2023 Updates on the Treatment of Head and Neck Cancer

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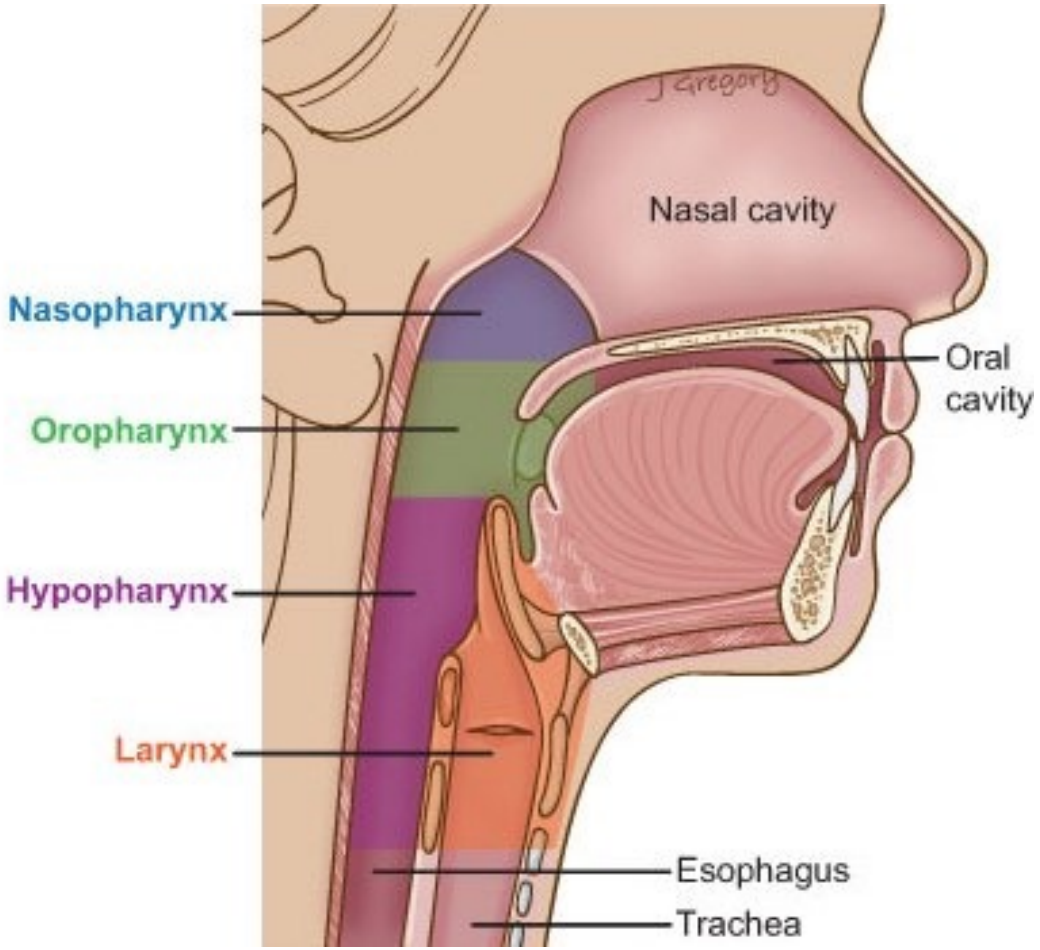
OUTLINE

- Introduction/Background
- Locally advanced head and neck cancer (LAHNSCC)
- Recurrent/metastatic head and neck cancer (RMHNSCC)

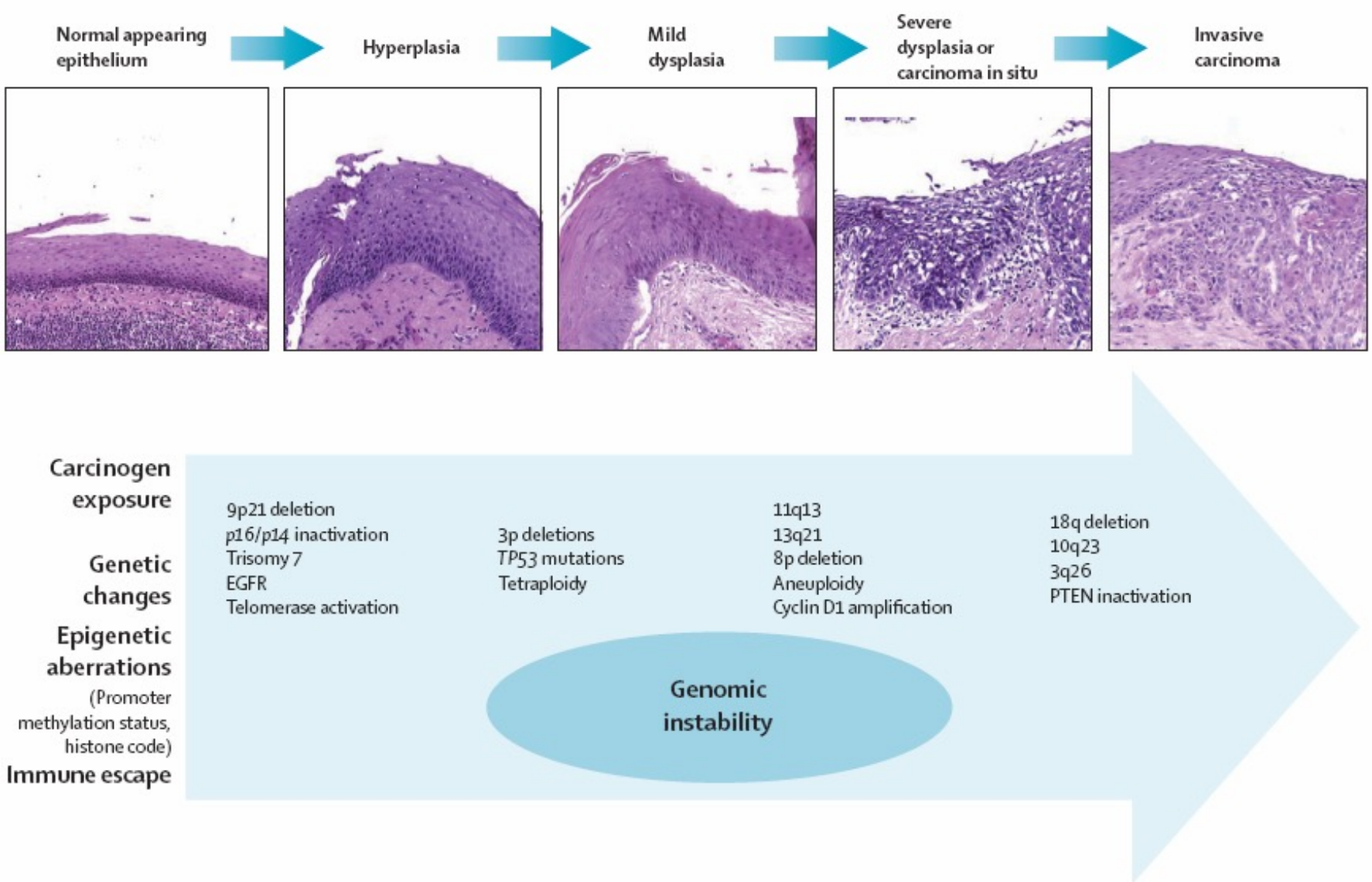
Epithelial malignancies of the head and neck



