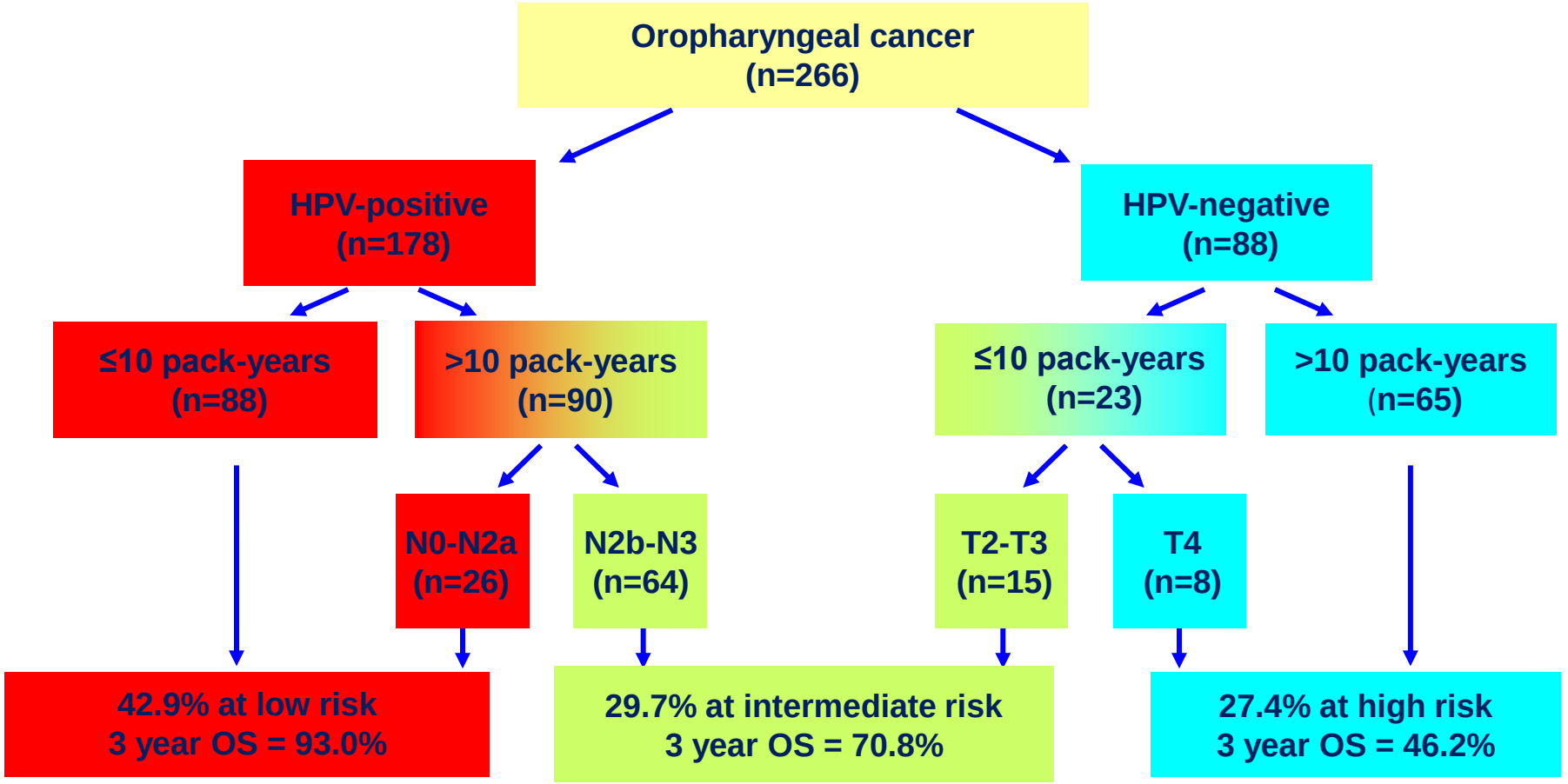
Regimen	Time	HPV + vs HPV -	P value
Induction + CRT (ECOG)	2 year	95% vs 62%	0.005
CRT (TROG2.2)	2 year	94% vs 77%	0.007
CRT (RTOG0129)	3 year	79%vs 46%	0.002
Induction+CRT (TAX324)	5 year	93% vs 35%	<0.001
Radiation (DAHANCA)	5 year	62% vs 26%	0.003

OS: overall survival

HPV and Survival

- The relative survival for HPV positive patient is independent of therapy as long as this therapy is within the current standard of care
- Risk of death is consistently less than 60% that of HPV negative cancers
- The absolute survival difference is consistently higher than 30% across studies

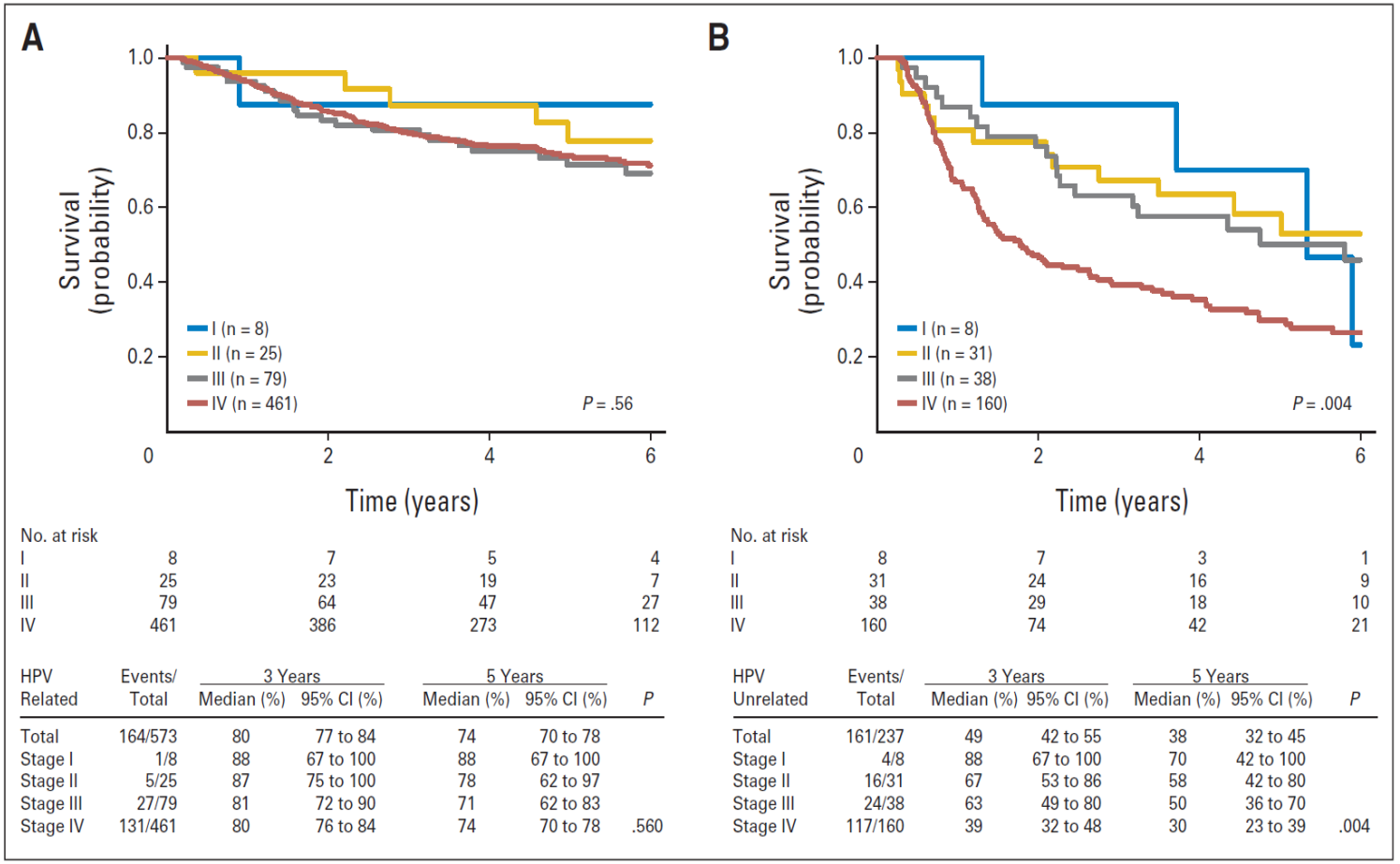
Oropharynx: Classification of patients into risk-of-death categories



