2022 ASCO Direct™ Highlights
Head and Neck Cancer

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August 25, 2022

FRED HUTCH

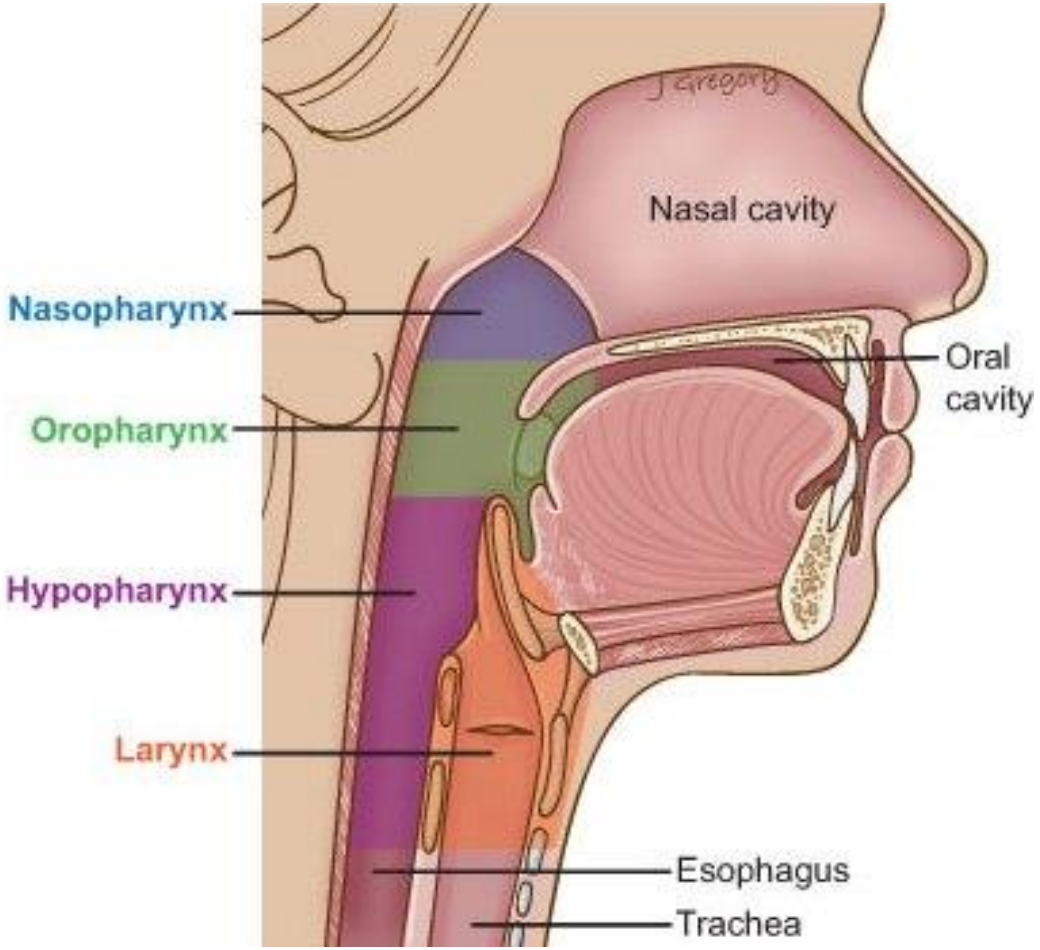
Disclosures

	Cristina Rodriguez (Presenter)	Stephen Smith (spouse)
Institutional Research Funding	AstraZeneca Bristol Myers Squibb Cue Biopharma Kura Prelude Merck	Astrazeneca Bayer Beigene De Novo Biopharma Genentech Incyte Corporation Merck Sharp and Dohme Corp. Portola Pharmaceuticals
Advisory Board/ Consultancy	Cue Biopharma Coherus	Astrazeneca Millenium/Takeda Beigene Karyopharm KITE pharma Incyte ADC Therapeutics Abbvie
DSMC	Pionyr	

OUTLINE

- Introduction/Background
- Locally advanced head and neck cancer (LAHNSCC)
  - Abstracts 6003, 6004, and 6005
- Recurrent/metastatic head and neck cancer
  - Abstracts 6008 and 6036

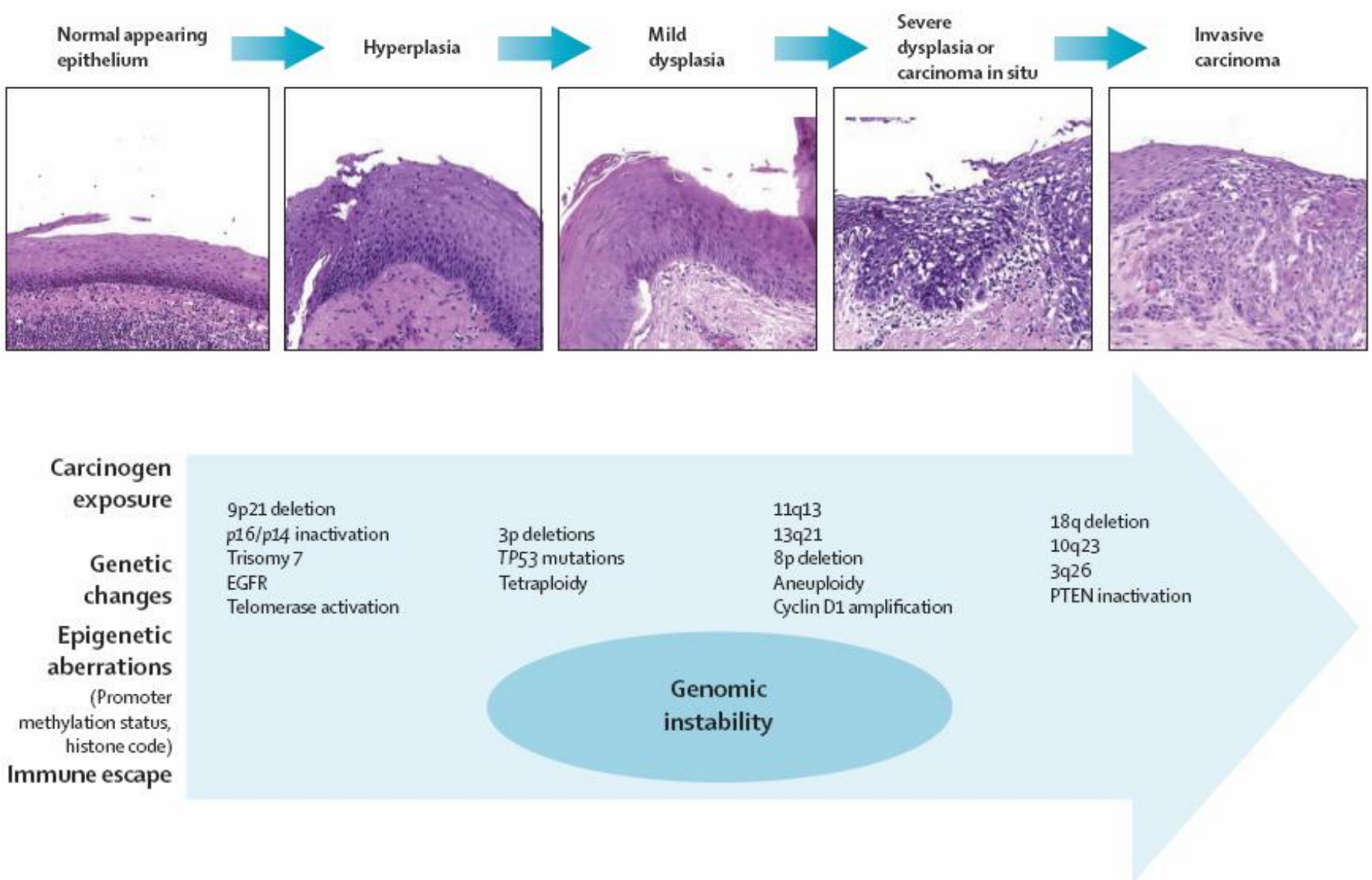
Epithelial malignancies of the head and neck



- 90% squamous cell carcinomas
- Most common mucosal sites oropharynx, oral cavity, larynx, hypopharynx
- 85% locally advanced at diagnosis and candidates for curative intent therapy