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

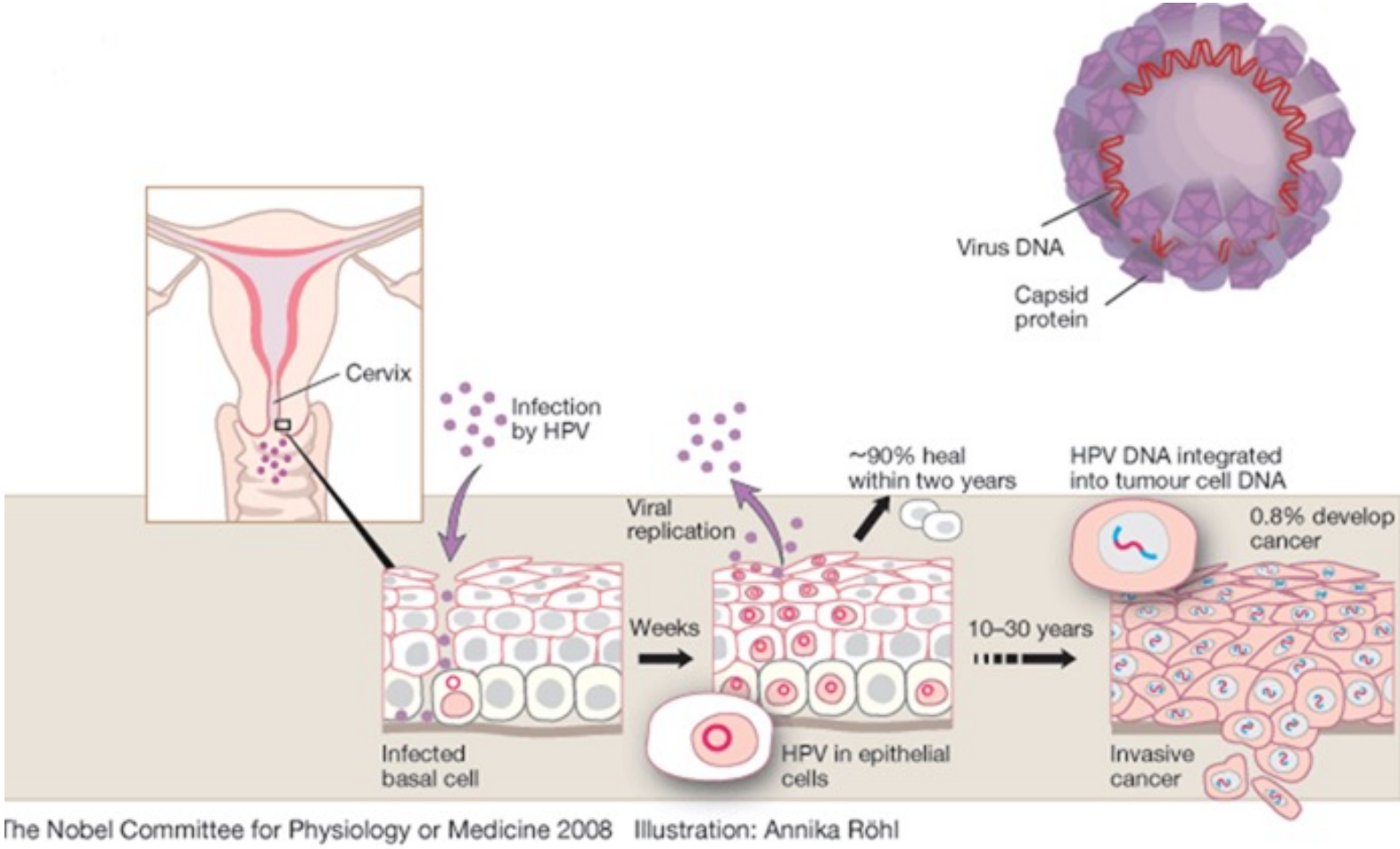
Pathogenesis

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**

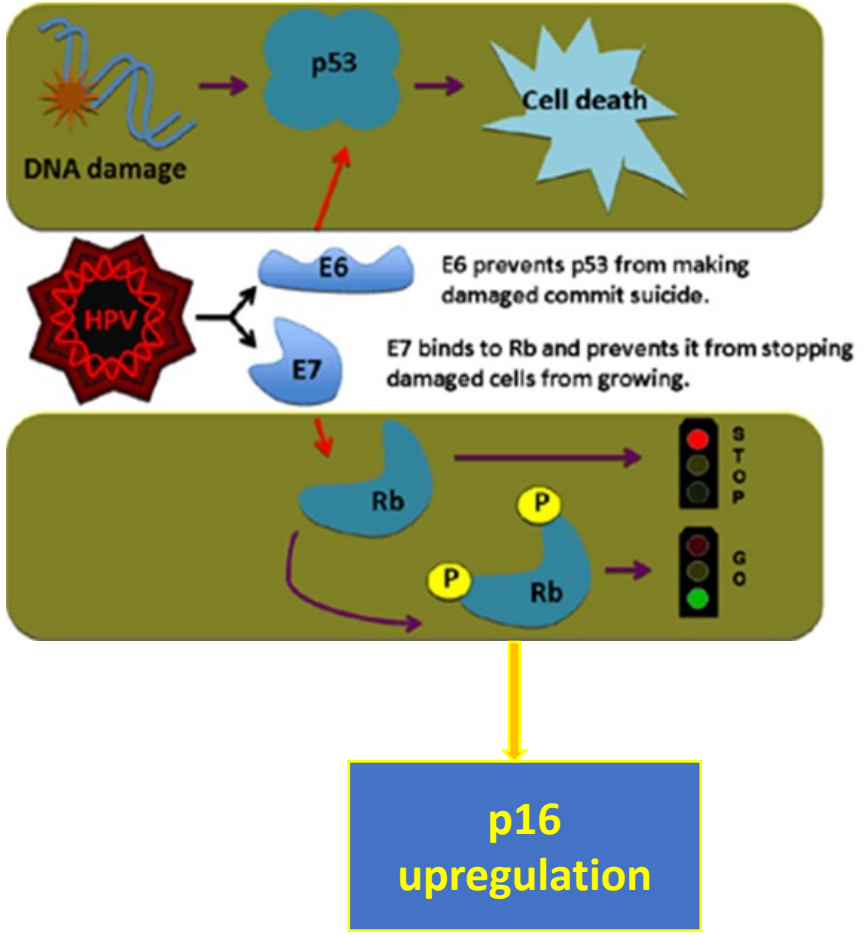


Argiris et al. Lancet. 2008 May 17;371(9625):1695-709.

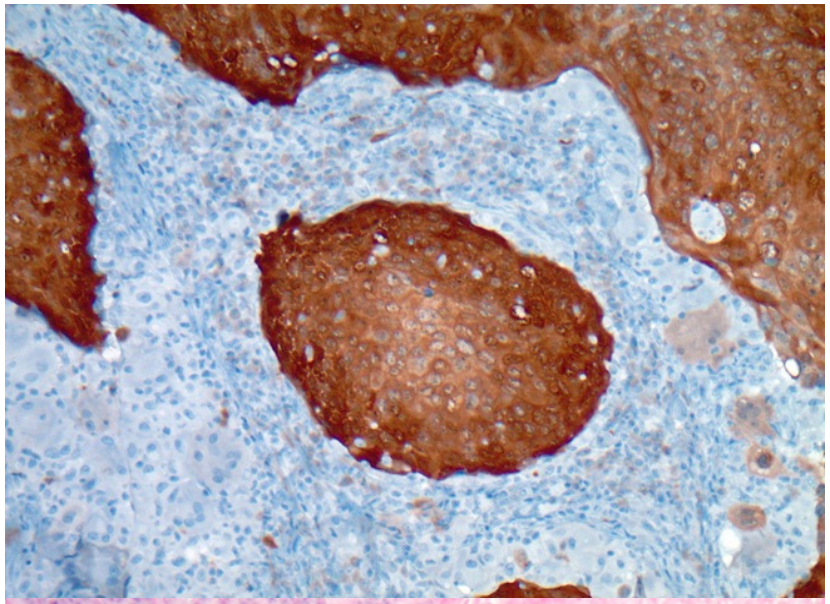
HPV+ oropharynx cancer: a distinct entity with a viral association