Recursive-partitioning analysis identified prognostic factors with the most predictive significance

Ang KK, et al. NEJM 2010;363:24–35

OS by UICC/AJCC TNM Stage (7th edition)



No. at risk				
I	8	7	5	4
II	25	23	19	7
III	79	64	47	27
IV	461	386	273	112

No. at risk				
I	8	7	3	1
II	31	24	16	9
III	38	29	18	10
IV	160	74	42	21

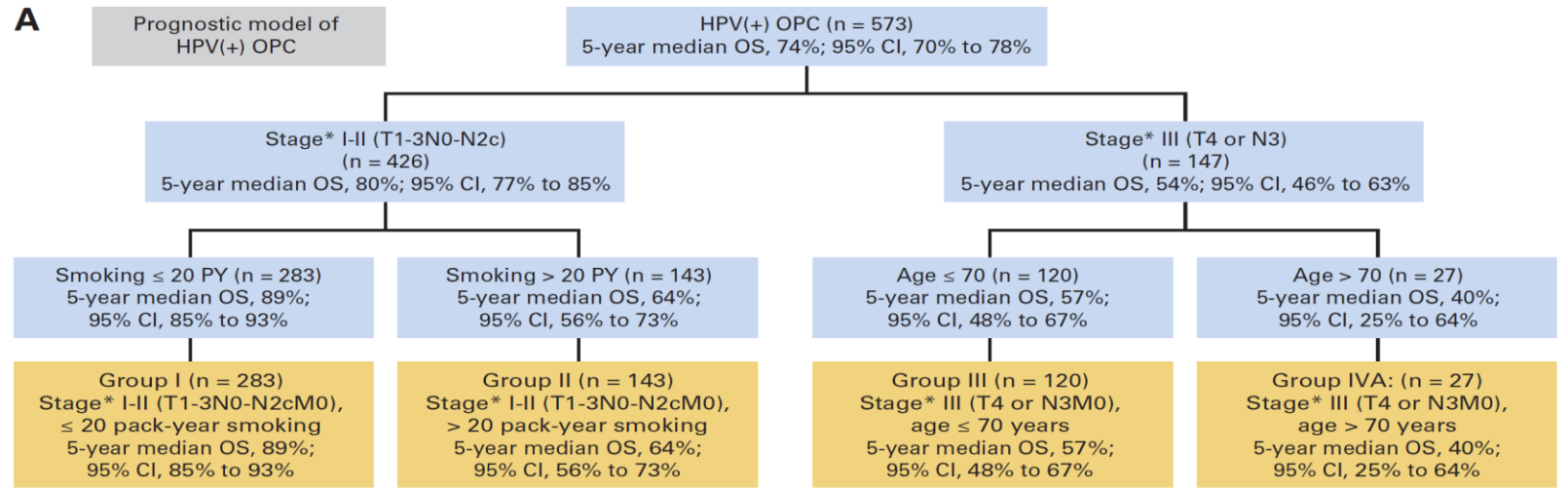
HPV Related	Events/ Total	3 Years Median (%)	3 Years 95% CI (%)	5 Years Median (%)	5 Years 95% CI (%)	P
Total	164/573	80	77 to 84	74	70 to 78	
Stage I	1/8	88	67 to 100	88	67 to 100	
Stage II	5/25	87	75 to 100	78	62 to 97	
Stage III	27/79	81	72 to 90	71	62 to 83	
Stage IV	131/461	80	76 to 84	74	70 to 78	.560

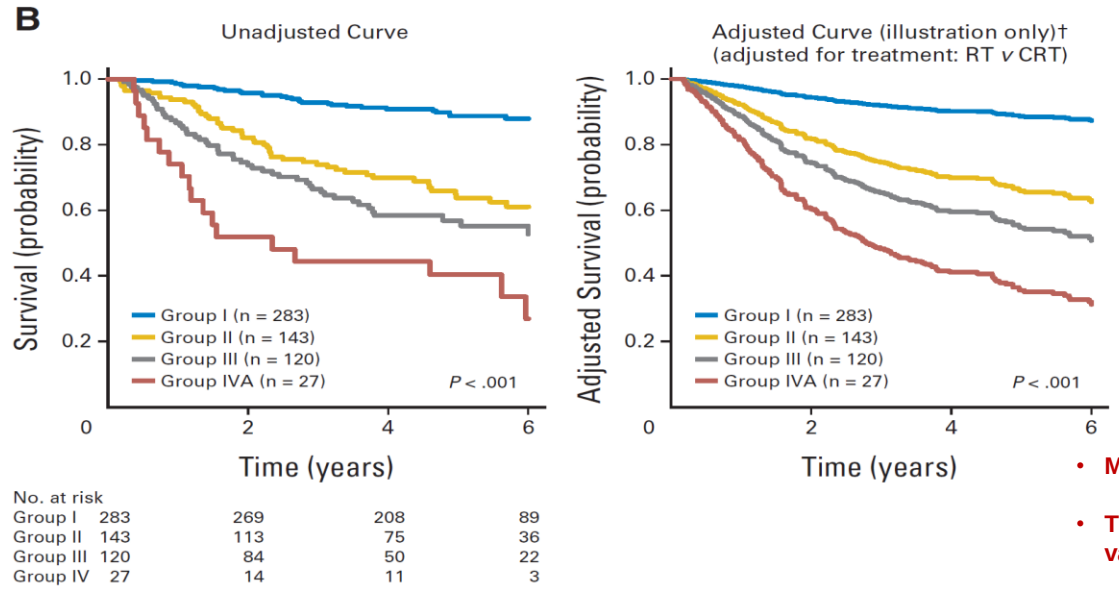
HPV Unrelated	Events/ Total	3 Years Median (%)	3 Years 95% CI (%)	5 Years Median (%)	5 Years 95% CI (%)	P
Total	161/237	49	42 to 55	38	32 to 45	
Stage I	4/8	88	67 to 100	70	42 to 100	
Stage II	16/31	67	53 to 86	58	42 to 80	
Stage III	24/38	63	49 to 80	50	36 to 70	
Stage IV	117/160	39	32 to 48	30	23 to 39	.004

Fig 1. Overall survival by current American Joint Committee on Cancer/Union for International Cancer Control TNM stage in (A) human papillomavirus (HPV) –related and (B) HPV-unrelated oropharyngeal carcinomas.

Huang, O'Sullivan et al. JCO, 2015

Prognostic Grouping Model of HPV(+) OPC





C

Prognostic group	T	N	M	Age	Smoking PY
I	T1-3	N0-N2c	M0	Any	≤ 20
II	T1-3	N0-N2c	M0	Any	> 20
III	T4, Any N	Any T, N3	M0	≤ 70	Any
IVA	T4, Any N	Any T, N3	M0	> 70	Any
IVB	Any T	Any N	M1	Any	Any

- **M1 disease considered Group IVB**
- **Too few cases to analyse; policies too varied**

Huang, O'Sullivan et al. JCO, 2015

Clinical Utility

- NCCN guidelines: “HPV testing recommended for all oropharynx tumors”

- U.S Cooperative Groups and European Organization for Research and Treatment of Cancer: “HPV-positive oropharynx cancer is a distinct disease entity”

