ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancers

Alain Algazi, MD

University of California San Francisco

AMERICAN ACADEMY OF EMERGENCY MEDICINE

ACCC
Association of Community Cancer Centers

sitc
Society for Immunotherapy of Cancer

Disclosures

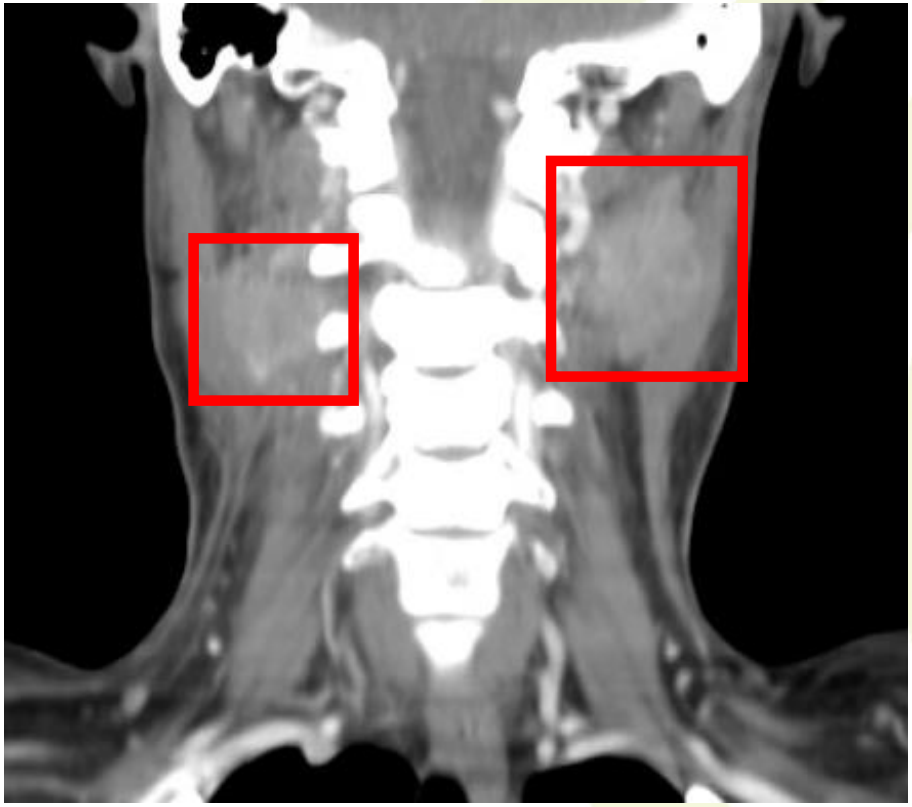
I serve as an investigator for trials funded by –

- Acerta
- AstraZeneca
- Bristol-Myers-Squibb
- Celgene
- Celldex
- Medimmune
- Merck
- Novartis
- OncoSec
- Plexxicon
- Tessa

I serve as an advisor for –

- Nektar
- OncoSec

Case 1



51 year old woman with NPC

18 months prior in China

- Neoadjuvant carbo/5FU
- 30 Fractions ChemoXRT

6 mos after treatment

- p/w FDG avid LAD

Lost to f/u for 12 months

Presentation to UCSF

- 2.4 cm R neck mass
- 3.6 cm L neck mass adj ICA
- Biopsy with recurrent NPC

Case 2 – Treatment – Please Vote!

A. Chemoradiation

B. Induction chemotherapy then radiation

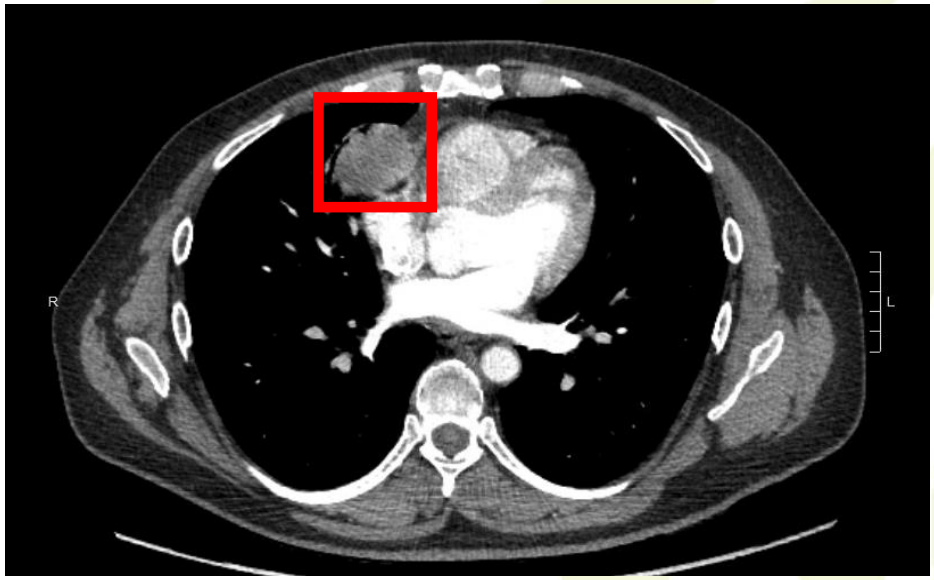
C. Surgery

D. Chemotherapy

E. Pembrolizumab or nivolumab

F. Ipilimumab and nivolumab

Case 2



51 year old man with p16+ OPC

8 months prior in Canada

- Definitive ChemoXRT
- Distant metastases within 6 mos

Presentation to UCSF

- Mediastinal LAD
- Bilateral lung nodules

Case 2 – Treatment – Please Vote!