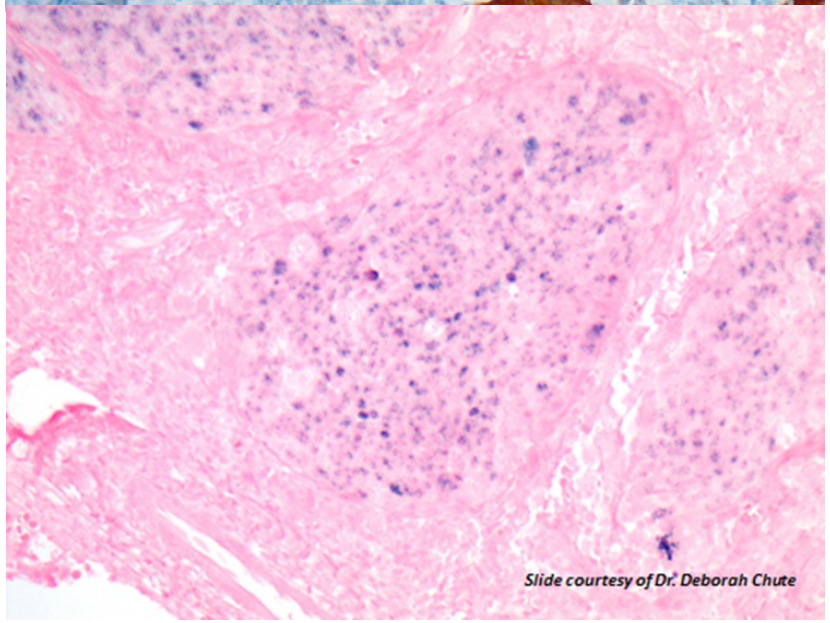


HPV+ **oropharynx** cancer: a distinct entity



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





Therapeutic goals in LAHNSCC

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

Systemic therapy in LAHNSCC: Definitive nonsurgical 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

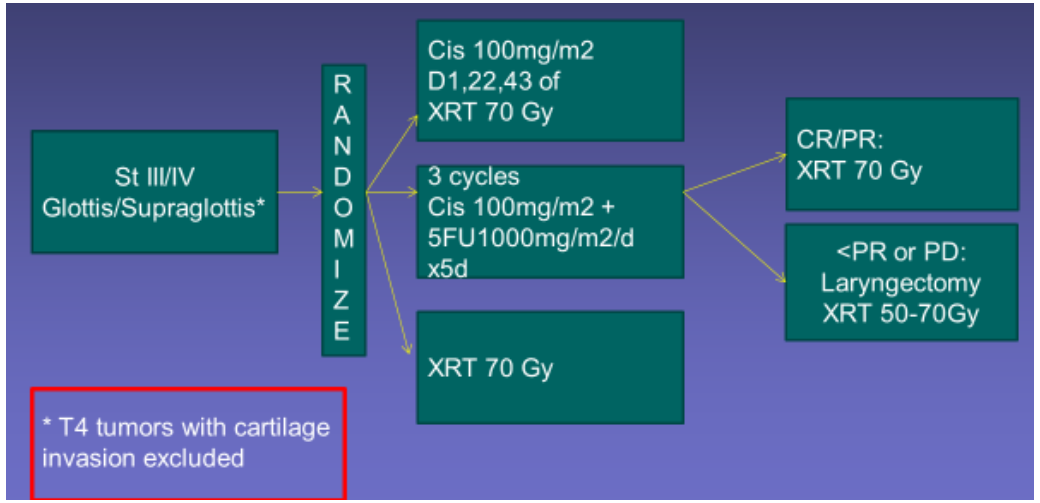
[1]Gillison et al. 2019 Jan 5;393(10166):40-50
[2]Mehanna et al. Lancet. 2019 Jan 5;393(10166):51-60
[3]Adelstein et al. J Clin Oncol, 2003; 21(1):92-8.
[4]Bonner JA. NEJM 2006:354:567-78.
[5]Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.

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



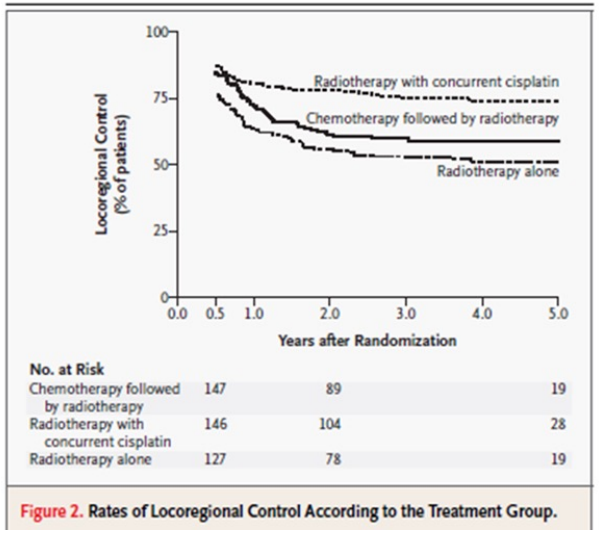


Figure 2. Rates of Locoregional Control According to the Treatment Group.

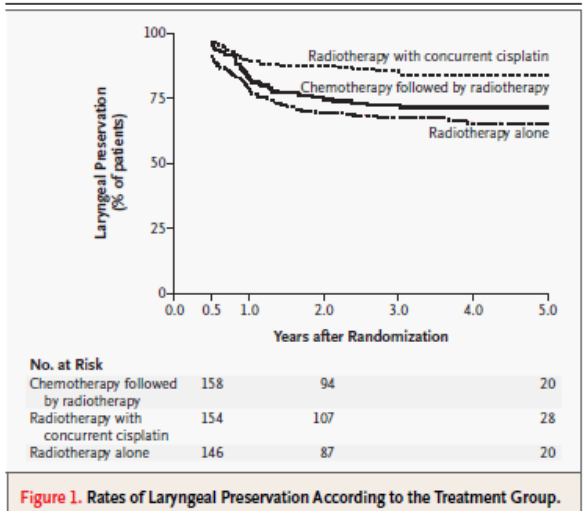


Figure 1. Rates of Laryngeal Preservation According to the Treatment Group.

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
- In high risk populations, oncologic outcomes are suboptimal