Treatment of HPV-associated HNSCC

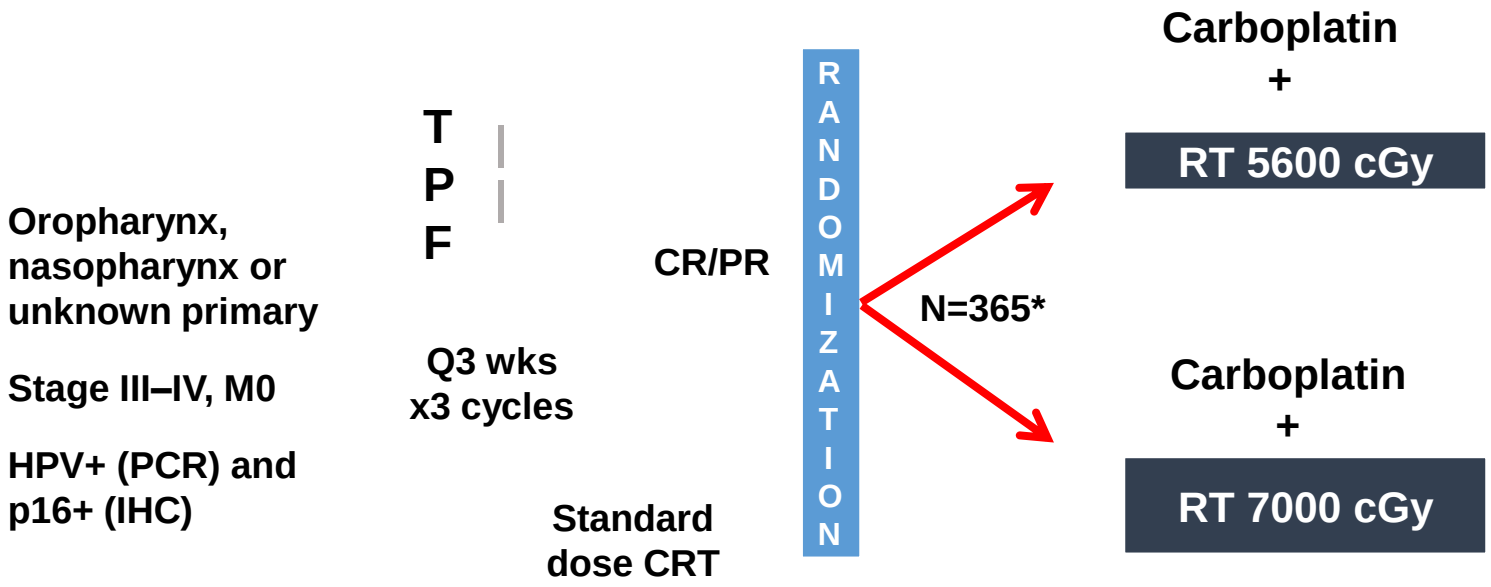
- Guidelines do not currently recommend using HPV status to direct treatment
- However, strategies to treat HPV+ LA-SCCHN have been proposed that take advantage of its tendency to respond to treatment, and are being investigated

Rationale for treatment de-intensification

- The better outcome of HPV+ HNSCC raises the question as to whether we can reduce the intensity of treatment in this patient population
- These patients are young and should not suffer the consequences of unnecessary overtreatment
- Deintensification strategies for LA HNSCC include radiation alone, reducing the dose of radiotherapy, substituting chemotherapy with cetuximab

QUARTERBACK: TPF → CT + reduced or standard dose RT in HPV+ SCCHN (OPC, unknown or NP)

Lead investigator: M Posner
Mount Sinai School of Medicine



Primary endpoint:
LRC (3 yr)

Secondary endpoints:
OS (5 yr), toxicity (5 yr), QoL

Status: recruiting

*Estimated number TPF, docetaxel + cisplatin + 5-FU

www.clinicaltrials.gov/ct2/show/NCT01706939

ADEPT

- A phase 3 trial that seeks to deintensify adjuvant therapy following surgery in patients with p16+ oropharyngeal tumors with extracapsular spread in their lymph nodes
- Following surgery, patients are randomized to either IMRT alone or weekly cisplatin/IMRT. Primary endpoints are DFS and LRC. Secondary endpoints are rates of distant failure, DSS, toxicity, and QoL

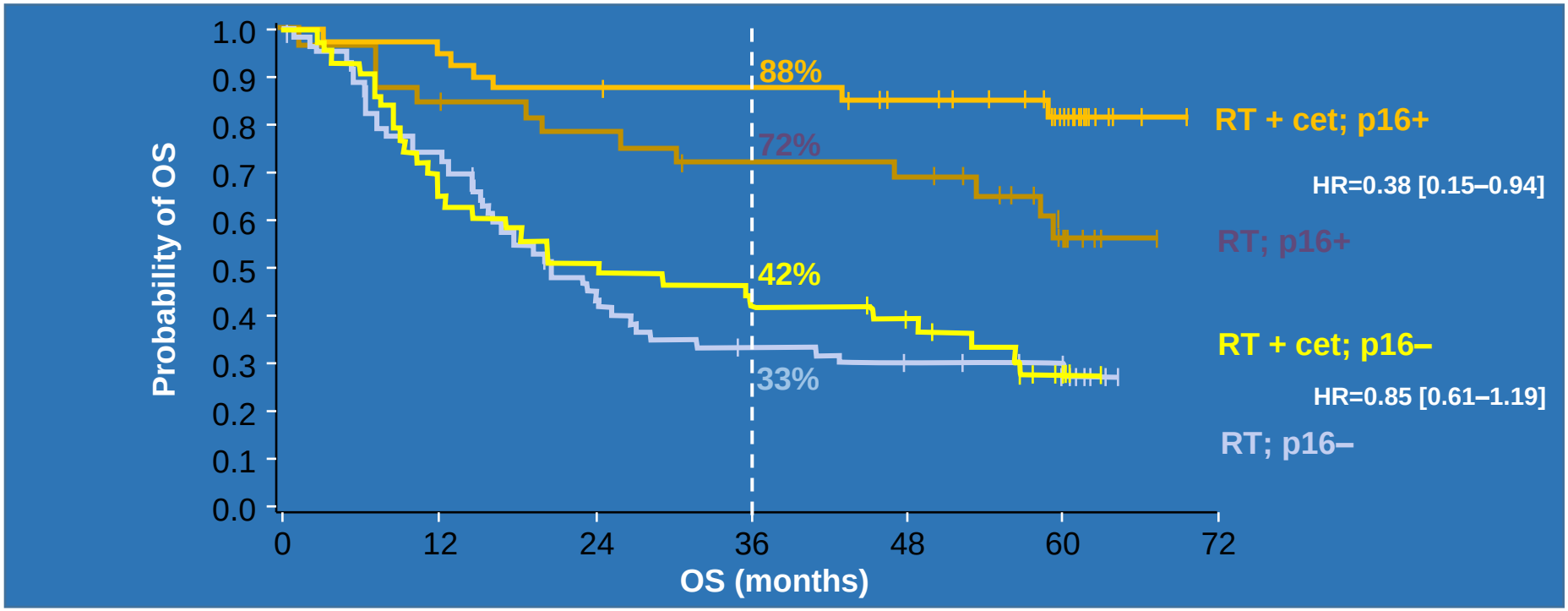
Late toxicity (cis vs cetuximab)

Variable	Cisplatin No =58	Cisplatin %	Cetuximab No=56	Cetuximab %
Residual Renal Dysfunction	13	22.4	0	
Grade III-IV toxicity				
Mucosal	2	3.5	1	1.8
Xerostomia	6	10.3	8	5.9
Subcutaneous Fibrosis	4	7	1	2
Neuropathy	2	3.4	0	0
Laryngoesophageal	5	8.6	5	9

Lefebvre et al JCO March 2013

OS in OPC subpopulation according to p16 status and treatment effect of RT + cetuximab vs RT alone