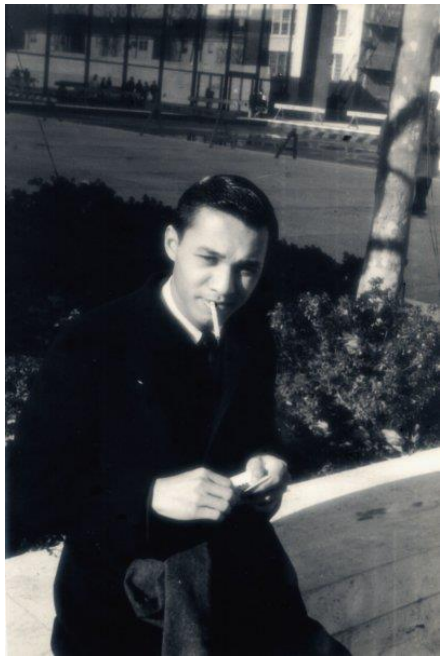
Pathogenesis

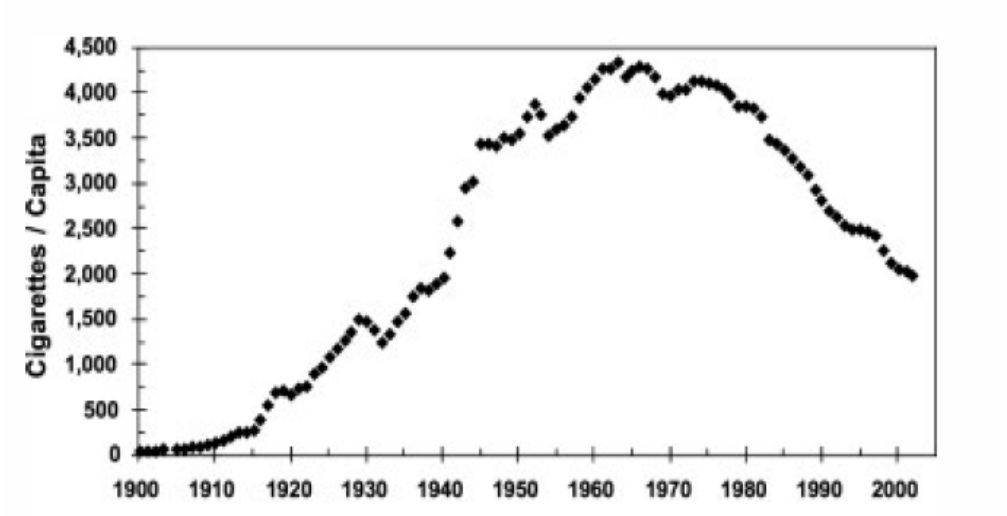
1. **Tobacco and alcohol**
   - oral cavity, larynx, hypopharynx
   - declining in incidence
   - economic and racial disparity
2. **Viral infection**
   - HPV in oropharynx primaries, NPC
   - HPV+ OPC increasing in incidence

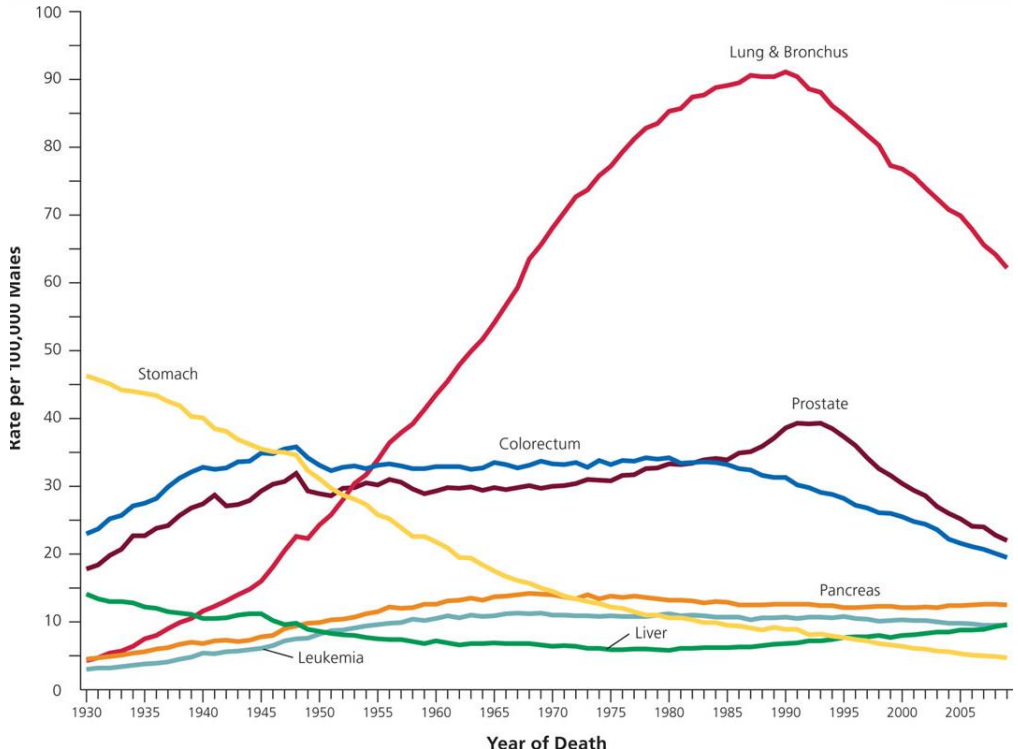


Argiris et al. Lancet. 2008 May 17;371(9625):1695-709.