A. Chemoradiation

B. Induction chemotherapy then radiation

C. Surgery

D. Chemotherapy

E. Pembrolizumab or nivolumab

F. Ipilimumab and nivolumab

Head and Neck Cancers

Nasopharynx
NPC (EBV)

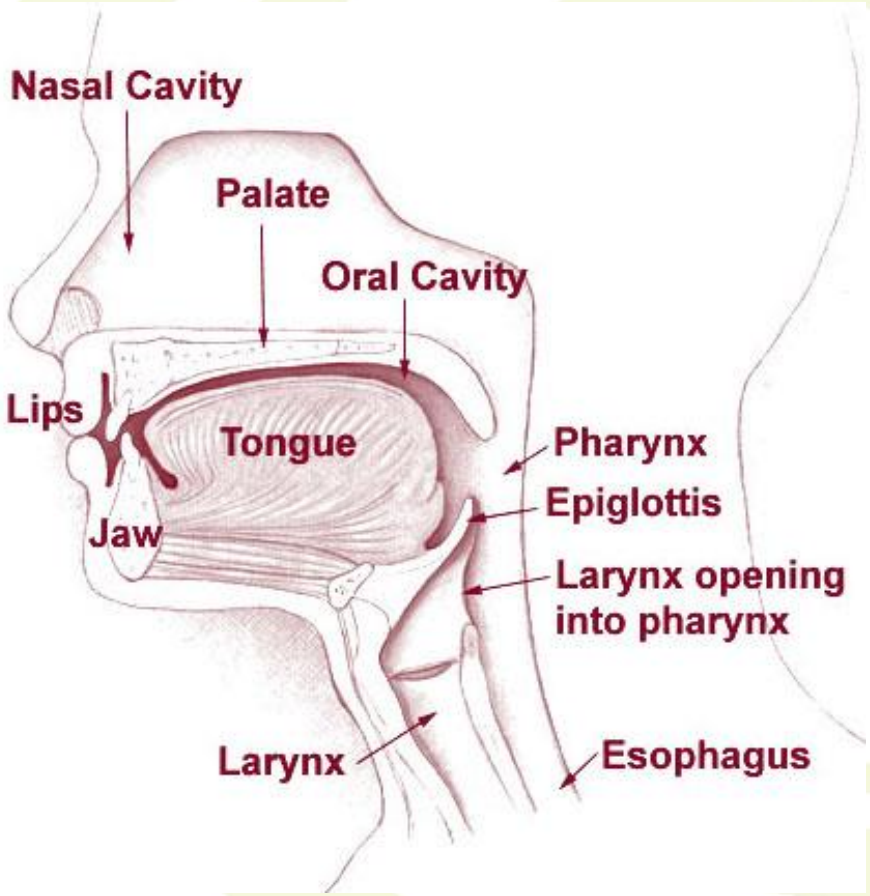
Oropharynx
SCC (HPV)

SCC (non-HPV)

Oral cavity
SCC

Hypopharynx
SCC

Larynx
SCC



Sinus
Squamous cell
Esthesioneuroblastoma
SNUC
SNEC
Melanoma

Salivary
Adenocarcinoma
Mucoepidermoid
Adenocystic
Salivary duct

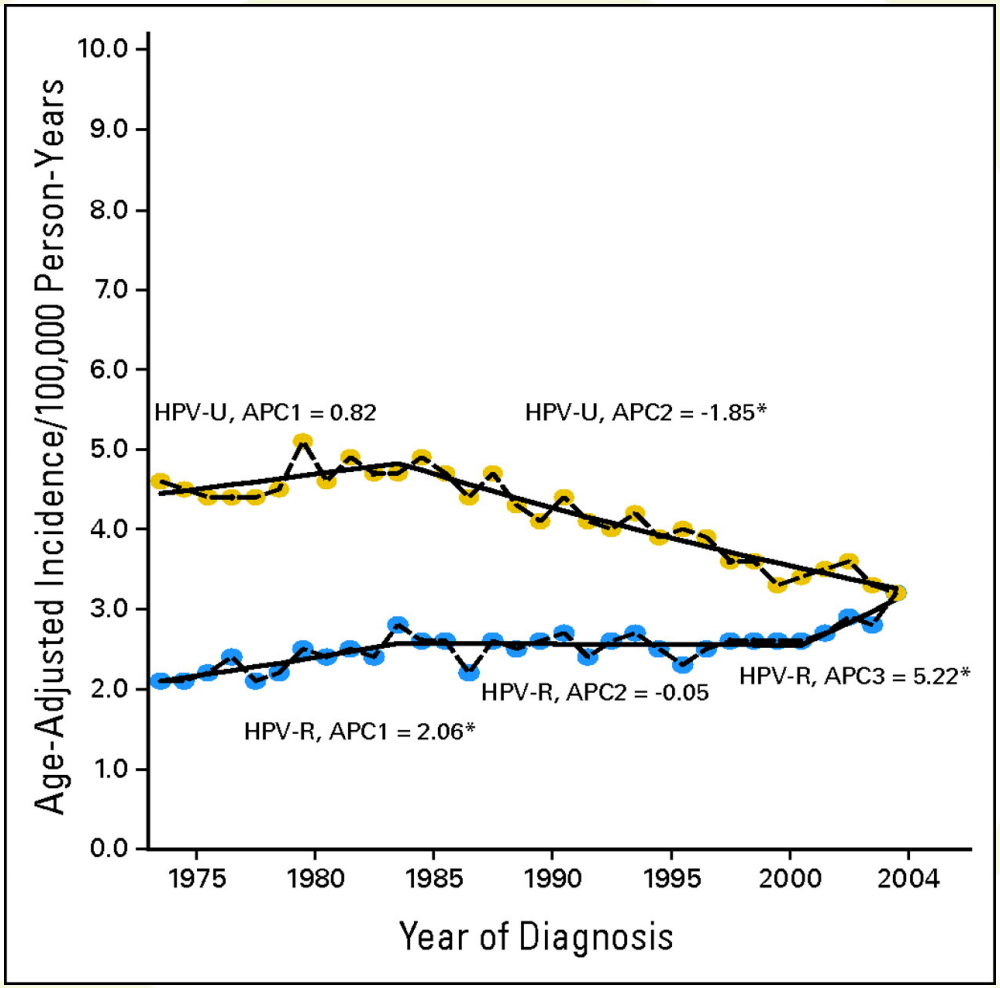
Skin
Basal cell
Squamous cell
Melanoma
Merkel cell

Thyroid
Papillary
Follicular
Medullary
Anaplastic
Castle Carcinoma

HNSCC Incidence and HPV

Estimated New Cases*

	Male	Female
	Prostate 217,730 (28%)	Breast 207,090 (28%)
	Lung & bronchus 116,750 (15%)	Lung & bronchus 105,770 (14%)
	Colon & rectum 72,090 (9%)	Colon & rectum 70,480 (10%)
	Urinary bladder 52,760 (7%)	Uterine corpus 43,470 (6%)
	Melanoma of the skin 38,870 (5%)	Thyroid 33,930 (5%)
	Non-Hodgkin lymphoma 35,380 (4%)	Non-Hodgkin lymphoma 30,160 (4%)
	Kidney & renal pelvis 35,370 (4%)	Melanoma of the skin 29,260 (4%)
#8	Oral cavity & pharynx 25,420 (3%)	Kidney & renal pelvis 22,870 (3%)
	Leukemia 24,690 (3%)	Ovary 21,880 (3%)
	Pancreas 21,370 (3%)	Pancreas 21,770 (3%)
	All sites 789,620 (100%)	All sites 739,940 (100%)