OS interaction test p=NS

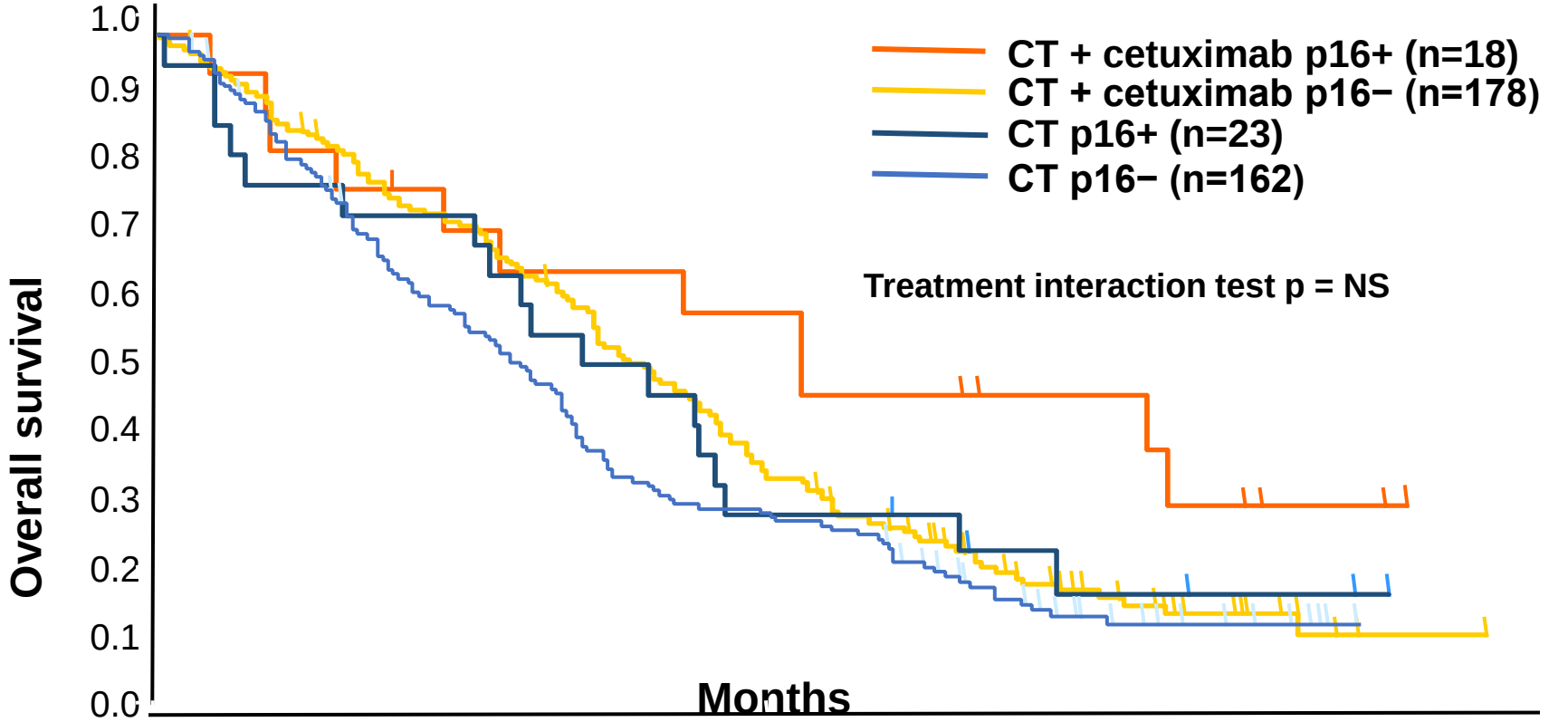


No. at risk OPC p16 evaluable (n=182)

RT p16 negative	64	47	27	19	16	13	0
RT p16 positive	34	28	25	22	21	10	0
RT + cet p16 negative	43	29	22	18	15	6	0
RT + cet p16 positive	41	39	36	35	31	17	0

Rosenthal DI ASCO 2015

OS in OPC subpopulation according to p16 status and treatment effect of chemo+cetuximab vs chemo alone

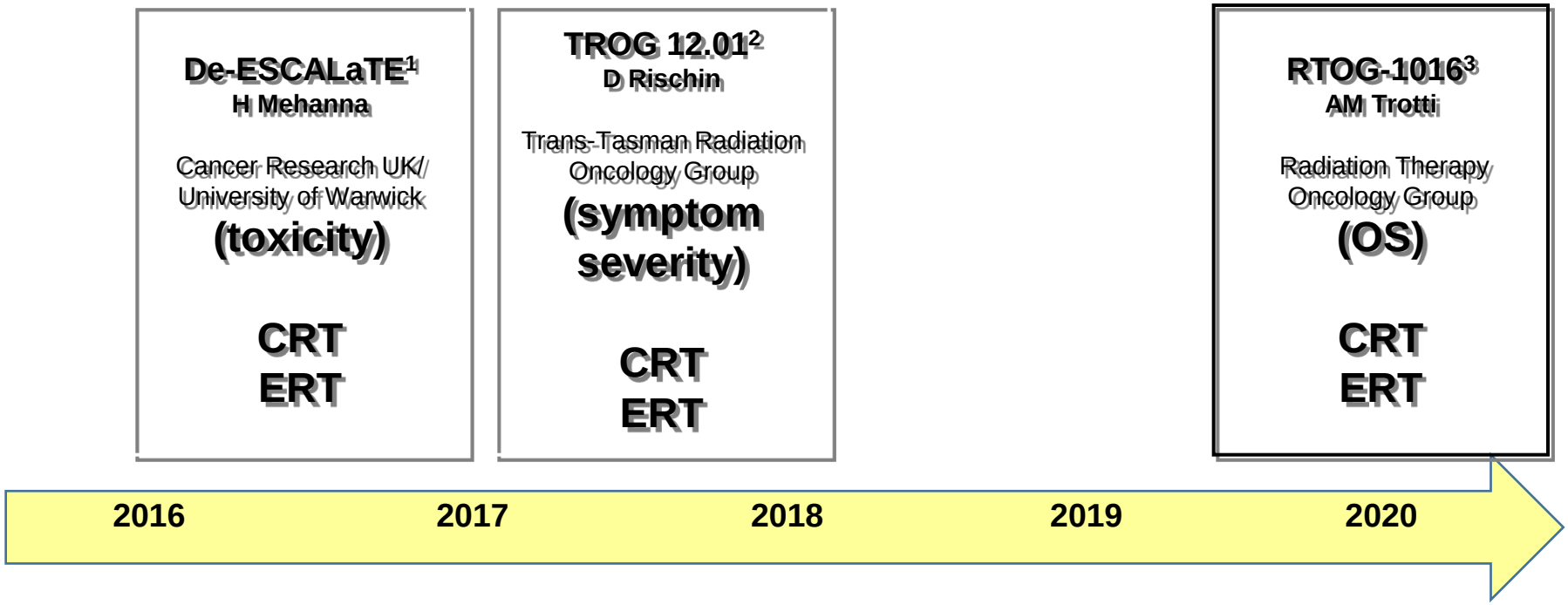


Number of patients at risk										
	178	150	126	93	61	40	19	10	1	0
	18	15	12	11	10	8	6	4	1	0
	23	18	17	12	7	6	3	2	1	0
	162	128	92	56	47	33	15	6	0	0