Trends in tobacco use and tobacco related cancers

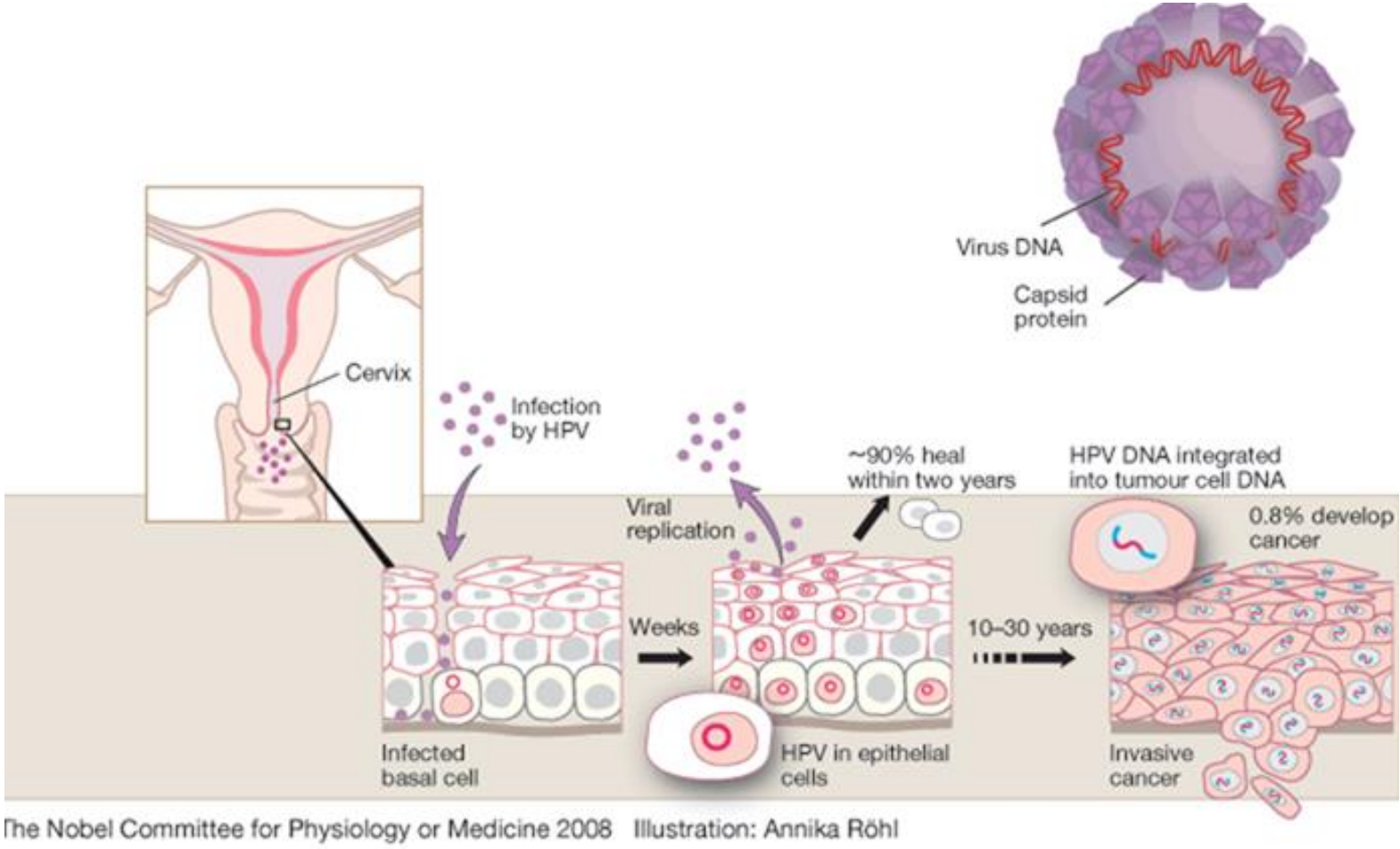




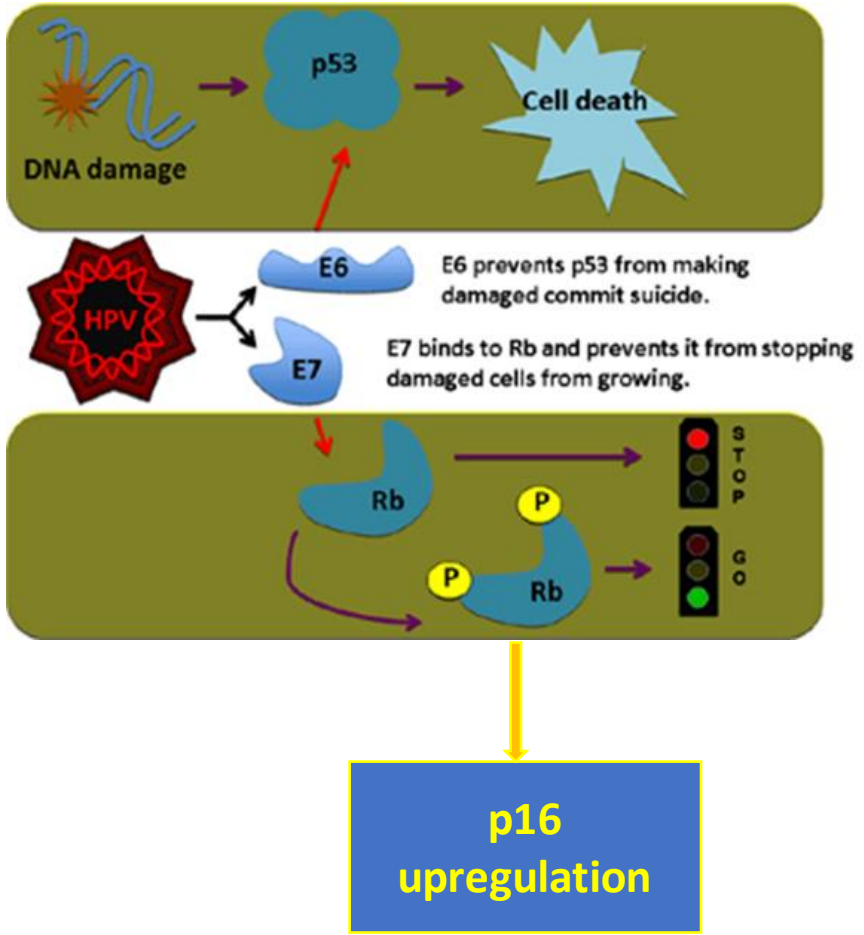


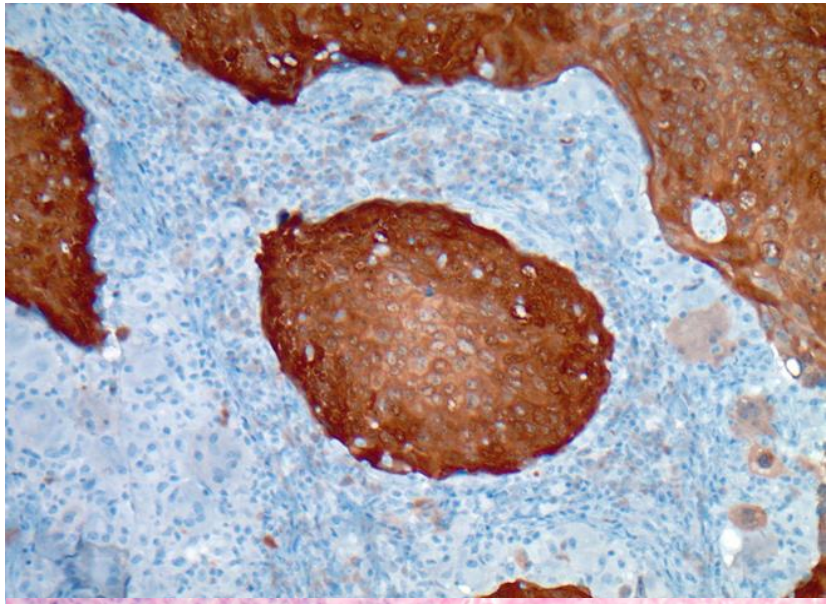
Sturgis et al. Cancer. 2007 Oct 1;110(7):1429-35

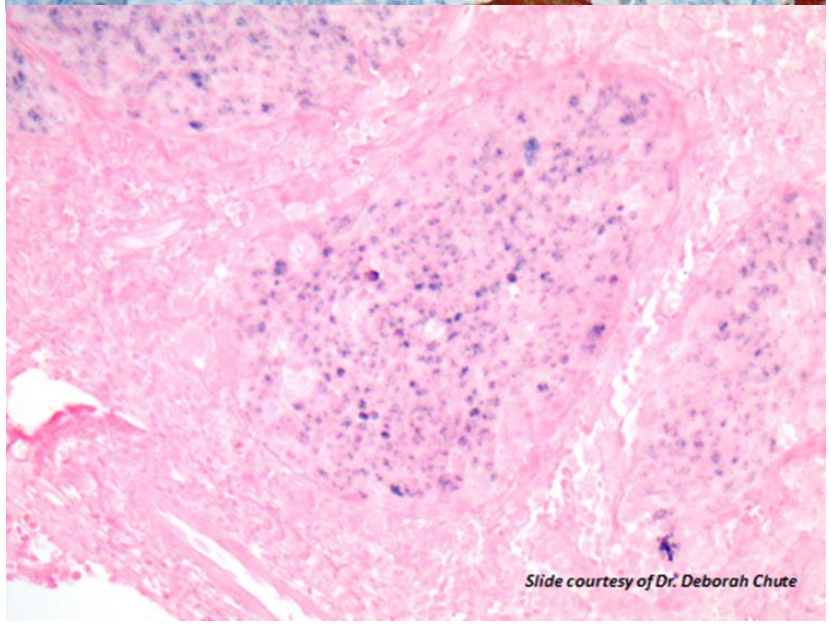
HPV+ oropharynx cancer: a distinct entity with a viral association



HPV+ **oropharynx** cancer: a distinct entity







http://genetics.thetech.org/ask/ask359

Therapeutic goals in LAHNSCC

- Candidates for curative intent therapy
- Dual challenge of optimizing oncologic and functional outcomes
- Multidisciplinary evaluation is critical

Systemic therapy in LAHNSCC: Definitive non surgical therapy

Disease	Standard/s of Care	Evidence
Locally advanced p16+ oropharynx cancer	cisplatin 100mg/m2 day 1, 22, 43 + XRT	**RTOG 1016**[1] **DE-ESCALaTE**[2] OS, LRC benefit vs. cetuxXRT
Unresectable HNSCC of OC, OP, L, HP	cisplatin 100mg/m2 day 1, 22, 43 of XRT	**Intergroup Study**[3] OS, DSS and LRC advantage vs XRT or splitXRT
Unresectable HNSCC of OC, OP, L, HP	cetuximab weekly concurrent with XRT	**Bonner Study**[4] OS, LRC and PFS advantage vs XRT
St III-IVB Larynx CA (supraglottis or subglottis)	cisplatin 100mg/m2 day 1, 22, 43 of XRT	**RTOG 91-11**[5] Larynx Preservation and LRC benefit vs XRT or ind.+ XRT