Treating Head and Neck Cancer

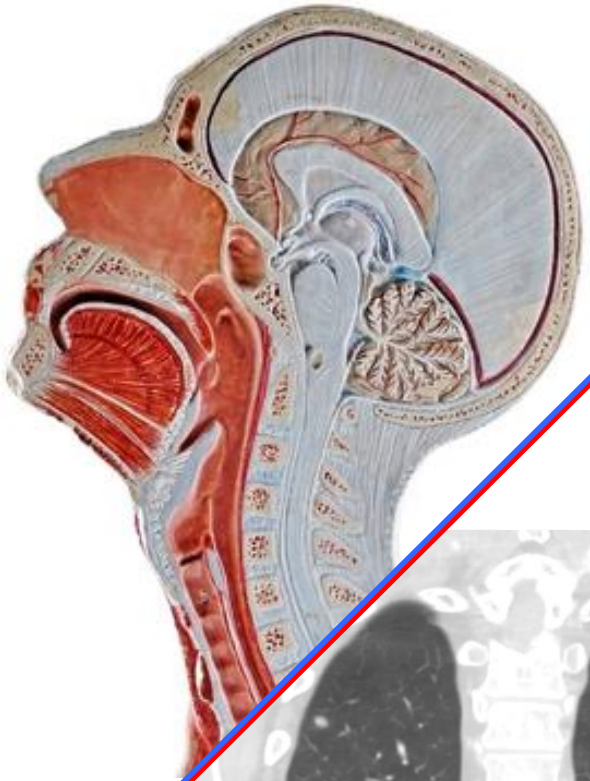
Primary Treatment

Radiation or Chemoradiation

Residual Disease →

← Risk Features

Surgery



Locoregional

Distant Metastases

or No Further Surgery / Radiation

Treatment for Locoregional Recurrence

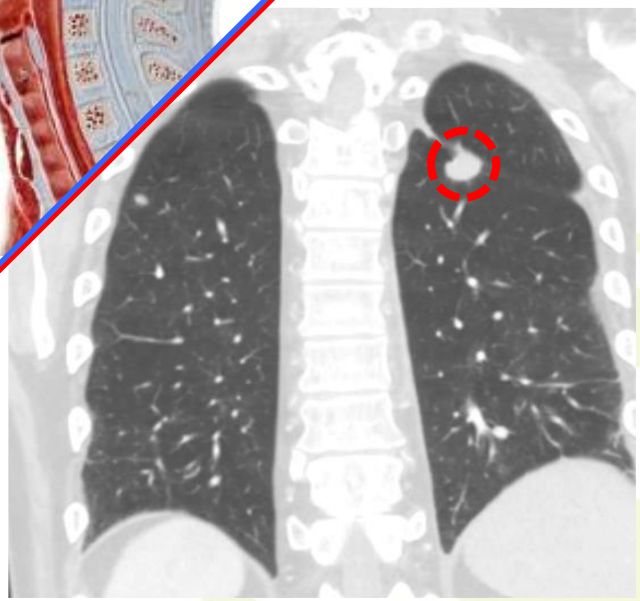
Surgery

If Feasible

Radiation or Chemoradiation

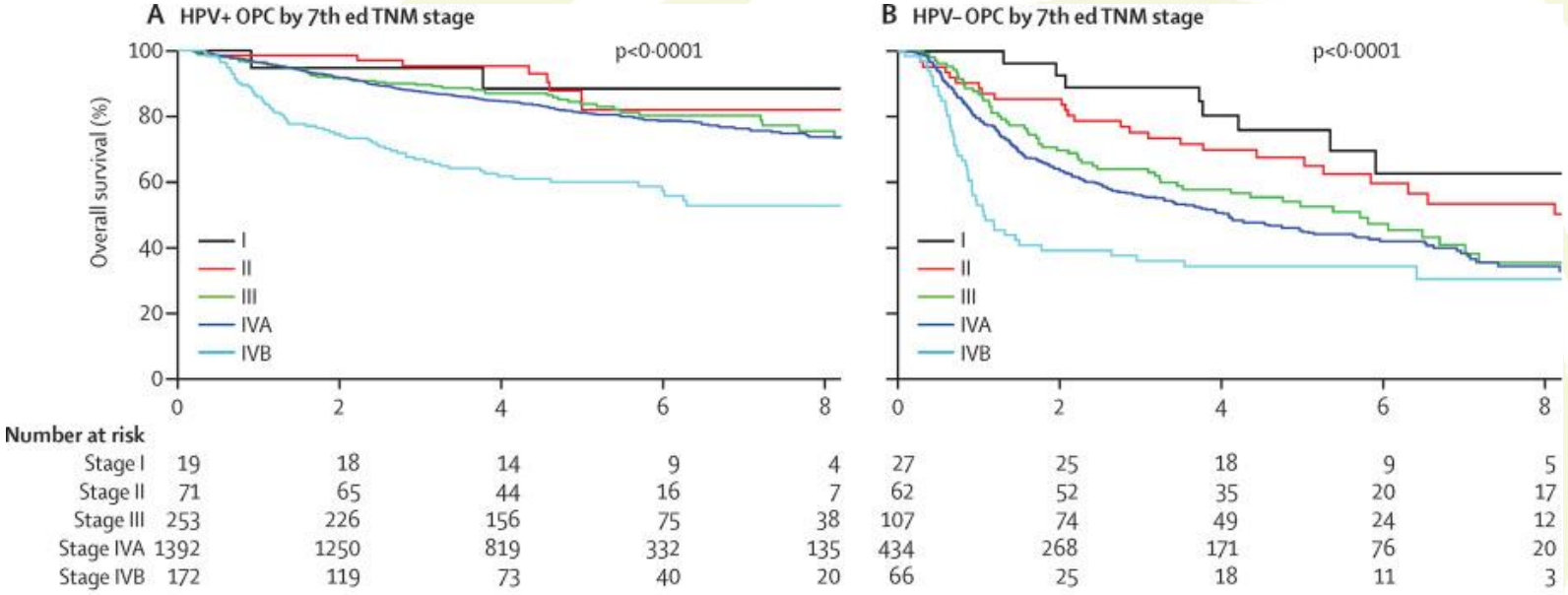
If Maximum Exposure Not Exceeded and Long Disease Free Interval

Poorer Outcomes
Increased Morbidity



Chemo → Chemo → Chemo

Locoregional OPC Prognosis and HPV



Lancet Oncol. 2016;17(4):440.