[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***

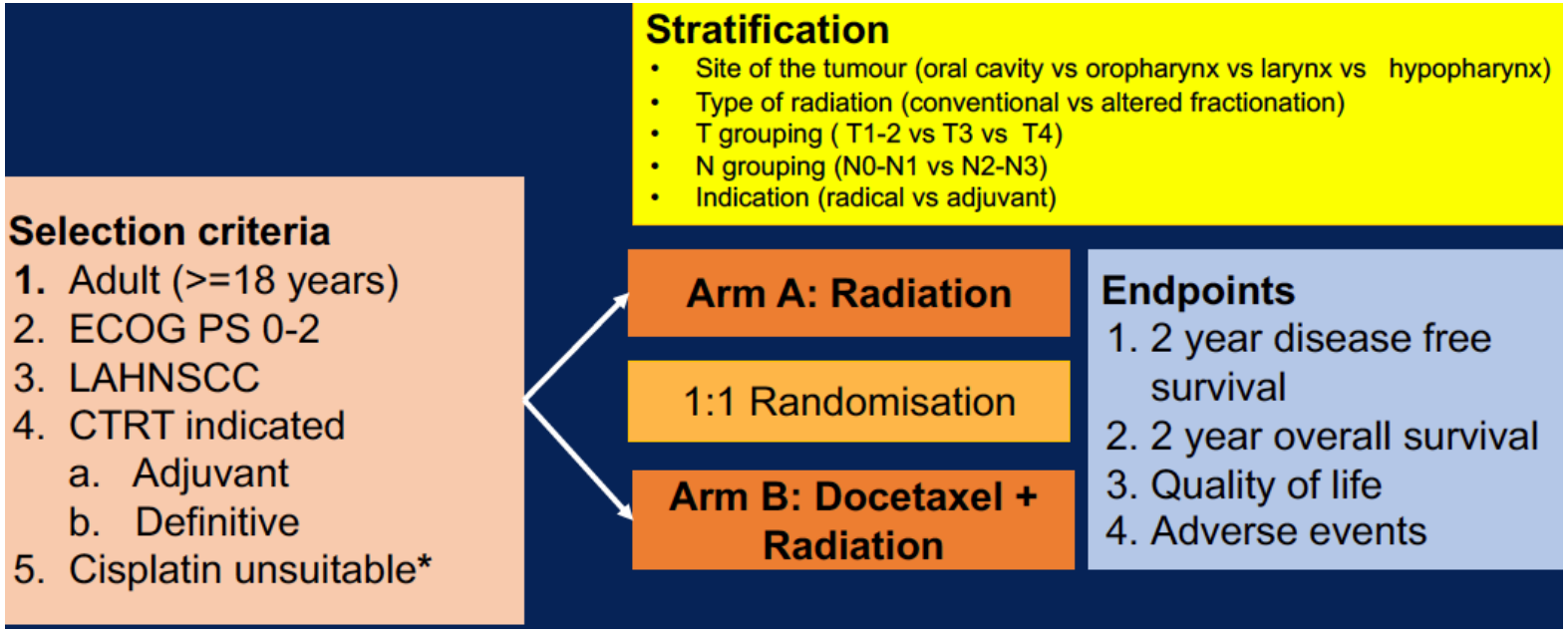
ASCO 2022 Abstracts 6003, 6004,
ASTRO 2022 LBA02
ESMO 2022 LBA5

Key questions addressed by these studies:

- Can we improve outcomes in patients who are cisplatin ineligible?
  - 6003
  - ASTRO LBA02
- Can we reduce toxicity without compromising efficacy in the platinum eligible patient?
  - 6004
- Can we improve outcomes with CCRT by adding immunotherapy?
  - ESMO LBA5

ASCO'22 Abstract 6003: Design

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

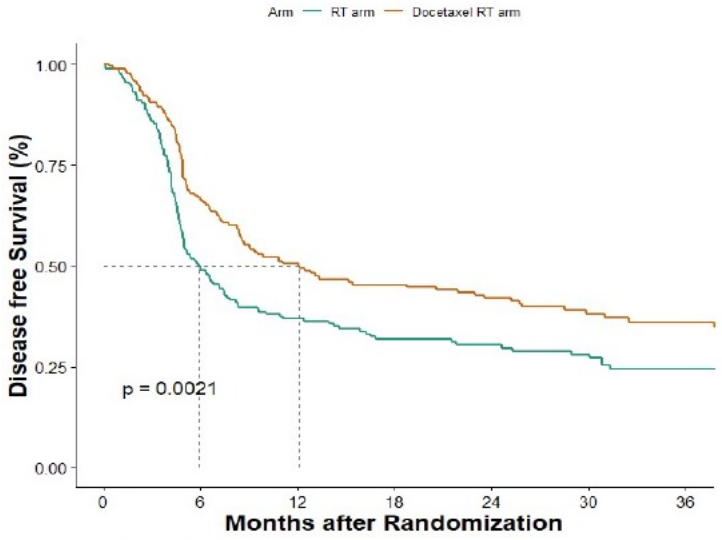
[1]*Ahn et al. Oral Oncol. 2016 Feb;53:10-6*

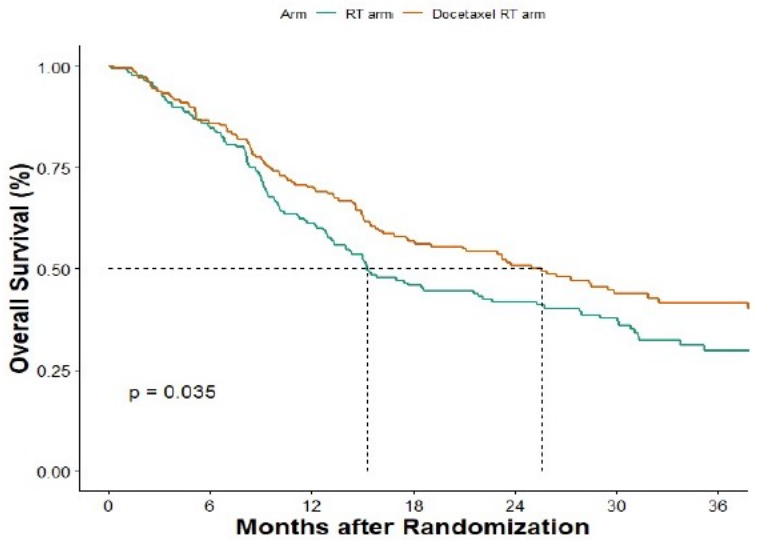
ASCO’22 Abstract 6003: Results

- 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

ASCO’22 Abstract 6003: Results

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





- Docetaxel XRT 2 year DFS: 42%, 2 year OS 50%
- Unplanned subset analysis appears to benefit all subgroups (HR most robust for definitive XRT)
- PRQOL at 6 mos post XRT favorable for docetaxel XRT

ASCO'22 Abstract 6003: Discussion

- The cisplatin ineligible pt 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	ASTRO LBA2 Discussed today

[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

- Trials not specific to platinum ineligible population
- Appropriate control arm for this group is unknown