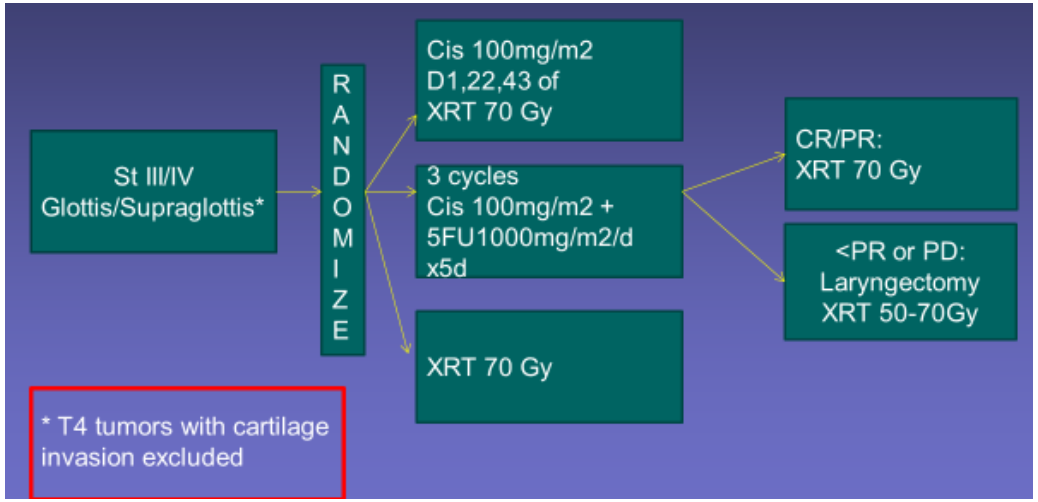
[1]*Gillison et al. 2019 Jan 5;393(10166):40-50*
[2]*Mehanna et al. Lancet. 2019 Jan 5;393(10166):51-60*
[3]*Adelstein et al. J Clin Oncol, 2003; 21(1):92-8.*
[4]*Bonner JA. NEJM 2006:354:567-78.*
[5]*Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.*

Systemic therapy in LAHNSCC: Postoperative therapy for high risk features

Disease	Standard/s of Care	Evidence
Resected OP/OC/L/HP with + margins and/or ECE	cisplatin 100mg/m2 bolus + XRT	EORTC 22931[1] RTOG 95-01[2]
Unresectable HNSCC of OC, OP, L, HP	Posoperative radiation with cisplatin 40mg/m2	JCOG 1008[3]

[1]Bernier et al. N Engl J Med. 2004;350(19):1945
[2]Cooper et al. N Engl J Med. 2004;350(19):1937
[3]Kiyota et al. J Clin Oncol. 2022 Jun 20;40(18):1980-1990

RTOG 91-11: organ preservation in larynx cancer



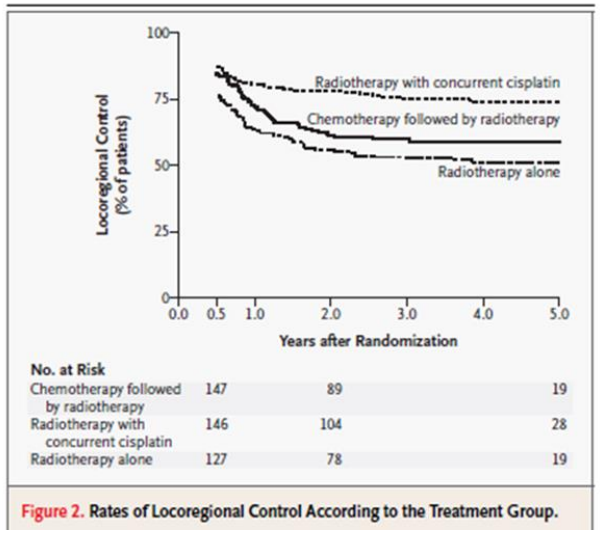


Figure 2. Rates of Locoregional Control According to the Treatment Group.

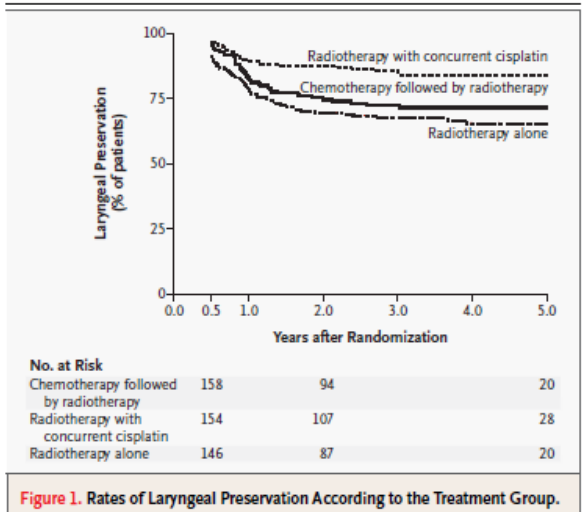


Figure 1. Rates of Laryngeal Preservation According to the Treatment Group.

RTOG 91-11: organ preservation in larynx cancer

Table 2. Grade 3 or 4 Acute Toxic Effects, According to the Treatment Group.*

Toxic Effect	Cisplatin plus Fluorouracil Followed by Radiotherapy						Radiotherapy with Concurrent Cisplatin (N=171)			Radiotherapy Alone (N=171)		
	Chemotherapy Period (N=168)			Radiotherapy Period (N=156)								
	grade 3	grade 4	total	grade 3	grade 4	total	grade 3	grade 4	total	grade 3	grade 4	total
	number of patients (percent)											
Hematologic	43	44	87 (52)	13	10	23 (15)	64	17	81 (47)	3	2	5 (3)
Infection	4	5	9 (5)	2	0	2 (1)	7	0	7 (4)	2	0	2 (1)
Mucosal (stomatitis)	27	7	34 (20)	36	2	38 (24)	64	9	73 (43)	40	1	41 (24)
Pharyngeal or esophageal	—	—	—	30	0	30 (19)	60	0	60 (35)	32	0	32 (19)
Laryngeal	—	—	—	20	1	21 (13)	29	2	31 (18)	23	5	28 (16)
Dermatologic (in radiation field)	—	—	—	16	0	16 (10)	10	2	12 (7)	15	0	15 (9)
Nausea or vomiting	20	3	23 (14)	0	0	0	28	7	35 (20)	0	0	0
Renal or genitourinary	3	0	3 (2)	2	0	2 (1)	6	1	7 (4)	0	0	0
Neurologic	5	1	6 (4)	0	0	0	8	1	9 (5)	0	0	0
Other	20	7	27 (16)	16	2	18 (12)	58	11	69 (40)	9	1	10 (6)
Overall maximal severity	62	49	111 (66)	66	13	79 (51)	99	32	131 (77)	71	9	80 (47)

Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.

Cisplatin-based chemoradiation (CCRT) in locally advanced HNSCC (LAHNSCC)

- A therapeutic standard in definitive[1-4] or postoperative[5,6] settings
- Toxicities are a significant burden to patients and health care systems
- Comorbidity overrepresented in HPV - subset and can preclude CCRT

[1]*Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.*
[2]*Adelstein et al. J Clin Oncol, 2003; 21(1):92-8.*
[3]*Gillison et al. 2019 Jan 5;393(10166):40-50*
[4]*Mehanna et al. Lancet. 2019 Jan 5;393(10166):51-60*
[5]*Bernier et al. N Engl J Med. 2004;350(19):1945*
[6]*Cooper et al. N Engl J Med. 2004;350(19):1937*