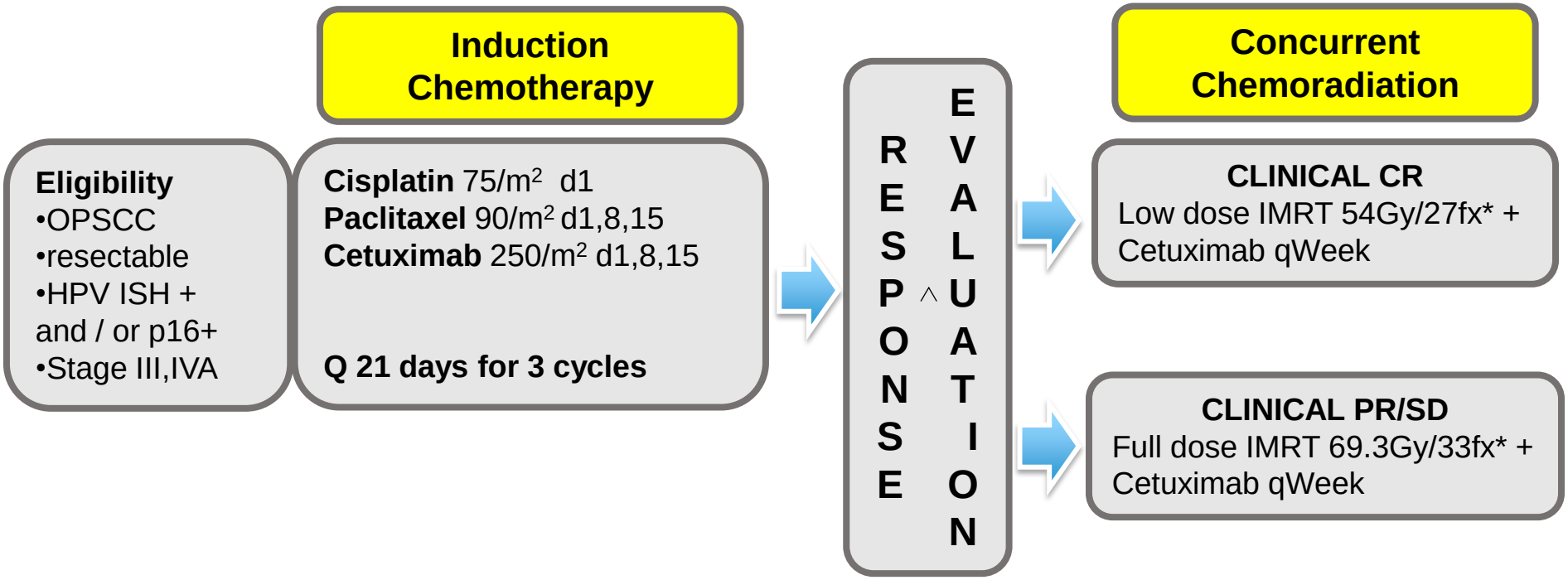
Psyrri et al ESMO 2012

Ongoing Phase 3 studies to assess cetuximab + RT vs CRT in unresectable HPV-associated OPC

- Investigator-sponsored studies ongoing in p16+ OPC in Europe and the US to evaluate the combination of cetuximab + RT vs CRT



ECOG 1308: Phase II Schema



IMRT margins for primary: 1.0 to 1.5cm around gross disease
Nodal margin: 1cm margin minimum, treat entire nodal level
Primary Objective: 2-year PFS after low-dose IMRT (stat aim: 2-year 85% or better)

IMRT: intensity modulated radiation therapy

Cmelak A et al, ASCO 2014

Endpoint: 2yr PFS and OS

Cohort (n)	2 year PFS (90% CI)	2 year OS (90% CI)
All low dose pts (62)	0.80 (0.70, 0.88)	0.93 (0.85, 0.97)
T4a (7)	0.54 (0.19, 0.79)	0.86 (0.45, 0.97)
Non-T4a (55)	0.84 (0.73, 0.91)	0.94 (0.86, 0.98)
N2c (19)	0.77 (0.56, 0.89)	0.95 (0.76, 0.99)
Non-N2c (43)	0.82 (0.69, 0.90)	0.93 (0.82, 0.97)
Smoker >10pk-yrs (22)	0.57 (0.35, 0.73)	0.86 (0.67, 0.94)
Smoker ≤10pk-yrs (40)	0.92 (0.81, 0.97)	0.97 (0.87, 0.995)
Smoker ≤10k-yrs, <T4, N2c (27)	0.96 (0.82, 0.99)	0.96 (0.82, 0.99)
All high-dose pts (15)*	0.65 (0.41, 0.82)	0.87 (0.63. 0.96)

* 3 high-dose pts did not go on to receive RT

Cmelak A et al ASCO 2014

HPV-targeted therapies

Prophylactic

- Prevent viral infection
- Humoral response

Therapeutic

- Treat virally infected cells
- Cellular response

HPV therapeutic vaccines

- **HPV E6 and E7 are attractive targets for tumor immunotherapy:**

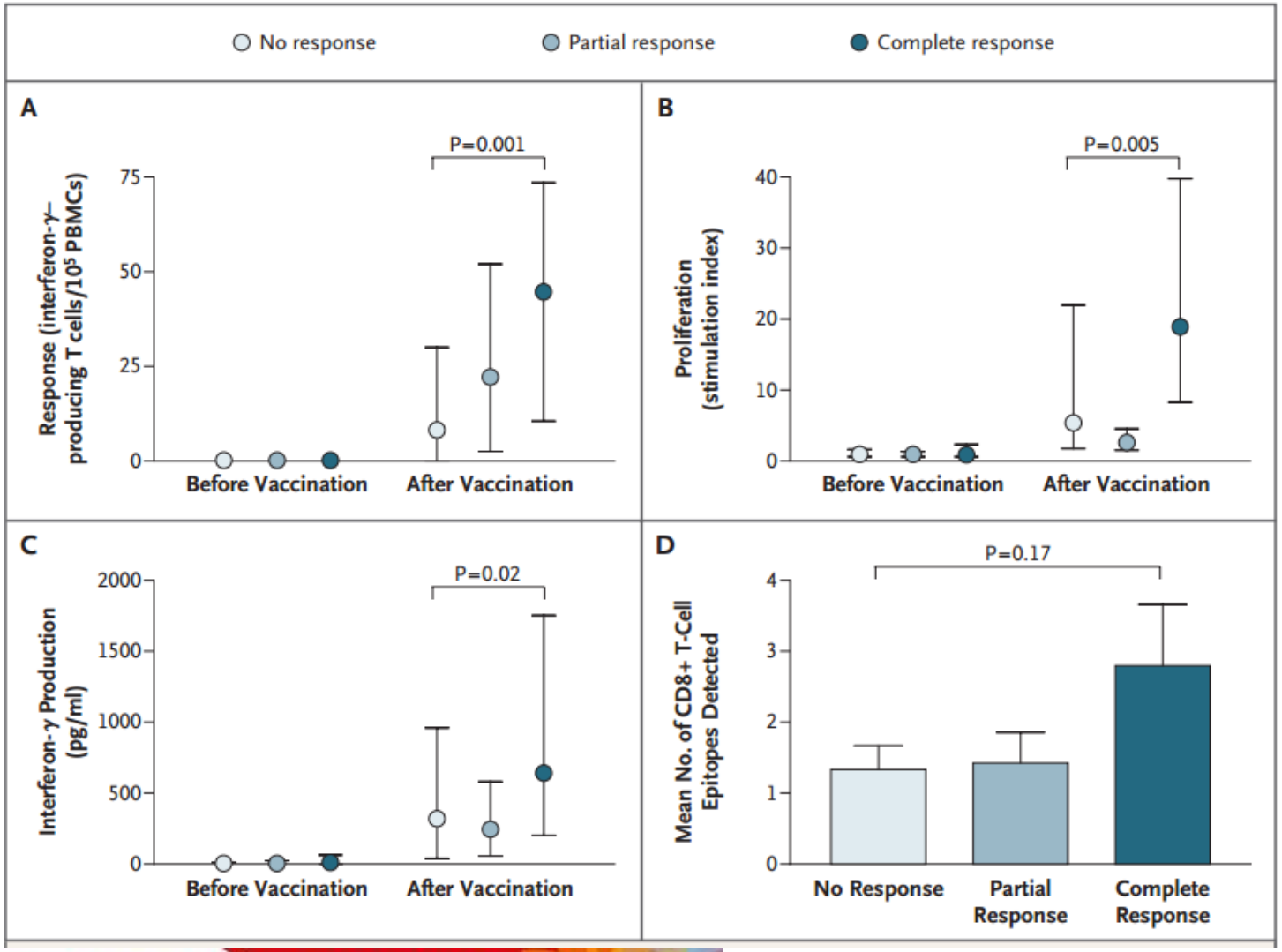
  - foreign viral proteins
  - uniquely expressed by cancer cells
  - constitutively expressed by cancer cells to maintain the malignant phenotype[+]