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

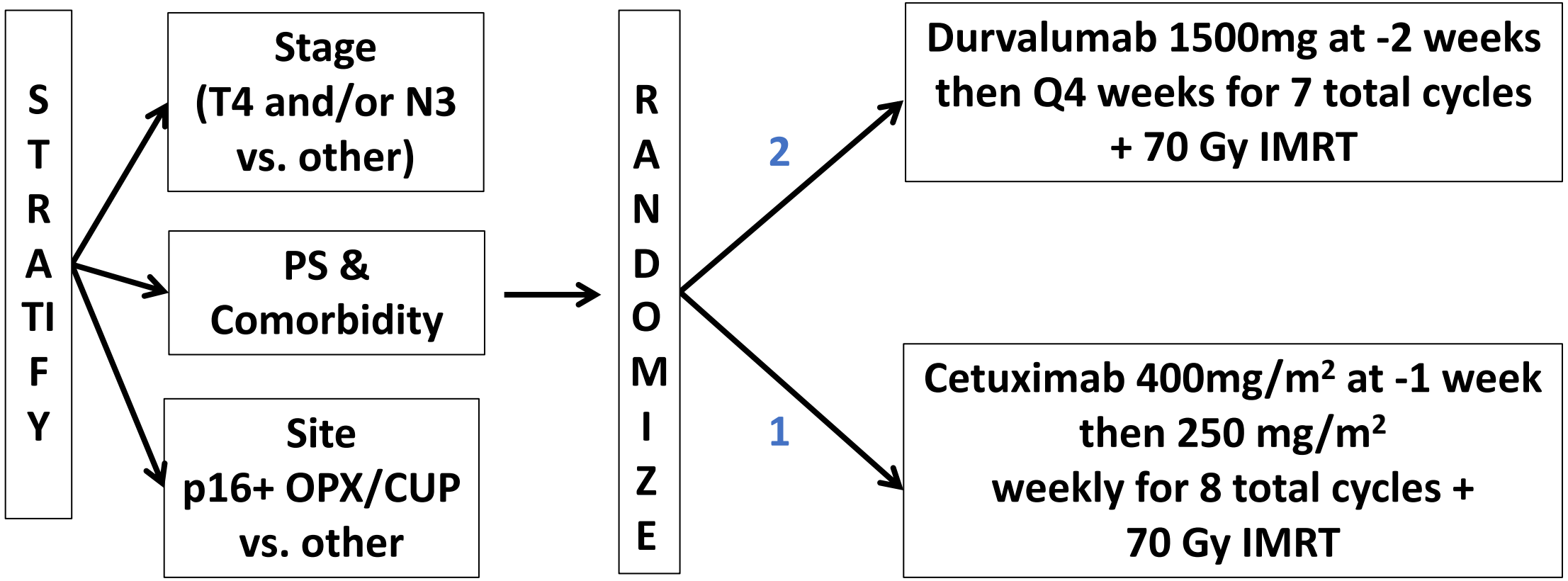
ASCO 2022 Abstract 6003: Discussion

- 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

ASTRO ’22 LBA02: Design



ASTRO ’22 LBA02: Design

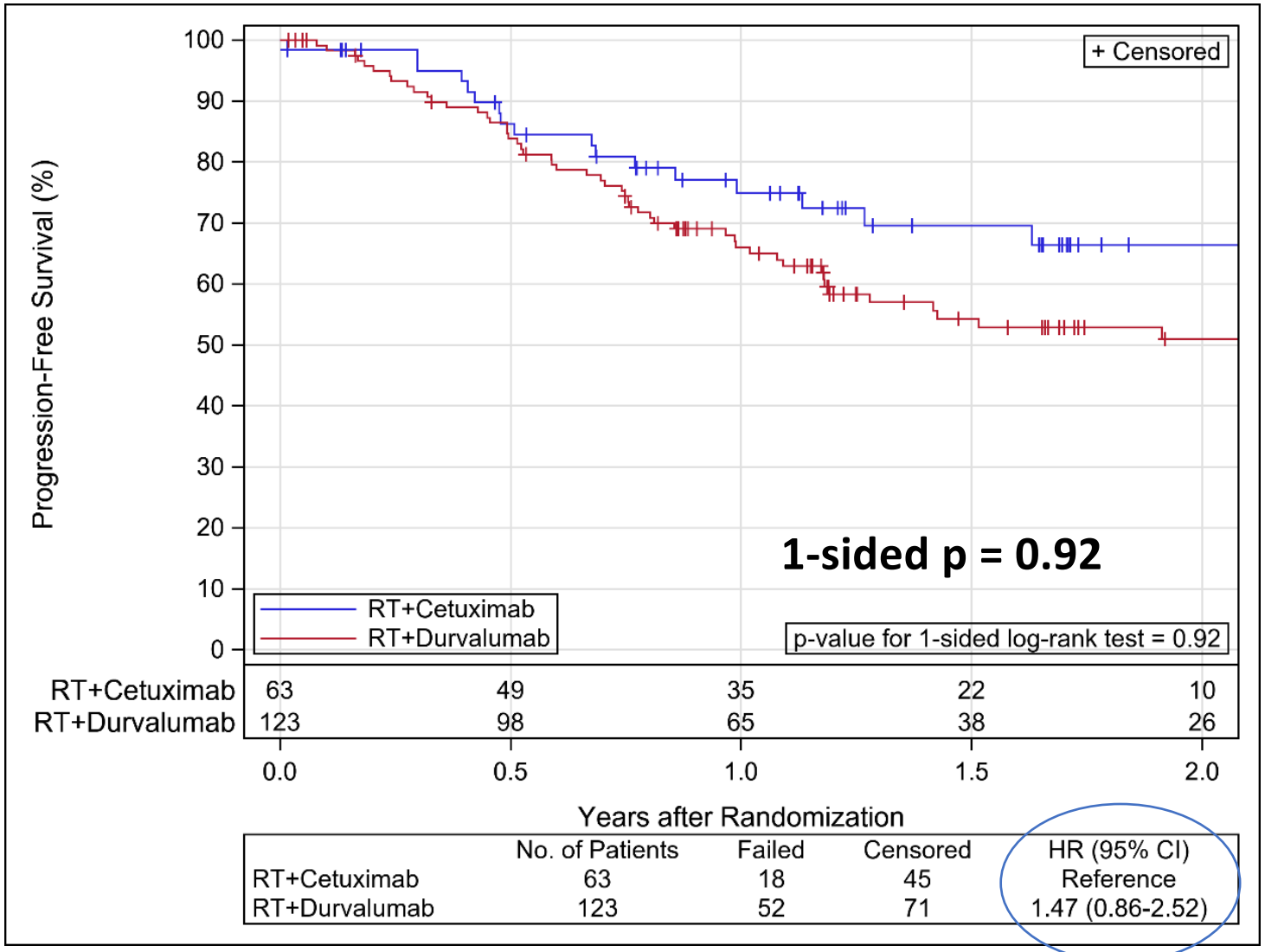
- **Design:** Phase II/III RCT with Safety Lead-In
- **Primary Endpoint & Sample Size**
  - Lead-In: Safety/Feasibility (N=10)
  - **Phase II: PFS (N=234; 69 events (35 for interim analysis))**
    - **80% Power; 1-sided α=0.20; “Go/No-Go” HR ≤ 0.806**
  - Phase III: OS (N=444)
- **Population**
  - Cisplatin-Ineligible, Age ≥ 18, Previously Untreated
  - Stage III-IVB SCC of larynx, HPX, OC, p16- OPX/CUP
  - Stage III or unfavorable risk stage p16+ OPX/CUP

ASTRO ’22 LBA02: Results

- **190 patients enrolled from Mar 2019-Jul 2021**
  - 186 randomized: 123 to durvalumab, 63 to cetuximab
- **Closed to accrual after interim futility analysis**
- **Key Sample Characteristics**
  - Median age was 72 years (59% $\geq$ 70).
  - 95% had $\geq$ 3 comorbidities (median 5)
  - 84% had absolute contraindication to cisplatin
  - 58% had T3-4, 49% had N2-3, 47% were p16+