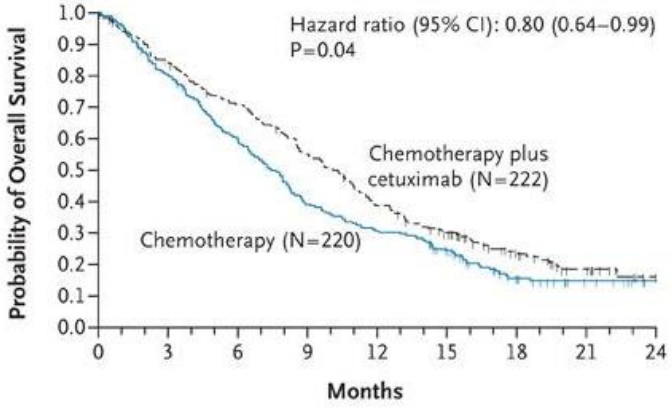
Stage	HPV+	HPV-
I	88%	76%
II	82%	68%
II	84%	53%
IVA	81%	45%
IVB	60%	34%

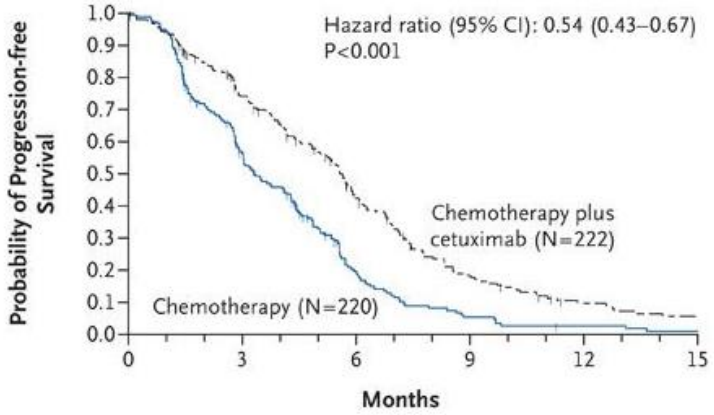
5 year OS

> 50%

< 50%

Chemotherapy for Recurrent / Metastatic HNSCC





No. at Risk

Chemotherapy	220	103	29	8	3	1
Chemotherapy plus cetuximab	222	138	72	29	12	7

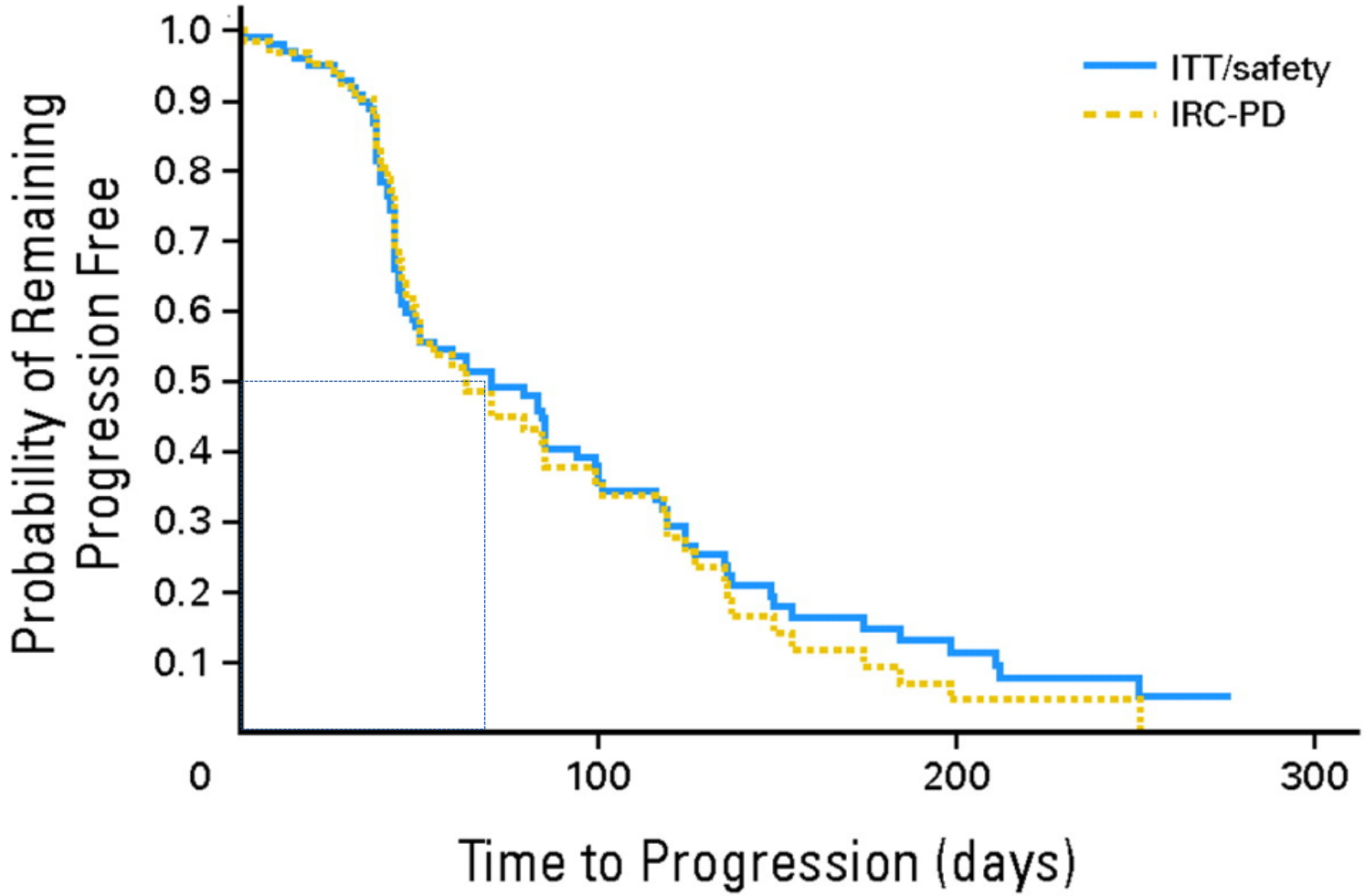
Platinum + 5FU + Cetuximab

ORR	36%
Median PFS	5.6 months
Median OS	10.1 months

Vermorken JB et al. N Engl J Med 2008;359:1116-1127.