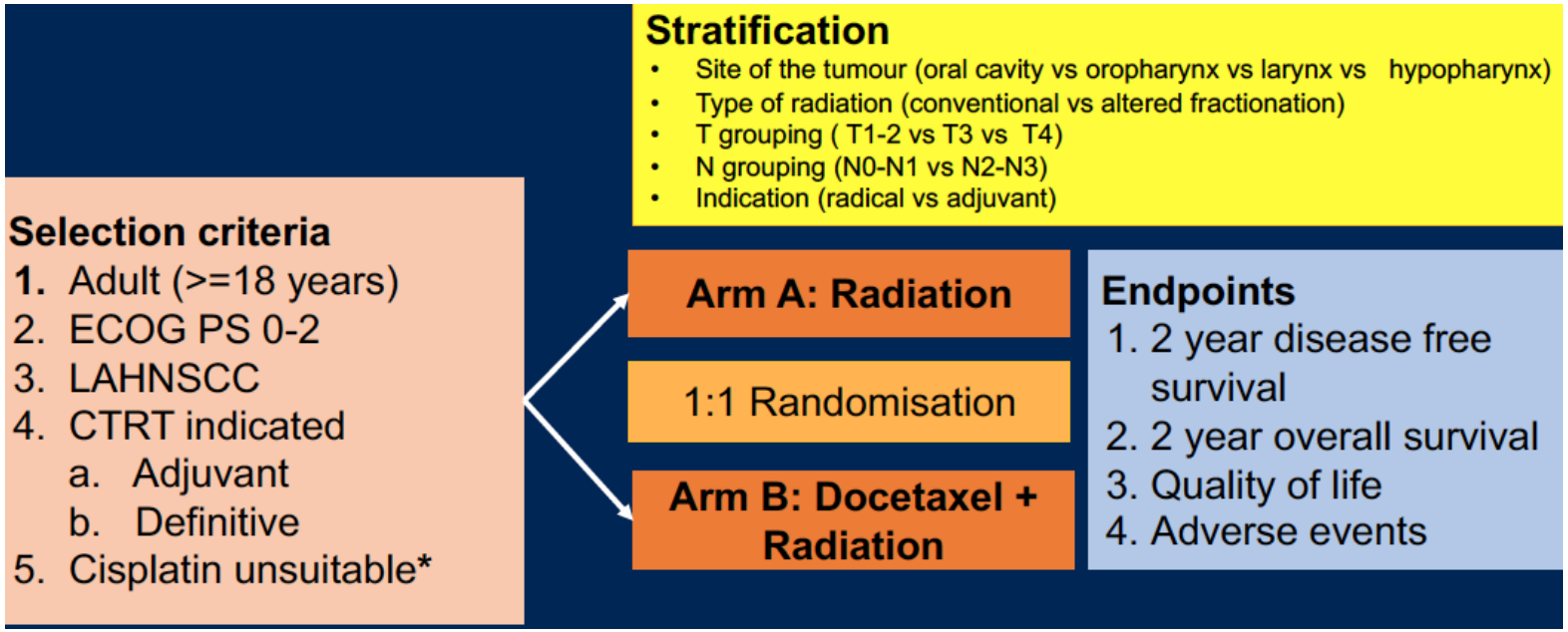
Abstracts 6003, 6004 and 6005

Key questions addressed by 3 studies:

- Can we improve outcomes in patients who are cisplatin ineligible?
  - 6003
- Can we reduce toxicity without compromising efficacy in the platinum eligible patient?
  - 6004
- Can we reduce high-grade mucositis during CCRT?
  - 6005

Abstract 6003:

Results of phase 3 randomized trial for use of docetaxel as a radiosensitizer in patients with head and neck cancer unsuitable for cisplatin-based chemoradiation.



Cisplatin ineligibility[1]

- ECOG PS ≥2
- Gr ≥2 organ dysfunction (CTCAE)
- CrCl of <50ml/min or comorbidities, nephrotoxic medications
- Wt loss >10% in last 6 mo, BMI ≤16 kg/m2

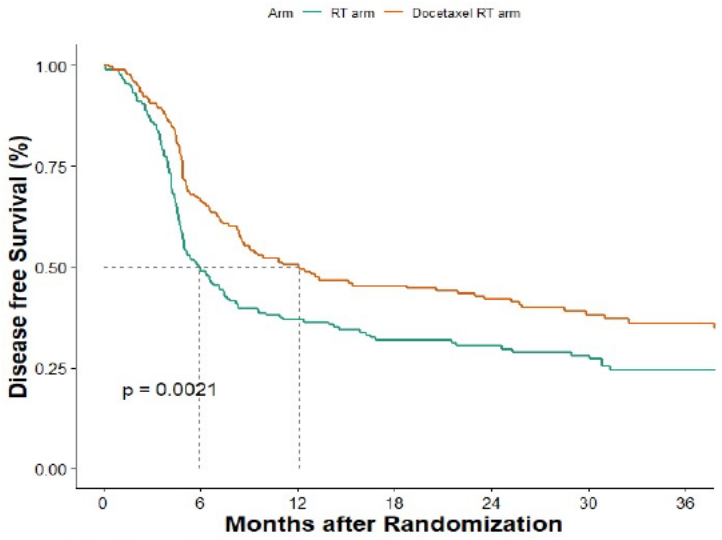
[1]*Ahn et al. Oral Oncol. 2016 Feb;53:10-6*

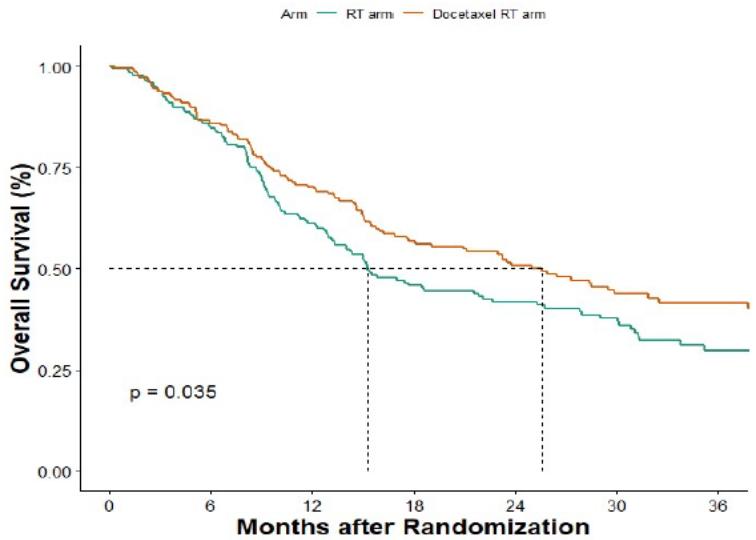
Abstract 6003: Results

- 356 of planned 600 patients accrued
  - 16% were ≥70 y.o.
  - ECOG of 2 in 40% vs 50% (nonsignificant)
  - p16+ OPC represented <5% of population
  - 80% of adjuvant XRT was for ECE
  - 65% had CrCl <50 or hearing loss
- Predominantly definitive XRT (60%) with 2D planning
  - High rates of administration of all XRT (91%) and chemo (86%) doses

Abstract 6003: Results

- Toxicity higher in docetaxel arm (mucositis, odynophagia, dysphagia)
- No difference in hematologic AEs





- Unplanned subset analysis appears to benefit all subgroups (HR most robust for definitive XRT)
- PRQOL at 6 mos post XRT favorable for docetaxel XRT

Abstract 6003: Discussion

- The cisplatin ineligible population has been historically excluded from trials
- This is changing

Trial	N	Intervention	Primary endpoint/Results
NCT02707588[1] GORTEC 2015-01 PembroRad	133	Pembrolizumab/XRT vs Cetuximab/XRT	2 yr LRC No difference in both arms (60% vs 59%)
NCT02999087[2] GORTEC REACH	277	Avelumab/cetuximab/XRT vs Cetuximab/XRT	2 yr PFS No difference in both arms (44% vs 31%)
NCT03258554 NRG-HN004	523	Durvalumab/XRT vs Cetuximab/XRT	To be presented at ASTRO 2022

[1]Bourhis et al. ESMO 2021
[2]Tao et al. ESMO 2020

Noncisplatin concurrent regimens in definitive XRT

Trial	N	Intervention	Exp Arm Results	Exp arm Toxicities
GORTEC 9401[1,2]	226	Carboplatin/5FU/XRT vs. XRT	OS DFS superior	Mucositis/Skin/Nutrition/Heme toxicity worse
GORTEC 2007-01[3]	406	Carboplatin/5FU/Cetuximab/XRT Vs. Cetuximab XRT	PFS and LRC superior OS similar	LFT elevation, leucopenia, PEG, hospitalizations worse
Bonner IMCL9815[4]	253	Cetuximab/XRT vs. XRT	OS and LRC superior	More rash and infusion reactions

[1]*Calais et al. J Natl Cancer Inst 1999*
[2]*Denis et al. J Clin Oncol 2004*
[3]*Tao et al. J Clin Oncol 2018*
[4]*Bonner et al. N Eng J Med 2006*

Noncisplatin concurrent regimens in adjuvant XRT

- RTOG 0920
  - cetuximab + XRT vs XRT in intermediate risk resected LAHNSCC
  - Completed and awaiting results

- RTOG 1216
  - ❿ Initial randomized Ph II
    - cisplatin/XRT vs docetaxel/XRT vs docetaxel/cetuximab/XRT
  - ❿ Ongoing redesigned Randomized Ph III
    - cisplatinXRT vs atezolizumab/cisplatin/XRT vs docetaxel/cetuximab/XRT

Abstract 6003: Discussion

- Concurrent docetaxel and XRT
  - DFS and OS benefit in this cisplatin ineligible population (HPV neg)
  - increased non-hematologic toxicities

- Superiority over other nonplatinum definitive /adjuvant XRT regimens unknown

  - Other studies with noncisplatin regimens awaited (HN004, RTOG 1216)

Abstract 6004:

An open-label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (ConCERT trial)

- Addresses a longstanding controversy in our field (weekly vs. q3week)
  - Landmark studies of CCRT used cisplatin q3week 100mg/m^2
  - Weekly administration more accepted
    - Tolerability
    - Potential radiosensitization benefits