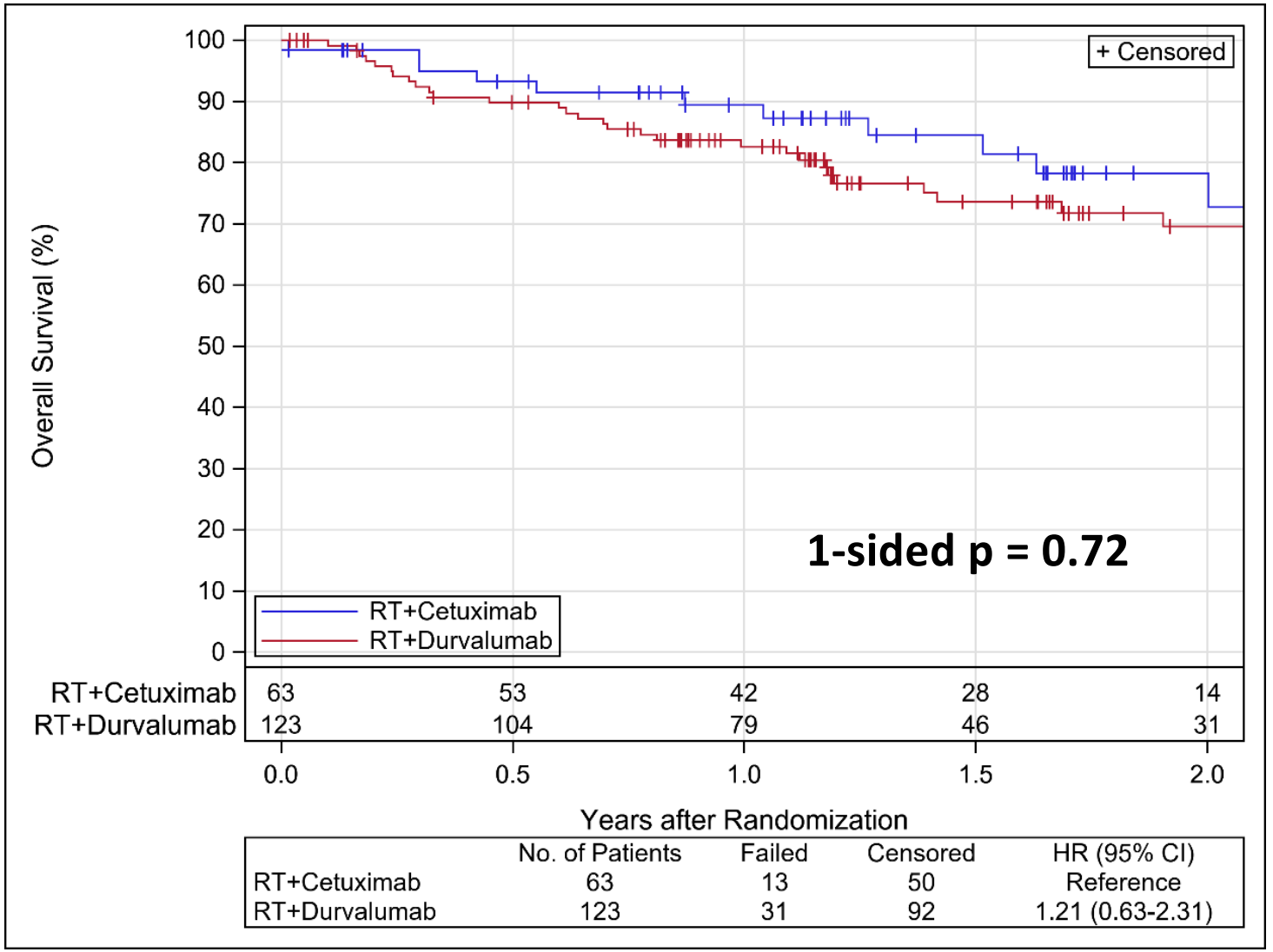
PFS by Treatment Arm

Phase II "Go/No-Go" Decision:
HR ≤ 0.806 to continue to phase III



2-yr rates:
Cetux: 66%
Durva: 51%

OS by Treatment Arm



2-yr rates:

Cetux: 78%

Durva: 70%

ASTRO ’22 LBA02: Discussion

- Immune checkpoint inhibition with definitive XRT does not confer PFS benefit in cisplatin ineligible cohort
- 2 yr PFS in control arm: 66%
- 2 yr OS in control arm: 78%
  - Higher than observed in docetaxel+XRT study
  - Population differences, p16+
  - Radiation technique differences, interruptions during COVID 19
- CetuxXRT may be appropriate control arm in subsequent studies

ASCO 2022 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

- 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

ASCO 2022 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

ASCO 2022 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

ASCO 2022 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

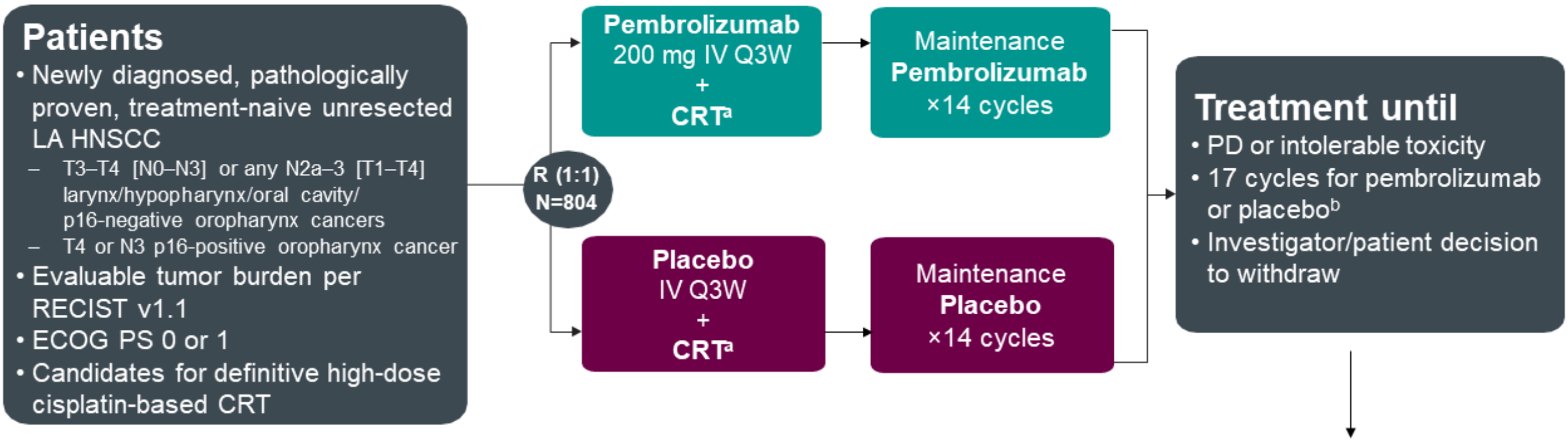
ESMO Abstract LBA5

- Immune checkpoint inhibitors have an established role in R/M HNSCC
- Incorporation into curative intent therapy under active investigation

Trial	Treatment Population	N	Intervention
KEYNOTE-412[1]	LAHNSCC (HPV+ for select stages/primary sites)	780	Pembro + cis + RT vs. placebo + cis + RT
IMSTAR-HN[2]	Stage III/IV p16- OPC, L, HP, OC	276	Neoadjuvant nivo, surgery, and adj chemoRT + adj nivo ± ipi vs SOC surgery + chemoRT
KEYNOTE-689[3]	Resectable stage III/IVa L, HP, OC, p16-OPC Stage III p16+ OPC	600	Pembro prior to surgery/with adj chemoRT vs surgery
IMvoke010[4]	LAHNSCC treated with curative-intent therapy	400	Atezo vs placebo after chemoRT
KEYCHAIN5	LAHNSCC p16+ OPC, L, OC	114	Cis + RT vs pembro + RT
HN005[6]	Locally advanced good risk p16+ OPC	711	Cis 70GyRT vs Cis 60GyRT vs Nivo 60GyRT
EA3161[7]	High risk p16+ OPC treated with cisXRT	744	Adjuvant nivolumab vs observation

1. NCT03040999, 2. NCT03700905, 3. NCT03765918, 4. NCT03452137, 5. NCT03383094, 6. NCT03952585, 7. NCT03811015

KEYNOTE-412 Study Design (NCT03040999)



Stratification Factors
- Radiotherapy regimen (AFX vs SFX)
- Tumor site/p16 status (oropharynx [p16+ vs p16-] or larynx/hypopharynx/oral cavity)
- Disease stage (III vs IV)

Primary endpoint
- Event-free survival (EFS)