Event	Cetuximab plus Platinum–Fluorouracil (N=219)	
	Grade 3 or 4	Grade 4
Any event	179 (82)	67 (31)
Neutropenia	49 (22)	9 (4)
Anemia	29 (13)	2 (1)
Thrombocytopenia	24 (11)	0
Leukopenia	19 (9)	4 (2)
Skin reactions‡	20 (9)	0
Hypokalemia	16 (7)	2 (1)
Cardiac events§	16 (7)	11 (5)
Vomiting	12 (5)	0
Asthenia	11 (5)	1 (<1)
Anorexia	11 (5)	2 (1)
Hypomagnesemia	11 (5)	8 (4)
Febrile neutropenia	10 (5)	2 (1)
Dyspnea	9 (4)	2 (1)
Pneumonia	9 (4)	3 (1)
Hypocalcemia	9 (4)	5 (2)
Sepsis (including septic shock)	9 (4)	6 (3)
Tumor hemorrhage	3 (1)	2 (1)
Decreased performance status	2 (1)	1 (<1)
Respiratory failure	1 (<1)	0

Cetuximab: PFS ~ 2.5 months, ORR 12%



Treating Head and Neck Cancer

Primary Treatment

Radiation or Chemoradiation

Residual Disease →

← Risk Features

Surgery

Treatment for Locoregional Recurrence

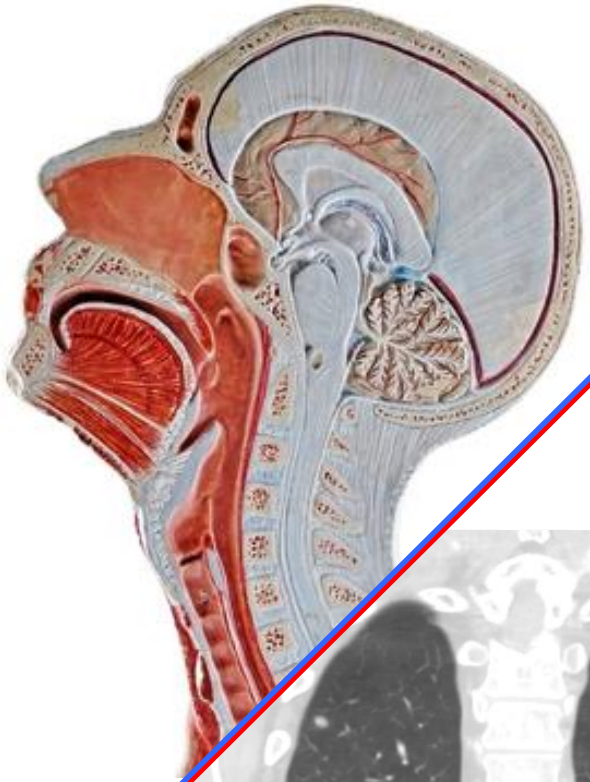
Surgery

If Feasible

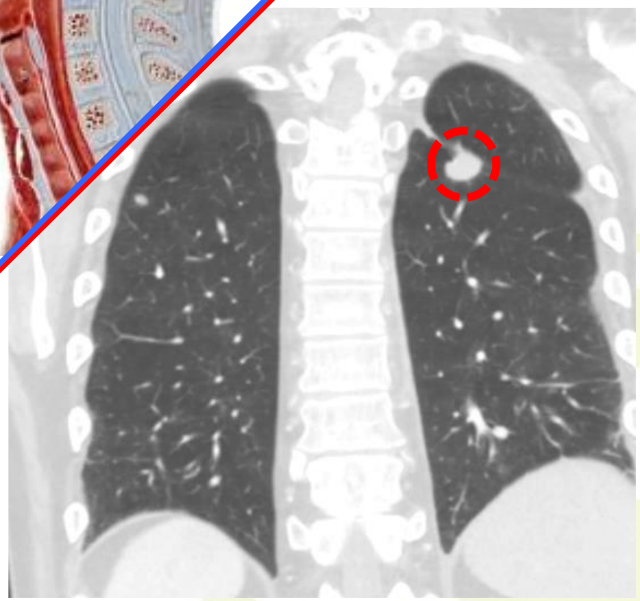
Radiation or Chemoradiation

If Maximum Exposure Not Exceeded and Long Disease Free Interval

Poorer Outcomes
Increased Morbidity



Locoregional
Distant Metastases
or No Further Surgery / Radiation

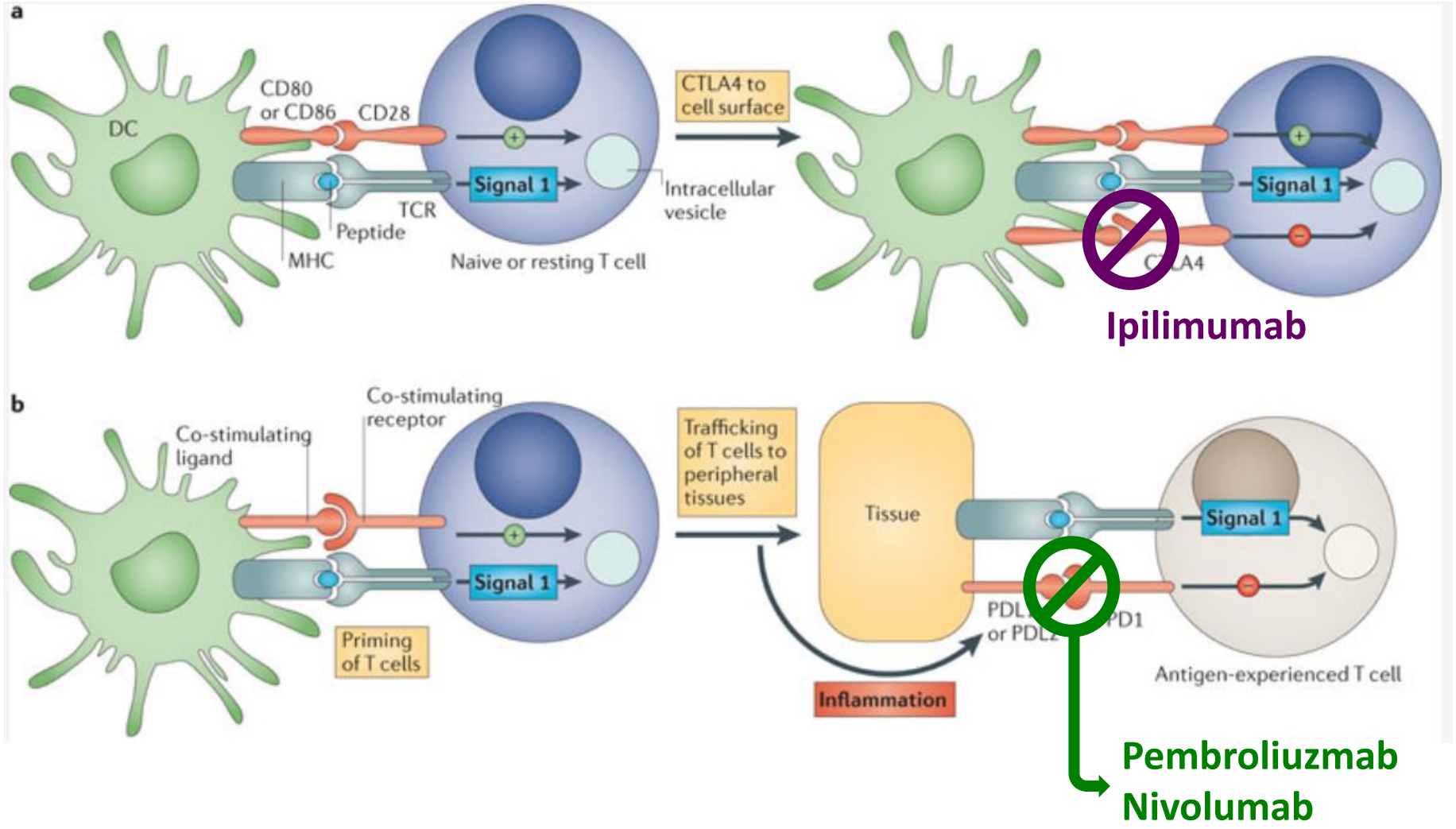


Chemo → Chemo → Chemo

Median Survival
= 10 months

82% Gr 3+ AEs

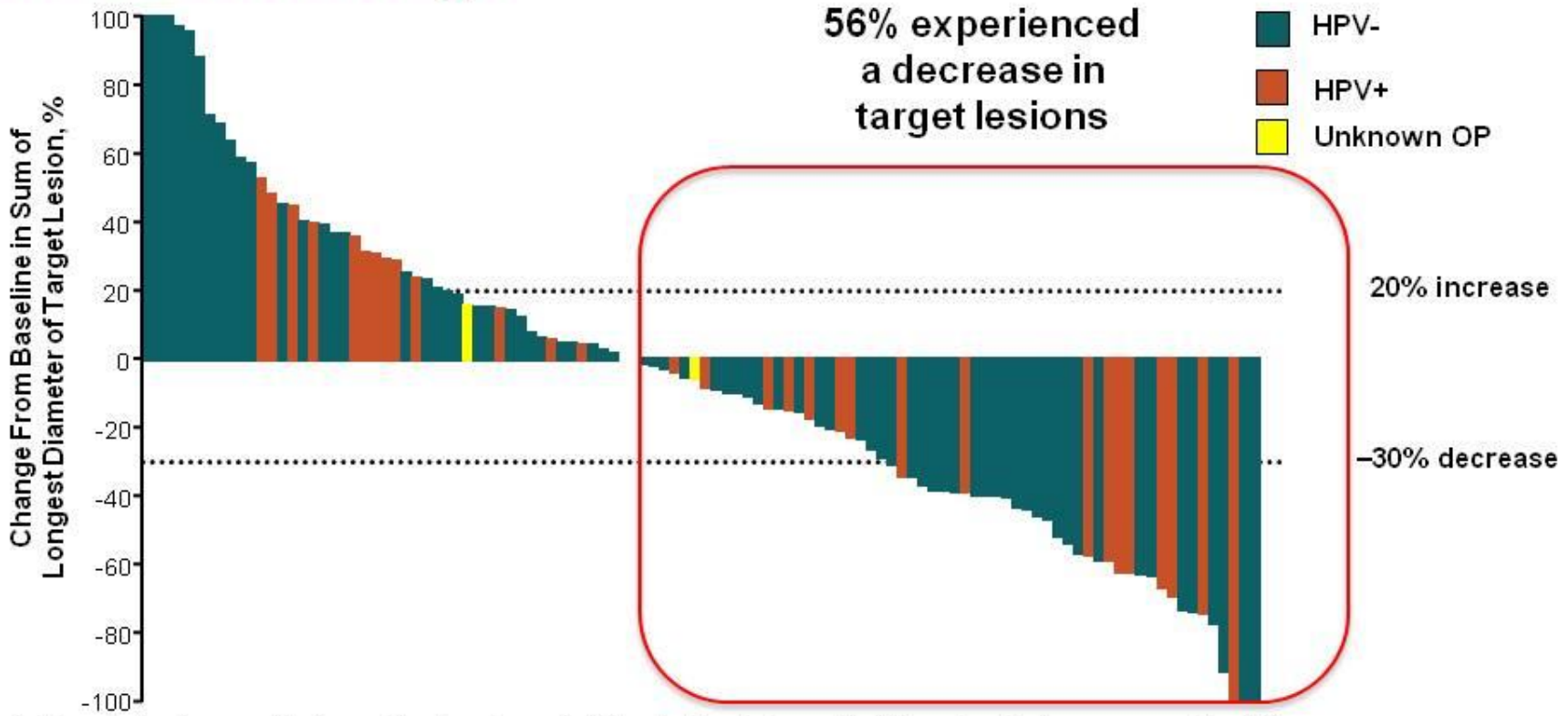
Immune Checkpoint Pathways