Abstract 6004: Design

- Randomized open label phase III study
  - Conducted in multiple institutions India
  - Weekly 40mg/m^2 vs q3 week 100mg/m^2 in definitive XRT setting

- Primary endpoint: LRC at 2 years

Abstract 6004: Results

- Patient population (N=278)
  - p16 positive in 5%
  - 20% with PS 2

- Treatment
  - 75% 2D planning
  - only 44% had no treatment delays
  - 17% received <200mg/m2 cisplatin dose density

Abstract 6004: Results

- 2 yr LRC similar 56% (q3week) vs 60% (weekly)
- Similar median OS in mos: 30 (q3week) vs 25 (weekly)
- Toxicity favors weekly arm:
  - Grade 3 mucositis, myelosuppression, renal, vomiting
- Health care utilization metrics favor weekly arm
  - Reduced need for IVF, hospitalization, treatment interruption

Randomized studies of weekly 40mg/m^2 vs q3week 100mg/m^2

Author (year)	N	Setting/Disease	Results for weekly	Toxicity with weekly
Kiyota (2022)	261	Adjuvant high risk resected LAHNSCC	OS noninferior	Gr 3 neutropenia/ infection/renal/oto lower Gr 3Thrombocytopenia higher
Liang (abst 2017)	529	Definitive NPC	Similar 2yr FFS	Similar Gr 3/4 tox Neutropenia/ thrombocytopenia higher
Lee (2016)	109	Definitive NPC	Similar 3yr PFS	Similar Gr3/4 tox

Abstract 6004: Discussion

- Supports use of weekly cisplatin concurrent with XRT
  - Predominantly HPV negative population
  - Ongoing HN009 exploring both HPV+ and negative subset
- Acute toxicities more favorable and consistent with Kiyota et al.
  - Ototoxicity similar
- Attractive from healthcare utilization standpoint

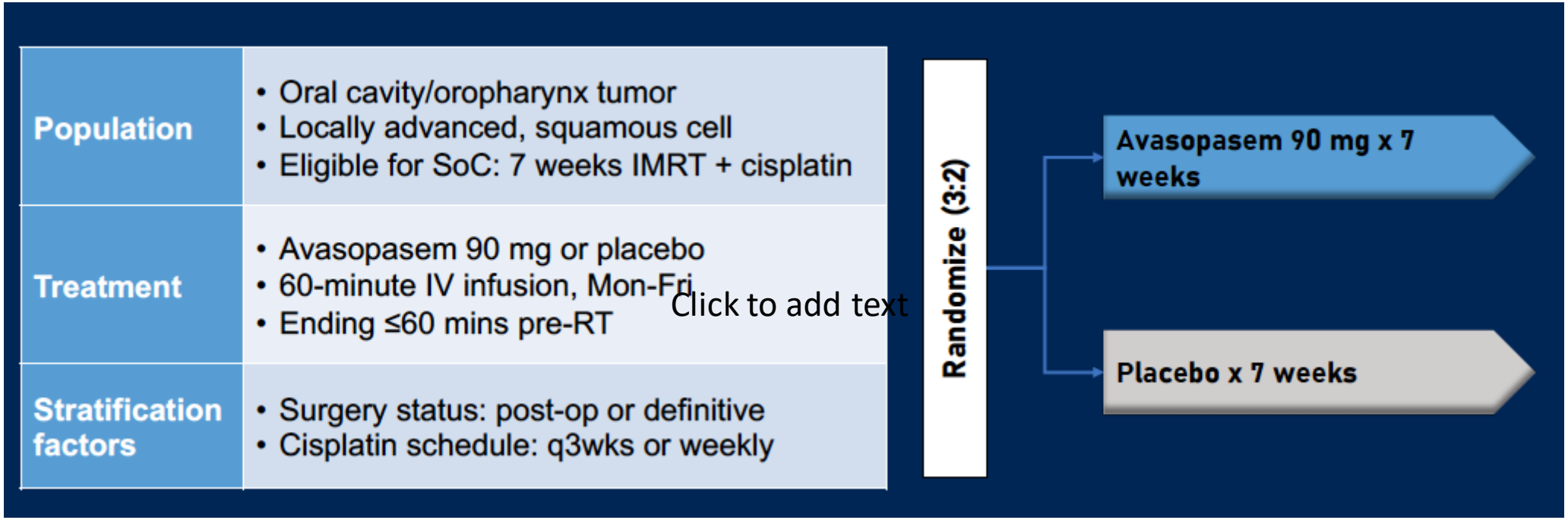
Abstract 6005:

ROMAN: Phase 3 trial of avasopasem manganese (GC4419) for severe oral mucositis (SOM) in patients receiving chemoradiotherapy (CRT) for locally advanced, nonmetastatic head and neck cancer (LAHNC).

- High grade mucositis toxicity occurs in most patients undergoing CCRT
- Aggressive supportive care is necessary
  - PEG, IV fluids, narcotics, hospitalization, treatment interruptions
- Avasopasem: dismutase mimetic with encouraging phase 2 data[1]

[1]*Anderson et al. J Clin Oncol. 2019 Dec*

Abstract 6005: Design



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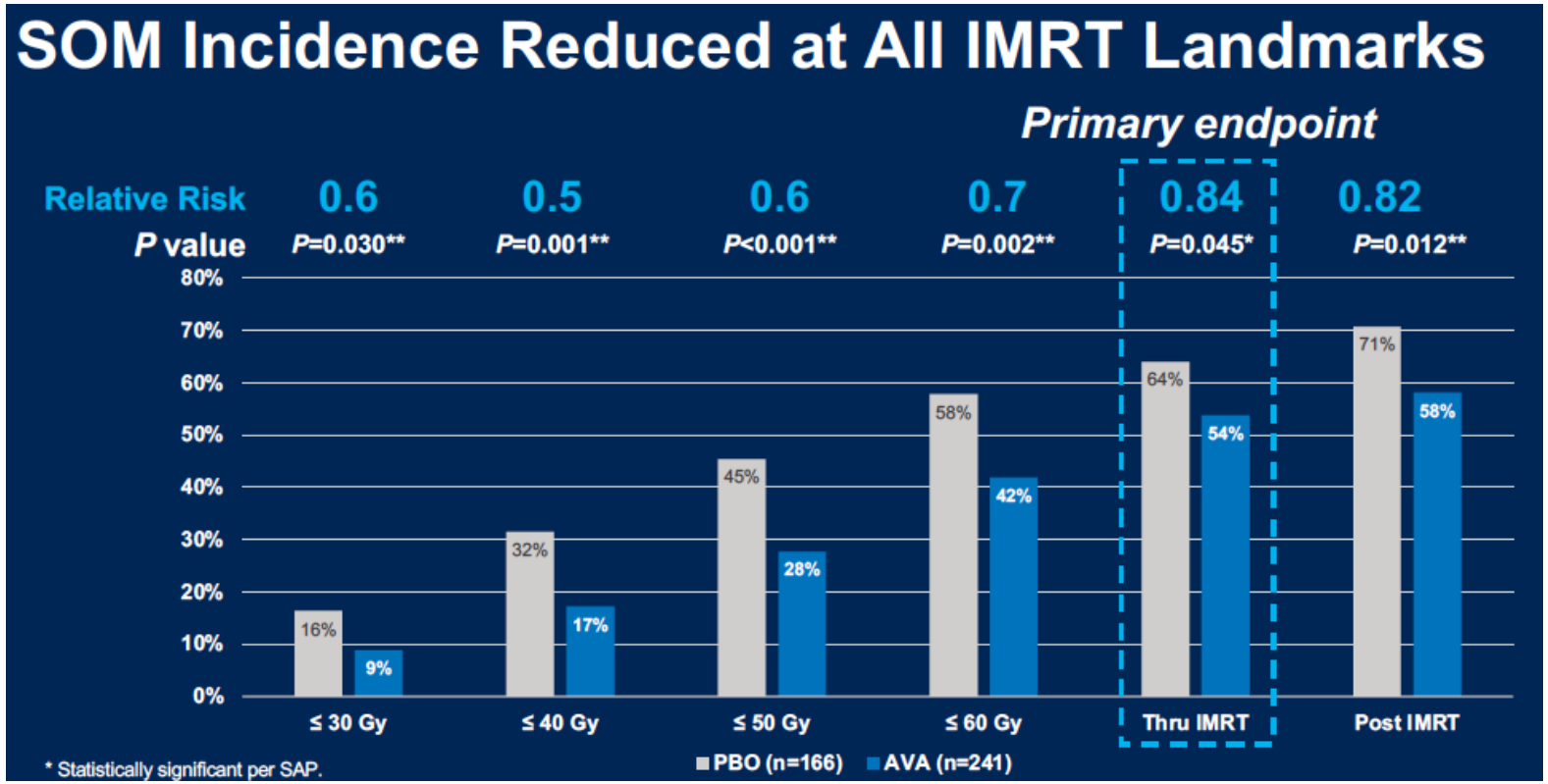
Primary endpoint: Incidence of SOM thru IMRT
Accrual goal : 455