Secondary endpoints included:
- OS
- Safety/tolerability

Efficacy boundary
- EFS: one-sided $P = 0.0242$
- OS: not tested

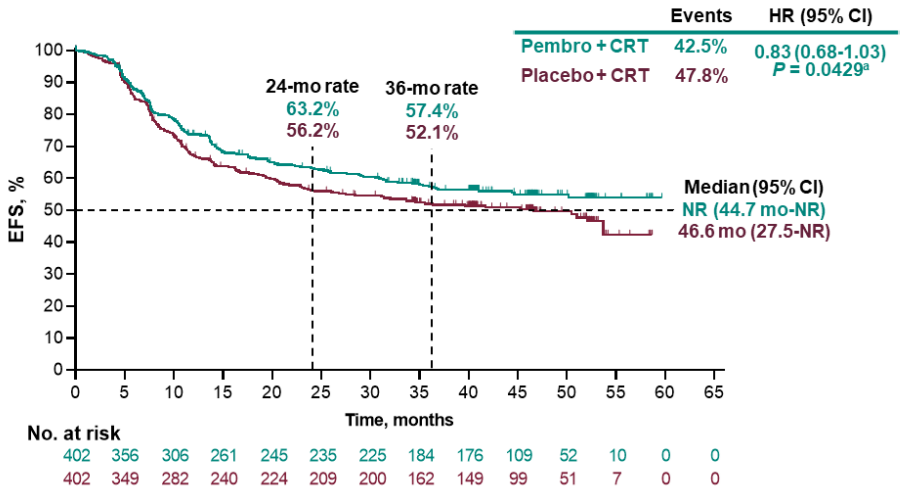
Post-treatment follow-up to assess
- Safety
- Disease status
- Survival

ESMO Abstract LBA5: Results

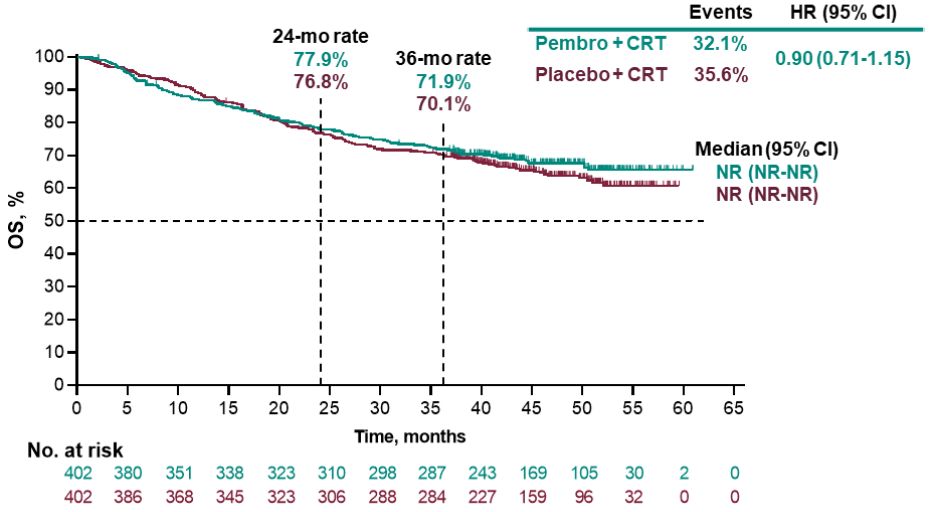
n (%)	Pembro + CRT N = 402	Placebo + CRT N = 402
Age, median (range), years	59.0 (27-81)	59.0 (36-79)
≥65 years, n (%)	109 (27.1)	96 (23.9)
Male	331 (82.3)	329 (81.8)
Race, white	311 (77.4)	311 (77.4)
Region		
North America	43 (10.7)	43 (10.7)
Western Europe	198 (49.3)	182 (45.3)
Rest of the world	161 (40.0)	177 (44.0)
PD-L1 CPS ≥1	339 (84.3)	346 (86.1)
PD-L1 CPS ≥20	146 (36.3)	145 (36.1)
ECOG PS 1	137 (34.1)	151 (37.6)
Primary tumor site		
Oropharynx	200 (49.8)	204 (50.7)
Oral cavity	39 (9.7)	39 (9.7)
Larynx	92 (22.9)	86 (21.4)
Hypopharynx	71 (17.7)	73 (18.2)
HPV+	109 (27.1)	104 (25.9)
Former/current smoker	346 (86.1)	346 (86.1)

ESMO Abstract LBA5: Results

Event-Free Survival, ITT Population



Overall Survival, ITT Population

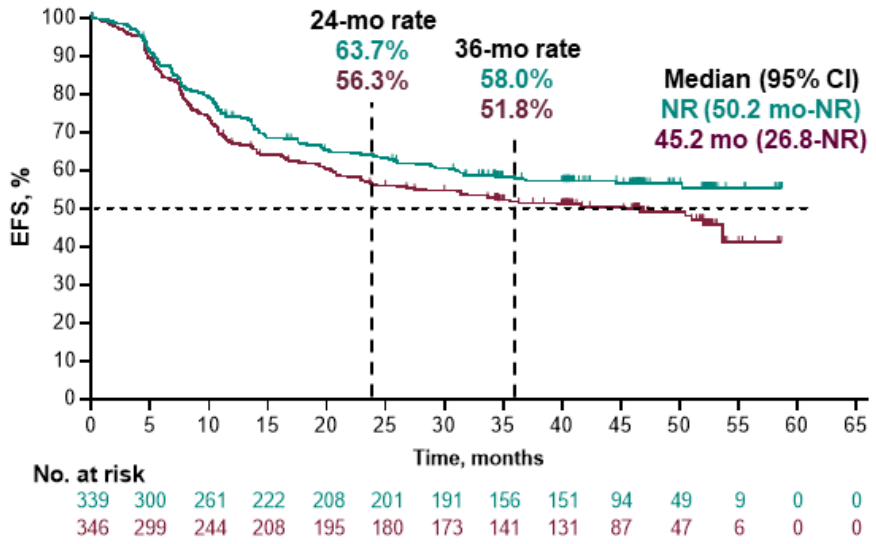


ESMO Abstract LBA5: Results

EFS and OS in Patients With PD-L1 CPS ≥1 (Prespecified Subgroup Analysis)