  [+]Rampias T…Psyrri A: JNCI 2007

Vaccination against HPV16 in vulval intraepithelial neoplasia (VIN)

- In this single-group study involving women with grade 3 vulvar intraepithelial neoplasia associated with human HPV-16, vaccination against HPV-16 infection with a peptide vaccine was related to a clinical response in 15 of 19 patients (79%) at 1 year
- This clinical response was associated with induction of HPV-16-specific T cells

Immune Response before and after Vaccination



Kenter GG et al. N Engl J Med 2009;361:1838-1847

Strategies to enhance vaccine efficacy

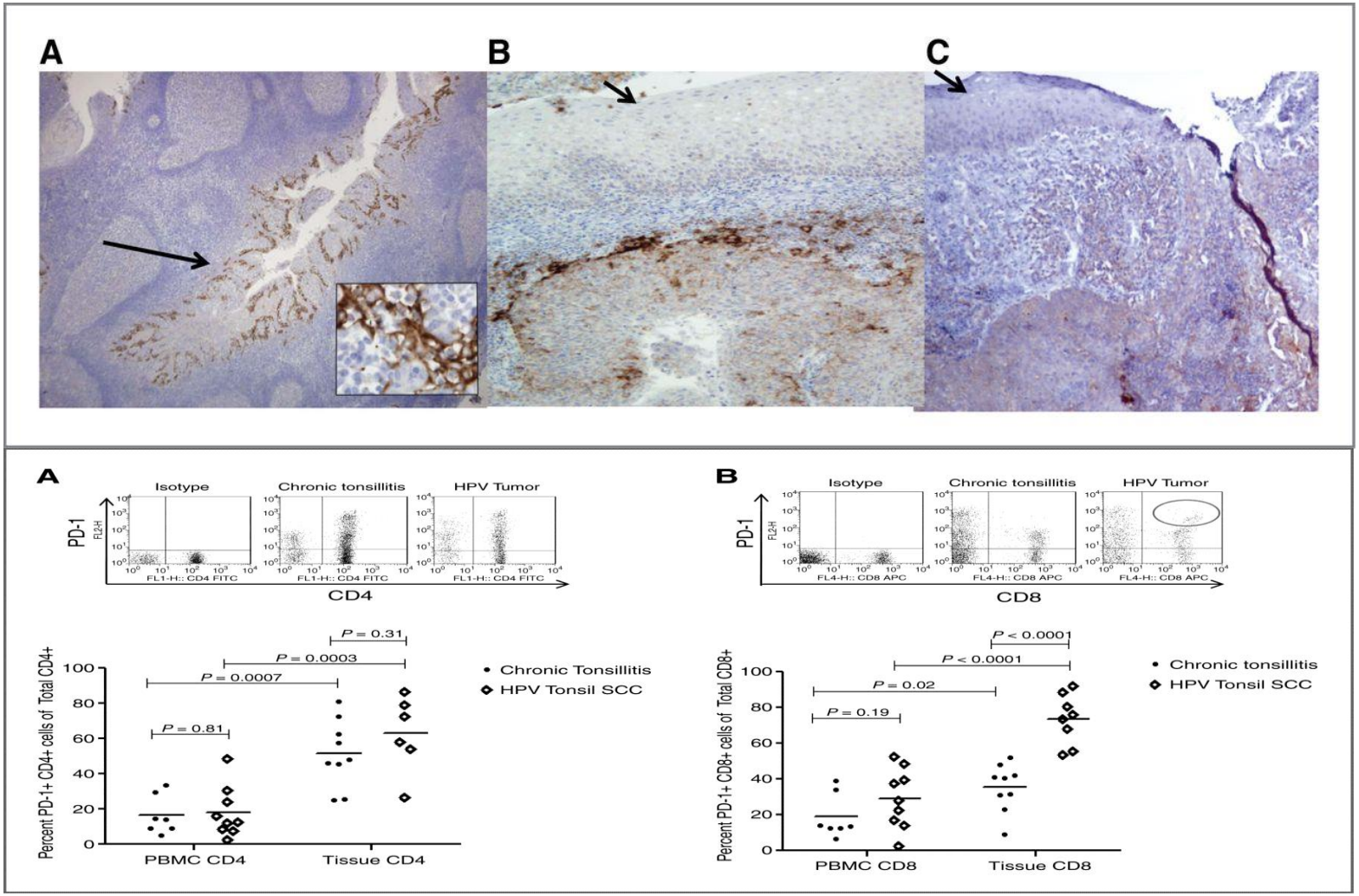
- **Optimize method of vaccination i.e. electroporation**
- **Address suppressive tumor microenviroment**
- **Combine with multimodality regimen i.e. chemoRT**

Addressing immunosuppressive microenvironment

- Treating tumor- bearing mice with HPV tumor cells with low-dose cyclophosphamide resulted in decrease in frequency of inhibitory Tregs as compared to no treatment with cyclophosphamide*
- Combination of HPV DNA therapeutic vaccine (CRT/E7 detox) with cyclophosphamide resulted in increase in the levels of HPV-specific responses, better control of tumor growth (as measured by tumor volume) and better long-term survival*

Pai et al: ASCO 2011

PD1 pathway and HPV-associated HNSCC



Lyford-Pike S et al. Cancer Res 2013;73:1733-1741

Addressing immunosuppressive microenvironment

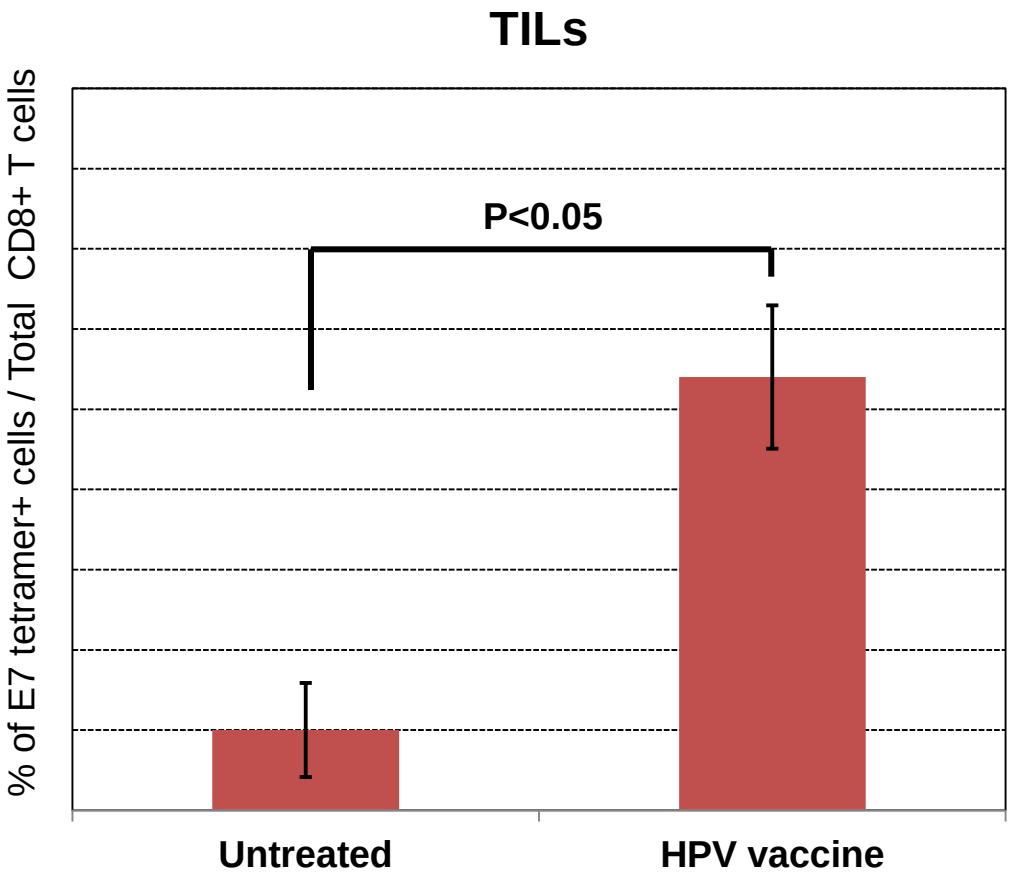
- PD1 is a negative immunoregulatory checkpoint, a negative signaling receptor expressed on activated T cells, CD4+CD25+ Foxp3-expressing Tregs
- Effective active modulation of immune response with anticancer vaccines would require blockading negative immunological checkpoints that impede an effective immune response
- Therefore combining an HPV therapeutic vaccine with anti-PD1 antibody is a promising therapeutic strategy