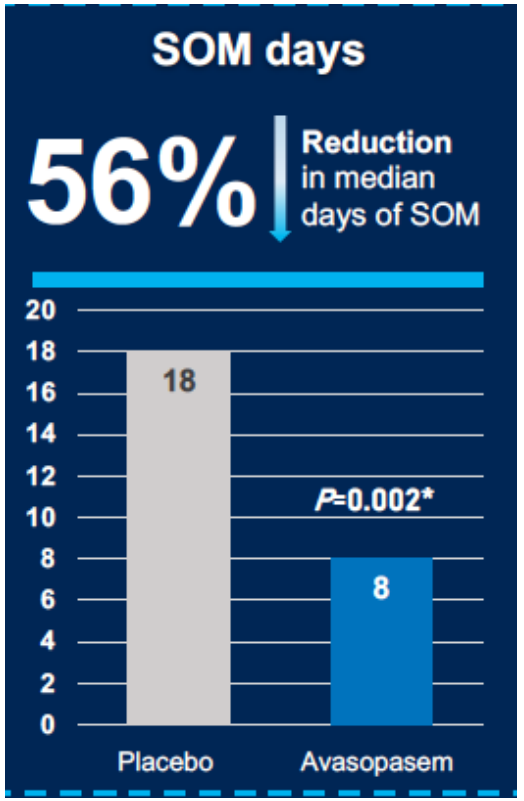
Abstract 6005: Results

- Patients
  - Most were p16+ OPC (80%)
  - Treated in definitive setting (80%)
  - Well balanced patient and treatment characteristics (including # of mucosal sites receiving >54Gy)

  - Approx 10% were randomized, but not treated or included ITT

Abstract 6005: Results

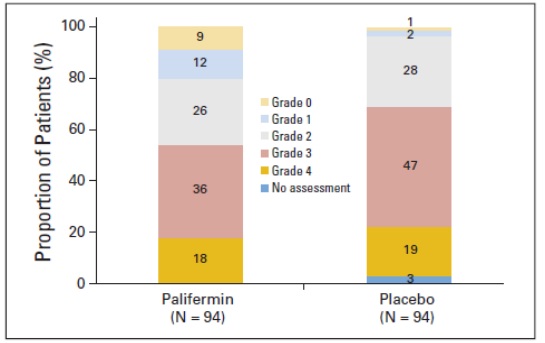


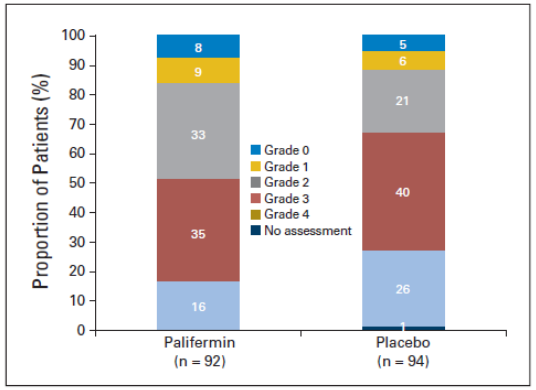


High grade toxicities similar
Any grade N/V higher with avasopasem

No approved agent for SOM in LAHNCC

- Palifermin (human recombinant keratinocyte GF)
  - Approved for heme malignancy pts undergoing SCT
  - Randomized studies in LAHNSCC for both definitive and adjuvant XRT[1,2]
  - Weekly dosing reduced SOM incidence and duration
  - No difference use of opioids, pain scores, treatment compliance, cancer outcomes





[1]*Le et al. J Clin Oncol July 2011*
[2]*Henke et al. J Clin Oncol July 2011*

Abstract 6005: Discussion

- This study addresses a key unmet need in LAHNSCC
- Clinical implications of primary endpoint?
- Dosing logistics; increased N/V; no data on therapeutic outcomes
- Endpoints relevant to patient care and outcomes needed

Metastatic head and neck cancer

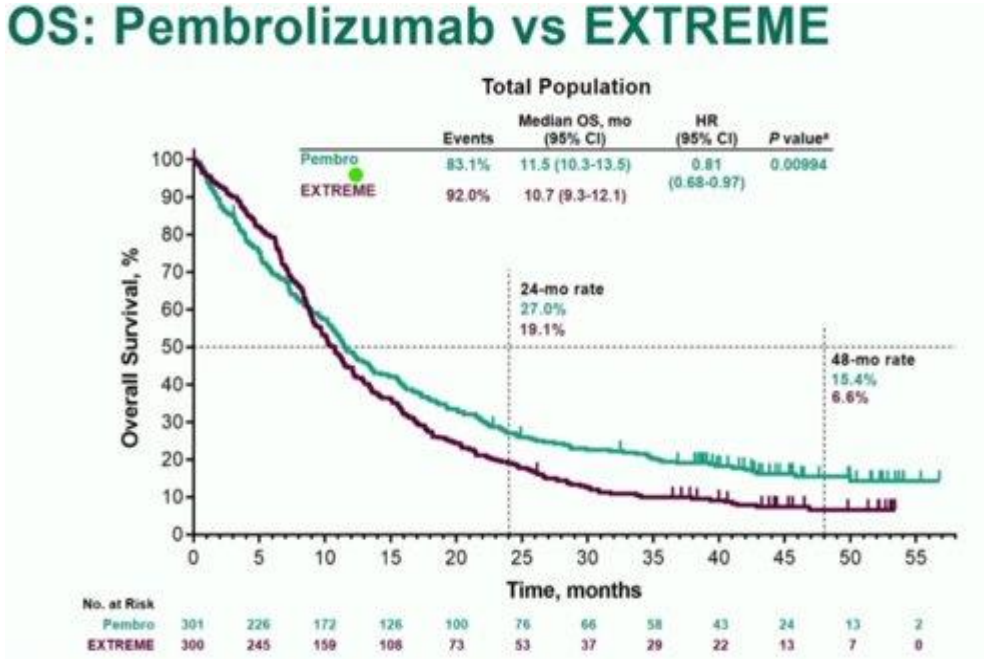
- Incurable disease with poor prognosis
- High symptom burden especially with local/regional recurrence
- Survival expectation is longer in HPV+ OPC
- Chemosensitive disease with multiple active agents
- Genomic instability/mutation status and viral mediation makes it ideal for immunotherapy approaches

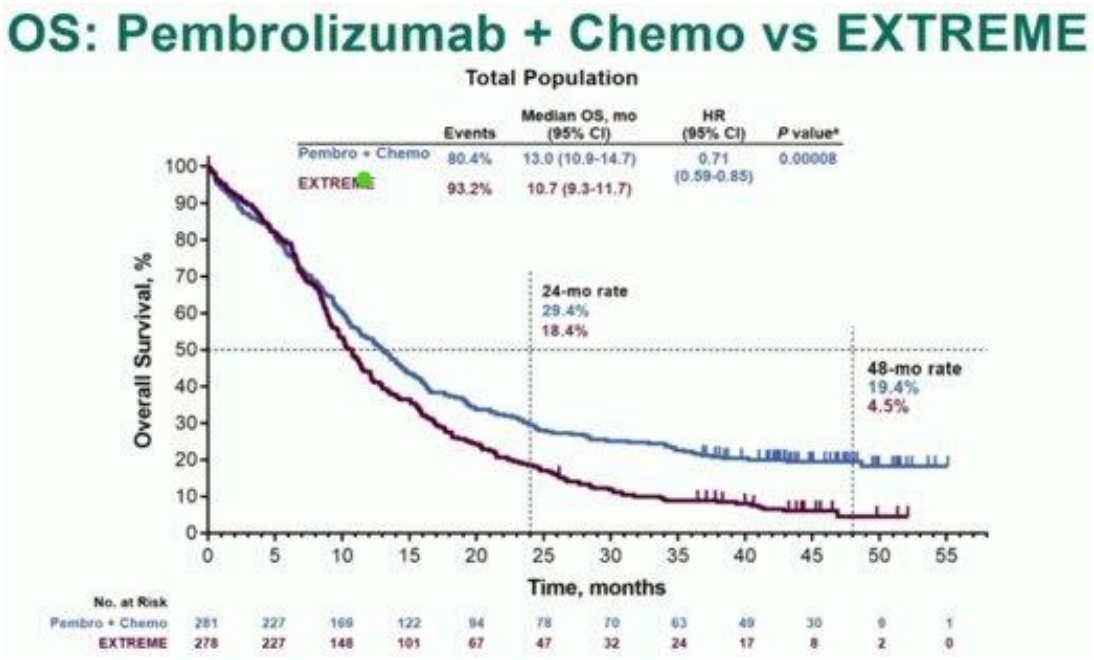
Immune checkpoint inhibitor indications in R/M HNSCC