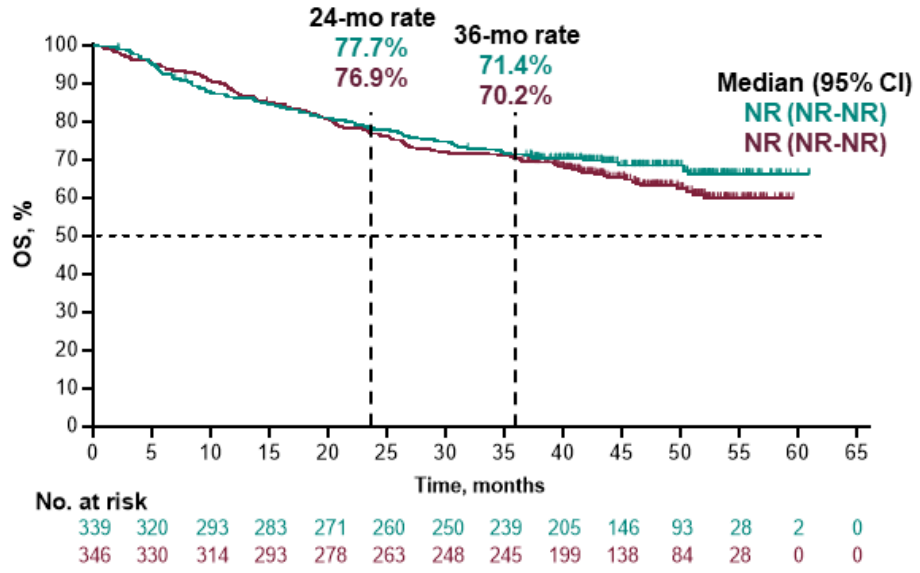
EFS

	Events	HR (95% CI)
Pembro + CRT	41.6%	0.80 (0.64-1.00)
Placebo + CRT	48.6%	



OS

	Events	HR (95% CI)
Pembro + CRT	31.6%	0.88 (0.68-1.14)
Placebo + CRT	36.1%	

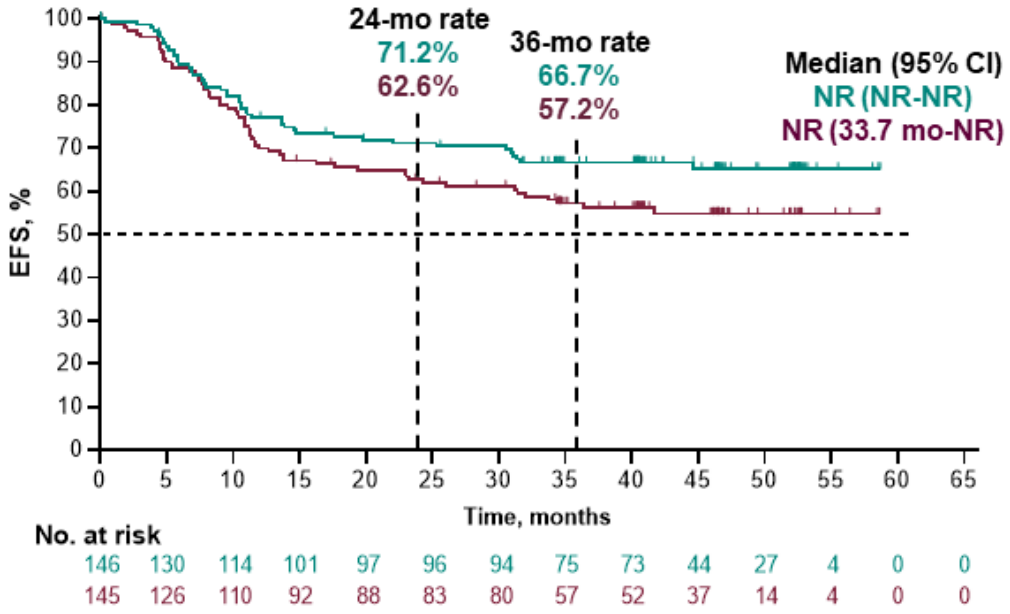


ESMO Abstract LBA5: Results

EFS and OS in Patients With PD-L1 CPS ≥20 (Post Hoc Analysis)

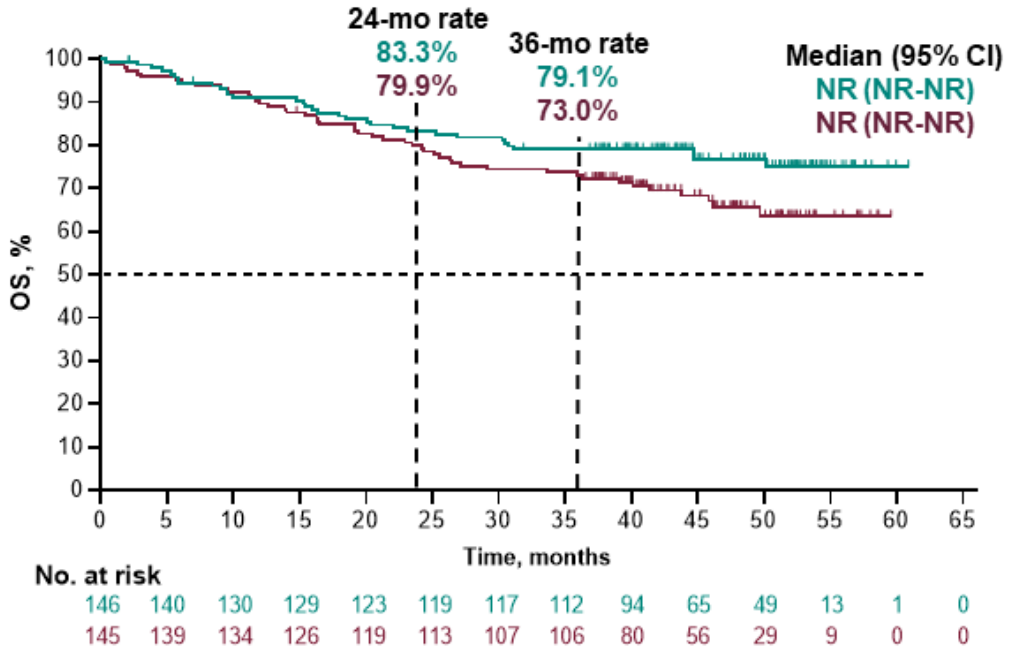
EFS

	Events	HR (95% CI)
Pembro + CRT	32.2%	0.73 (0.49-1.06)
Placebo + CRT	42.1%	



OS

	Events	HR (95% CI)
Pembro + CRT	22.6%	0.67 (0.43-1.04)
Placebo + CRT	32.4%	



ESMO Abstract LBA5: Discussion

- Consistent with 2 other randomized trials
  - JAVELIN HN001 (atezolizumab)
  - GORTEC-REACH (cisplatin eligible cohort, avelumab)
- Concurrent PD1 or PDL1 with q3 week cisplatin has no impact on outcome
- Timing or cisplatin dosing may be a factor
  - EA3161
  - RTOG 1216
  - HN005

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

ASCO 2022 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

ASCO 2022 Abstract 6036: Results

- Overall response rate to post IO chemo 63%
- ORR for taxane+ cetuximab 57%
- ORR for taxane+platinum+cetuximab 69%
  - Published pre-IO era ORR of combination is 48%[1]

[1]*Guigay et al. Lancet Oncol 2022 Vol. 22 (4) p463-475*

ASCO 2022 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

FHCC Head and Neck R/M Studies

Trial	Design Investigational Agent	Population/Line of therapy
OPEN AND ENROLLING		
RG1005866	Phase I/II CUE101: novel fusion protein to E7 CUE 101 with pembrolizumab	1st line R/M p16+ OPC
RG1122874	Phase I/II ONC-392 novel antiCTLA 4 agent Arm K2 (ONC-392 monotherapy) ARM D (ONC-392 + pembro)	1st line R/M HN, all squamous and nonadenoid cystic IO naïve NSCLC TPS ≥1%
RG1122942	Phase I/II Tisotumab vedotin (TF directed ADC) Part C: HN and lung squamous cell CA	2nd/3rd/4th line RM, cis and prior pembro required (looser language for lung)
RG1121396	Phase II Brentuximab vedotin + Pembro Cohort 6: HN	1st line, CPS ≥1
IN STARTUP		
Adagene NCT05405595	Phase I/II ADG126 novel antiCLTA4 Monotherapy In combination with pembro	HNSCC IO naïve and IO exposed

Trial	Design Investigational Agent	Population/Line of therapy
OPEN AND ENROLLING IN OTHER GROUPS		
RG1006384	Phase I/II Anti Integrin + Pembro	1st line R/M HNSCC
RG1121520	Phase I/II Oral CC4 agonist + Pembro	1st line p16+ OPC and endemic NPC
RG1121319	Phase I ICT-01 (γ9δ2 T Cell-activating mAb) + Pembro	Previously IO treated HNSCC Needs screening for γδ T cells
RG1006339	Phase I CYT-0851-01 with gemcitabine	HNSCC pretreated WAITLIST only
RG1122132	Phase I STAT 3 degrader	Any line of therapy, HN cancer preferred non squamous ok
NONTHERAPEUTIC STUDIES		
RG1007831	R01 Benaroya blood collection study	

The Head and Neck Oncology Program










THANK YOU!

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