Therapeutic HPV vaccine increases sensitivity of poorly immunogenic tumor to anti-PD-1 monotherapy S. Pai et al*

- **Objectives:** To evaluate whether an HPV vaccine can improve response rates to anti-PD-1 therapy by eliciting CD8+ anti-tumor immune responses
- **Materials and Methods:** CB7BL/6 mice were inoculated with TC-1 tumor cells and received either anti-PD-1 blocking antibody, CRT/E7 (detox) DNA vaccine or both. Mice were monitored for tumor growth and HPV-specific T cell responses. TC-1 tumors were excised and HPV 16 E7/specific $CD8^+$ T cells stained for PD-1 expression with flow cytometry

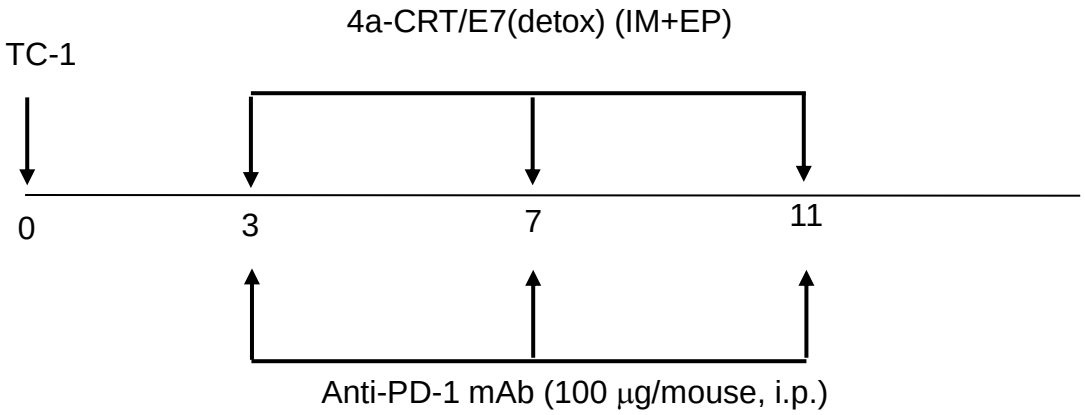
Pai et al: ICHNO 2015

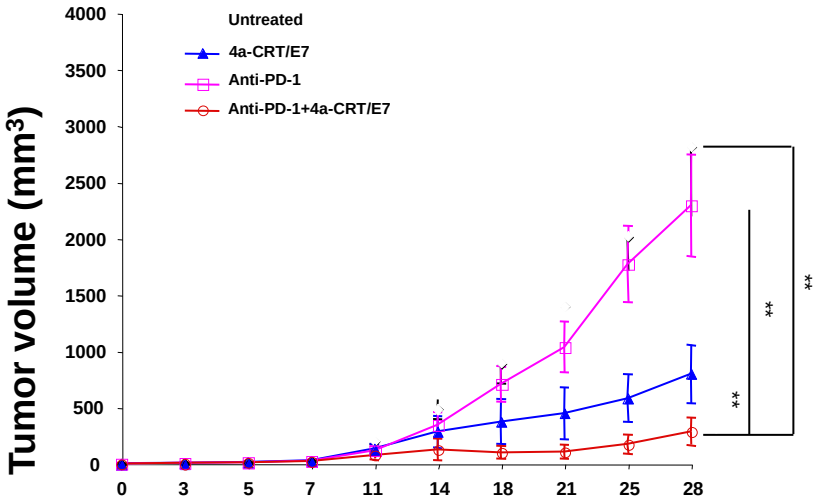
Frequency of E7-specific CD8+ T cells

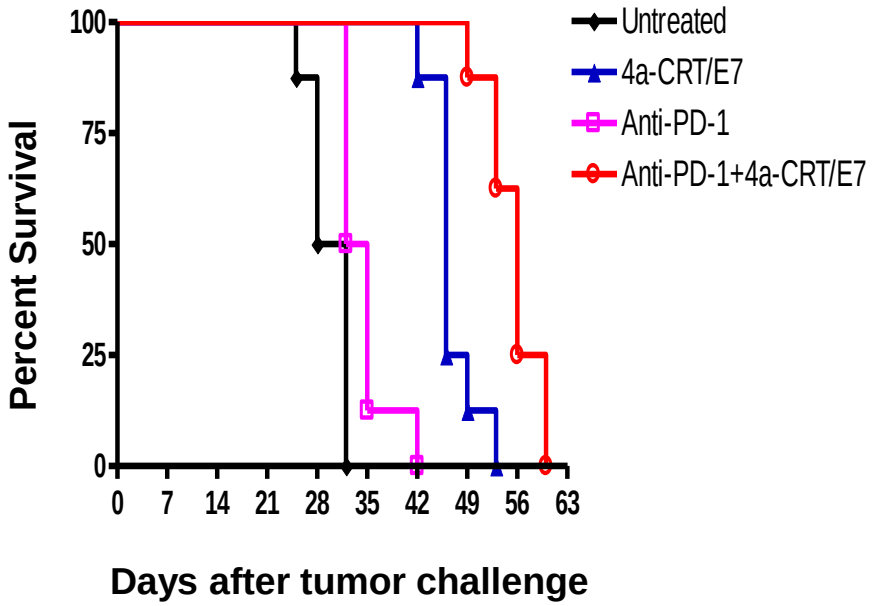


Pai et al: ICHNO 2015

Tumor Growth and Survival

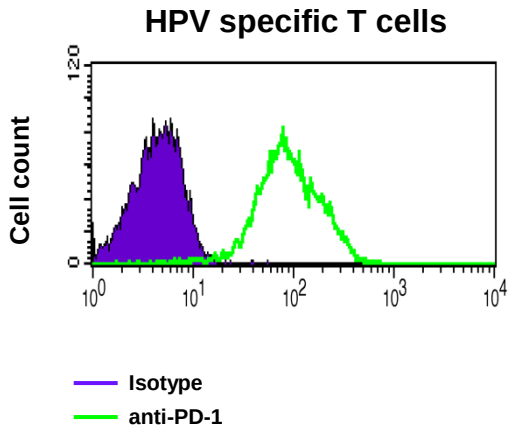


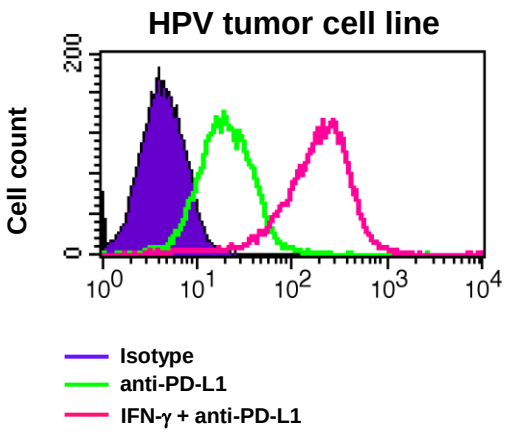


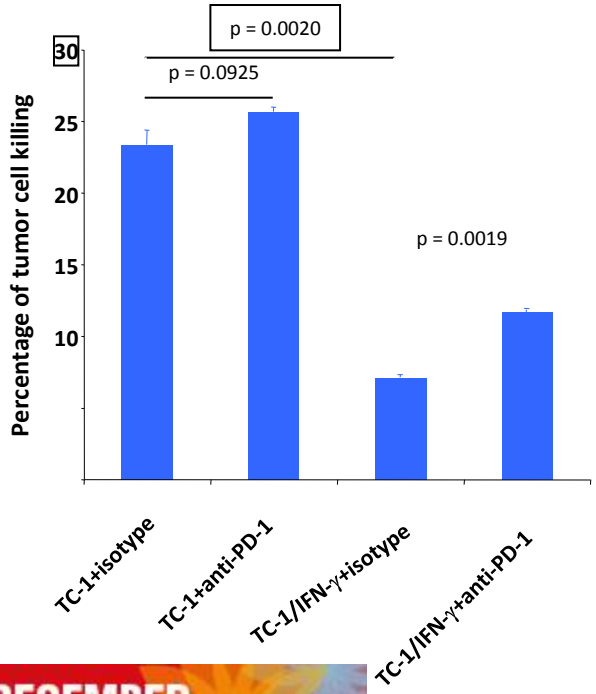


Pai et al: ICHNO 2015

Anti-PD-1 Blockade Reverses T cell Anergy







Pai et al: ICHNO 2015

HNSCC expansion cohort of the KEYNOTE-012 Nonrandomized, Phase 1b Multi-cohort trial*