Pardoll, Nat Rev Cancer, 2013

Pembrolizumab Phase 1b

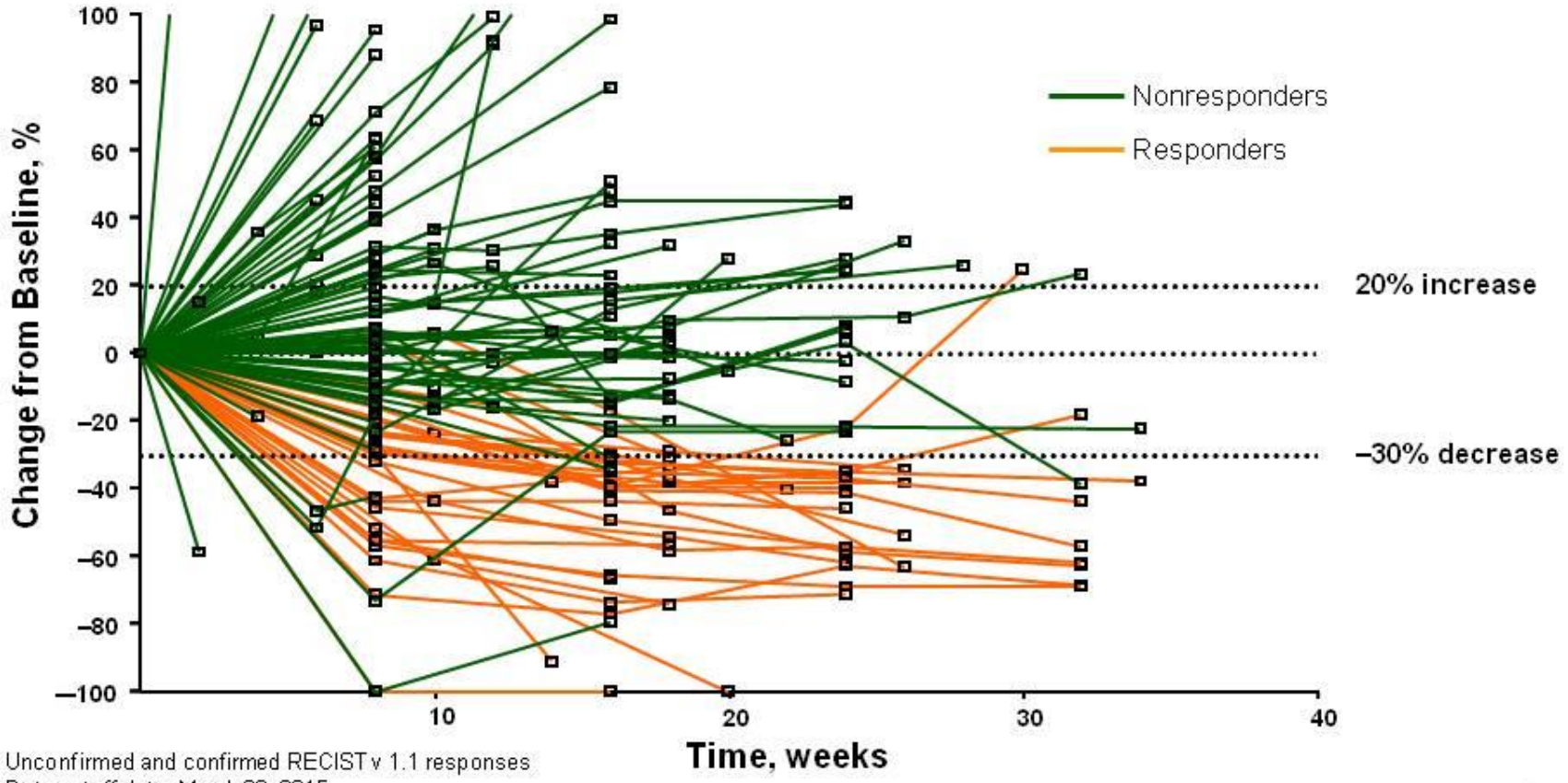
Tumor Shrinkage



Analysis includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and had ≥1 post-baseline tumor assessment (n = 106)
Unconfirmed and confirmed RECIST v 1.1 responses by site radiology review
*2 oropharynx cancer patient are HPV unknown. Cancers outside the oropharynx are considered HPV negative by convention
Data cutoff date: March 23, 2015. OP = oropharyngeal primary

Pembrolizumab Phase 1b

Tumor Shrinkage Over Time



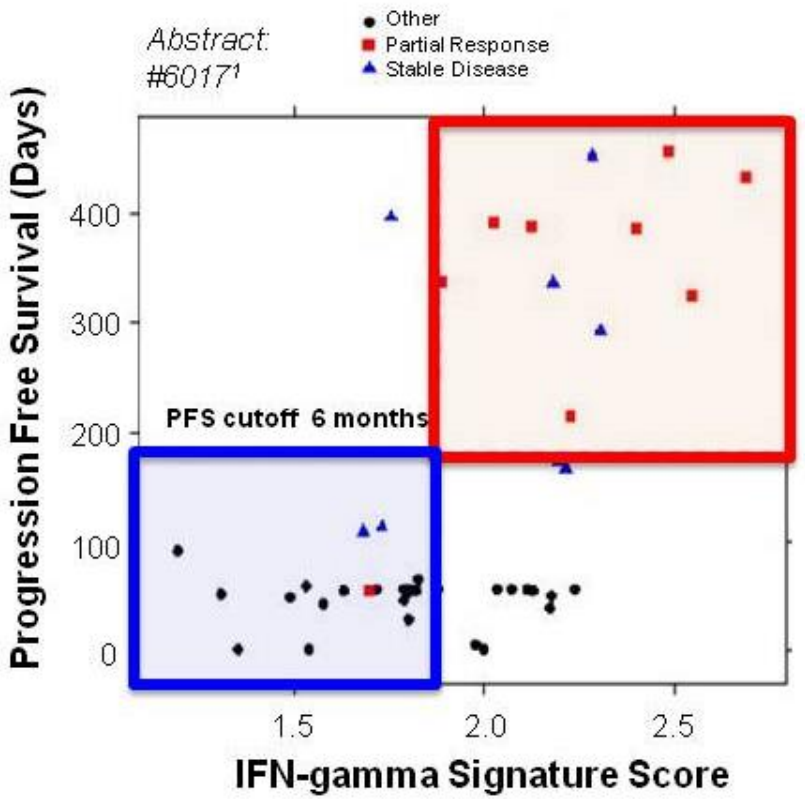
Unconfirmed and confirmed RECIST v 1.1 responses
Data cutoff date: March 23, 2015.