Line of therapy (biomarker)	Drug or Regimen	Evidence
1st line (CPS >1)	Pembrolizumab monotherapy	[1]Keynote-48 Phase III trial
1st line (any CPS)	Pembrolizumab + platinum + 5FU	[1]Keynote-48 Phase III trial
2nd line post cisplatin	Nivolumab	[2]Checkmate 141 Phase III trial
2nd line post cisplatin	Pembrolizumab	[3]Keynote-40 Phase III trial

[1]Burtness et al. Lancet 2019 Nov 23; 394 (10212): 1915-1928.
[2]Ferris, et al. NEJM 2016 Nov 10;375(19):1856-1867
[3]Cohen et al. Lancet 2019 Jan 12;393(10167):156-167

Overall survival: Keynote-48





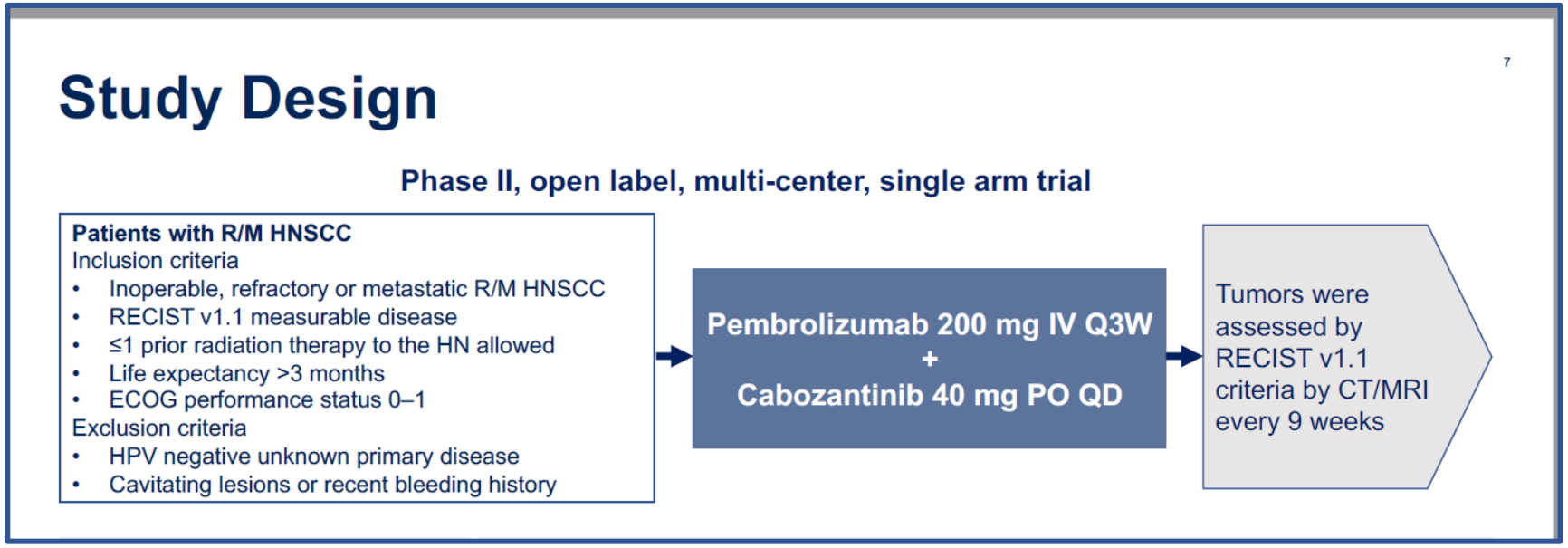
- Objective response rates from 20-35%, short DoR for chemoIO
- Grade ≥3 AEs high in chemoIO combinations

Abstracts 6008 and 6036

Key questions addressed by 2 studies:

- Can we improve response rates in first line immune checkpoint inhibition?
  - 6008
- What do we expect from systemic therapy in the post immune checkpoint inhibitor setting?
  - 6036

Abstract 6008



Primary objectives

- Determine the safety and tolerability of pembrolizumab + cabozantinib in this patient population
- Determine the objective response rate ORR per RECIST v1.1

Statistics

- ORR was tested based on the reported ORR for single-agent pembrolizumab of 18%
  - Estimated that ORR will improve to ≥35% with pembrolizumab + cabozantinib, yielding a type 1 error of 0.05 and a power of 80% when the true response rate is 35%
- For single-arm design with null hypothesis of ORR ≤15% vs one-sided alternative, 34 patients with evaluable responses are needed
- If the number of responses is ≤9 out of 34, the trial will be claimed as not promising

Abstract 6008

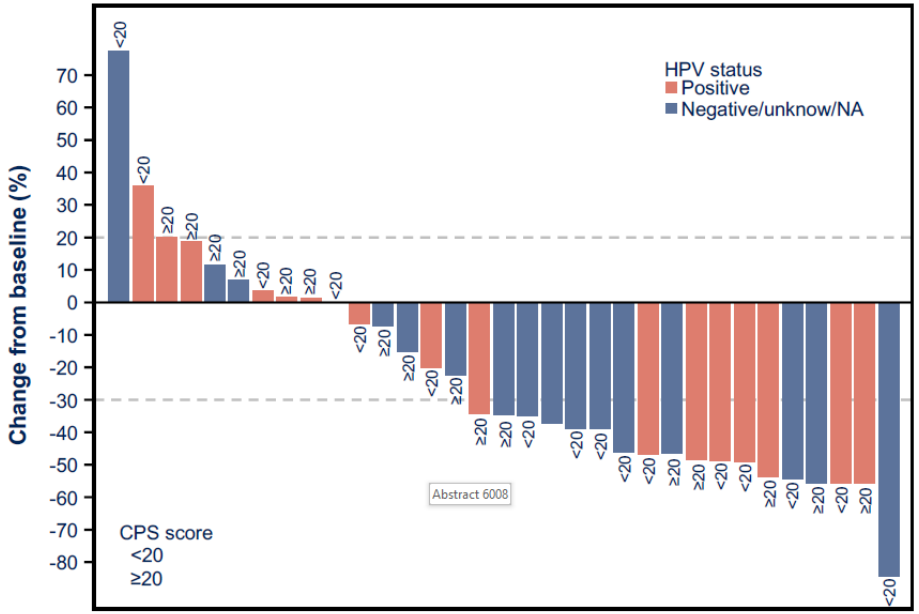
- 36 patients enrolled and treated
- 61% oropharynx cncer
- 50% CPS ≥20
- Fatigue most common AE (44%)
- 47% required cabozantinib dose reduction

Abstract 6008: Results

Best Overall Response in Evaluable Patients

15

	N=33 n (%)
ORR	18 (54)
CR	0 (0)
PR	18(54)
SD	12(36)
PD	3(9)
Clinical benefit	30(91)



CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease

Abstract 6008: Discussion

- Promising non-randomized data with combined VEGF and immune checkpoint inhibition
- Toxicities required TKI dose reduction
- In line with experience in other solid tumors (renal carcinoma), but awaits randomized comparison to immune checkpoint inhibitor alone

Abstract 6036

- Standard of care in post immune checkpoint inhibitor is undefined
- Retrospective study of R/M HNSCC in 7 French hospitals
- 99 patients included
  - 63 received taxane+cetuximab
  - 36 received taxane+platinum+cetuximab
- Oral cavity (35%) and oropharynx cancer (35%) most common primary sites

Abstract 6036: Results

- Overall response rate to post IO chemo 63%
- ORR for taxane+ cetuximab 57%
- ORR for taxane+platinum+cetuximab 69%

Abstract 6036: Discussion

- Taxane based combinations are efficacious in patients progressing on immune checkpoint inhibitors
- Represent active regimens for patients in need of systemic therapy in the second line palliative intent setting

THANK YOU!

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