Patients:

- **Recurrent or metastatic HNSCC, regardless of PD-L1 or HPV status**
- **Have measurable disease based on RECIST 1.1**
- **ECOG performance status of 0 or 1**

→ **Pembrolizumab 200 mg Q3W** →

- **Treatment for 24 months†**
- **Documented disease progression‡**
- **Intolerable toxicity**

Response assessment: Every 8 weeks

Primary end points: ORR per modified RECIST v1.1 by investigator review; safety

Secondary end points: PFS, OS, duration of response

*Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer
†Treatment beyond progression was allowed.
‡Re-treatment was permitted.

Seiwert TY et al ASCO 2015

Baseline Demographics

Characteristic	N = 132* N (%)
Median age (range), years	60 (25–84)
Male	110 (83.3)
Race	
White	96 (72.7)
Asian	28 (21.2)
Other	8 (6.1)
ECOG PS	
[0] Normal Activity	38 (28.8)
[1] Symptoms, but ambulatory	94 (71.2)

Characteristic	N = 132* N (%)
Prior adjuvant/neoadjuvant systemic therapy	
Yes	53 (40.2)
Prior lines of therapy for recurrent/metastatic disease	
0	22 (16.7)
1	30 (22.7)
2	28 (21.2)
3 or more	50 (37.9)
Unknown	2 (1.5)

Data cutoff date: March 23, 2015

***Includes patients who received ≥1 dose of pembrolizumab**

Seiwert TY et al ASCO 2015

Treatment-Related Adverse Events

AE in ≥5 % of Patients	N = 132* N (%)
Any	79 (59.8)
Fatigue	20 (15.2)
Hypothyroidism	12 (9.1)
Decreased appetite	10 (7.6)
Rash	10 (7.6)
Dry skin	9 (6.8)
Pyrexia	9 (6.8)
Arthralgia	7 (5.3)
Nausea	7 (5.3)
Weight decreased	7 (5.3)

Grades 3-5 (≥2 patients)	N = 132* N (%)
Any	13 (9.8)
Swelling face	2 (1.5)
Pneumonitis	2 (1.5)

- No treatment-related deaths occurred

***Includes patients who received ≥1 dose of pembrolizumab**
Data cut off date: March 23, 2015.

Seiwert TY et al ASCO 2015

Overall Response Rate [Site Radiology Review]*

Best overall response	Total N = 117†		HPV+ n = 34		HPV– n = 81	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
ORR	**29 (24.8)**	17.3-33.6	7 (20.6)	8.7-37.9	22 (27.2)	17.9-38.2
Complete Response	1 (0.9)	0.0-4.7	1 (2.9)	0.1-15.3	0 (0)	0-4.5
Partial Response	28 (23.9)	16.5-32.7	6 (17.6)	6.8-34.5	22 (27.2)	17.9-38.2
Stable Disease	29 (24.8)	17.3-33.6	9 (26.5)	12.9-44.4	19 (23.5)	14.8-34.2
Progressive Disease	48 (41.0)	32.0-50.5	13 (38.2)	22.2-56.4	34 (42.0)	31.1-53.5
No Assessment#	9 (7.7)	3.6-14.1	4 (11.8)	3.3-27.5	5 (6.2)	2.0-13.8
Non-evaluable±	2 (1.7)	0.2-6.0	1 (2.9)	0.1-15.3	1 (1.2)	0.0-6.7

Seiwert TY et al ASCO 2015

*Unconfirmed and confirmed RECIST v 1.1 responses
†Includes patients who received ≥1 dose of pembrolizumab, had measurable disease at baseline and ≥1 postbaseline scan or discontinued due to PD or DRAE. 15 patients not included in this analysis: 2 did not have baseline scans within screening window, 13 did not have post-baseline assessment and discontinued due to non-drug related AE (7), subject withdrawal of consent (4), other (2).
#No assessment: Discontinued without post-baseline radiographic assessment due to drug related AE (2 patients), clinical PD (6 patients), death due to PD (1 patient)
±Non-evaluable: Images were not of sufficient quality to be evaluable
HPV status missing for 2 patients with oropharynx cancer. Cancers outside the oropharynx are considered HPV negative by convention.
Data cutoff date: March 23, 2015.

Durvalumab/MEDI4736: Clinical Data – ASCO 2015

Table6: Tumor response by Subgroups*

	MEDI4736 10mg/kg			
	HPV+	HPV-	Former/current smoker	Never smoker
RECIST response (ORR)±‡, n/N(%) 95% CI	1/25 (4) 0.1-20.4	4/25 (16) 4.5-36.1	2/39 (5) 0.6-17.3	5/23 (22) 7.5-43.7
DCR 24 weeks±‡ , n/N (%) 95% CI	1/25 (4) 0.1-20.4	5/25 (20) 6.8-40.7	3/39 (8) 1.6-20.9	6/23 (26) 10.2-48.4

*** HPV status was collected at baseline from patient records; ± ORR (confirmed complete response (CR) and partial response (PR) and DCR (CR+PR+stable disease (SD)≥24 weeks) are based on RECIST v1.1; ‡ There were 2 responders among the 12 patients with unknown HPV status**
CI, confidence interval; DCR, disease control rate; HPV, human papilloma virus; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors

Segal et al, ASCO 2015

Durvalumab/MEDI4736: Clinical Data – ASCO 2015

Table5: Tumor Response Overall and by PD-L1 Status

	MEDI4736 10mg/kg		
	All patients (n=62)	PD-L1^{+} (n=22)	PD-L1^{-} (n=37)
RECIST response (ORR), n/N(%) 95% CI	7/62 (11) 4.7-21.9	4/22 (18) 5.2-40.3	3/37 (8) 1.7-21.9
DCR 24 weeks*, n/N (%) 95% CI	9/62 (15) 6.9-25.8	4/22 (18) 5.2-40.3	4/37 (11) 3.0-25.4
Range of ongoing DoR±, weeks	16.1+-55.4+	41.1+-53.1+	16.1+-55.4+
Ongoing responders, n/N(%)	5/7 (71)	2/4 (50)	3/3 (100)

- HPV(-) patients seemed to have improved responses over HPV(+) patients
- Durvalumab was safe and tolerable
  - Drug-related AEs: 60%
  - Grade ≥3 drug-related AEs: 7%

Segal et al, ASCO 2015

New concepts for HPV+ locally advanced disease

- Low risk disease: substituting chemo with immune checkpoint inhibitors

- Intermediate risk disease: adding immune checkpoint inhibitors to cisplatin-IMRT (RTOG, EORTC)

Conclusions

- Response rates and survival outcomes are clearly better for the HPV positive patients
- Tobacco is a negative prognostic factor in HPV-associated OPC
- At this point these patients should be treated similarly to stage-matched HPV negative patients
- Clinical trials of treatment deintensification are ongoing
- Immunotherapy appears promising in these patients
- We need to enroll patients on clinical trials to address these issues