ADVANCES IN Cancer IMMUNOTHERAPY™

Pembrolizumab Phase 1b

Biomarkers

- Evaluation of PD-L1 expression by IHC in the current cohort (B2) is ongoing
- The optimal cutoff for PD-L1 expression as well as potential clinical usefulness of PD-L1 as a clinical diagnostic for HNC remain to be determined
- An *Interferon-gamma* expression signature (abstract #6017) showed promise:[1]
  - 95% negative predictive value
  - 40% positive predictive value

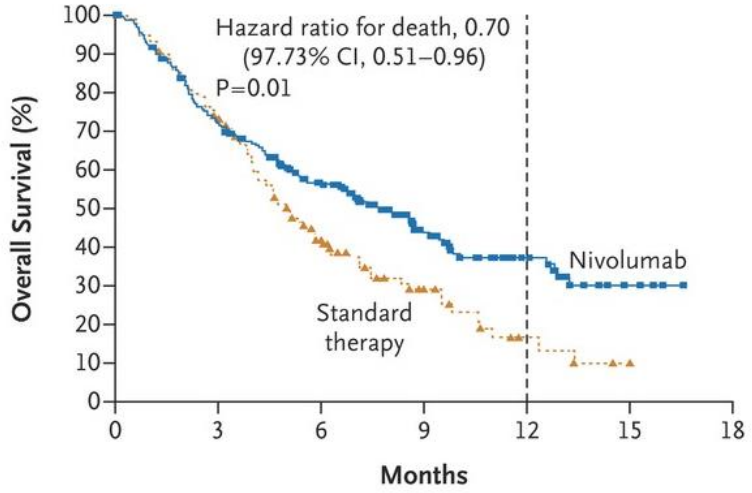


1. Seiwert TS, et al. ASCO 2015. Abstract#6017

Nivolumab Phase 3: OS and PFS

A Overall Survival

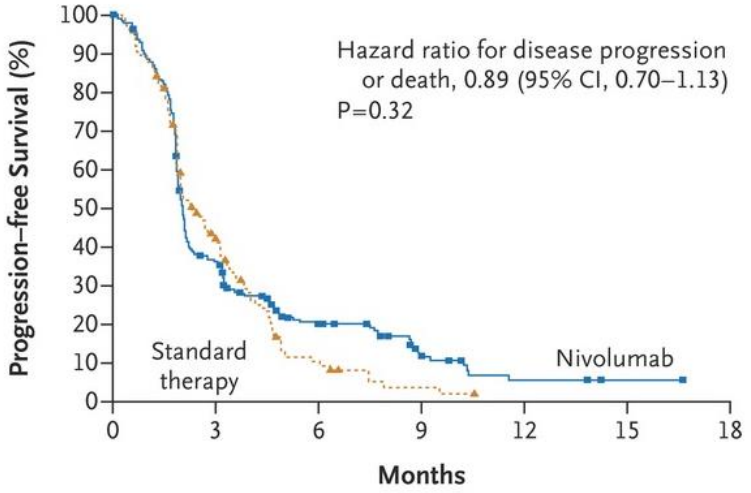
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

B Progression-free Survival

	No. of Patients	No. of Events	Median Progression-free Survival (95% CI) mo
Nivolumab	240	190	2.0 (1.9–2.1)
Standard Therapy	121	103	2.3 (1.9–3.1)



No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Standard therapy	121	43	9	2	0	0	0

Ferris RL et al. N Engl J Med 2016;375:1856-1867

ADVANCES IN Cancer IMMUNOTHERAPY™

PD-L1 Expression and HPV

Variable	Nivolumab (N=240)		Standard Therapy (N=121)		Hazard Ratio for Death (95% CI)
	Patients	Median Survival	Patients	Median Survival	
	no. (%)	*mo*	*no. (%)*	*mo*	
All patients	240 (100.0)	7.5	121 (100.0)	5.1	0.69 (0.53–0.91)
PD-L1 expression level					
≥1%	88 (36.7)	8.7	61 (50.4)	4.6	0.55 (0.36–0.83)
≥5%	54 (22.5)	8.8	43 (35.5)	4.6	0.50 (0.30–0.83)
≥10%	43 (17.9)	8.7	34 (28.1)	5.2	0.56 (0.31–1.01)
<1%	73 (30.4)	5.7	38 (31.4)	5.8	0.89 (0.54–1.45)
<5%	107 (44.6)	7.0	56 (46.3)	5.1	0.81 (0.55–1.21)
<10%	118 (49.2)	7.2	65 (53.7)	4.6	0.73 (0.50–1.06)
Not quantifiable	79 (32.9)	7.8	22 (18.2)	5.8	0.79 (0.44–1.44)
p16 status					
Positive	63 (26.2)	9.1	29 (24.0)	4.4	0.56 (0.32–0.99)
Negative	50 (20.8)	7.5	36 (29.8)	5.8	0.73 (0.42–1.25)
Combined subgroup					
PD-L1 ≥1% and p16-positive	23 (9.6)	8.8	14 (11.6)	3.9	0.50 (0.21–1.19)
PD-L1 ≥1% and p16-negative	17 (7.1)	8.8	16 (13.2)	5.6	0.44 (0.18–1.10)
PD-L1 <1% and p16-positive	24 (10.0)	10.0	10 (8.3)	6.4	0.55 (0.22–1.39)
PD-L1 <1% and p16-negative	14 (5.8)	7.1	12 (9.9)	7.4	0.82 (0.31–2.19)

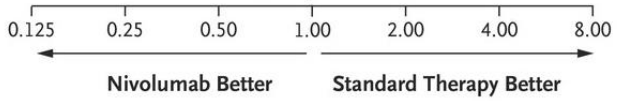
Ferris RL et al. N Engl J Med 2016;375:1856-1867

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Nivolumab Phase 3: Subgroups

Subgroup	Nivolumab	Standard Therapy	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall	240	121	0.69 (0.53–0.91)
Age			
<65 yr	172	76	0.64 (0.45–0.89)
≥65 yr and <75 yr	56	39	0.93 (0.56–1.54)
≥75 yr	12	6	—
ECOG performance-status score			
0	49	23	0.60 (0.30–1.23)
≥1	190	97	0.71 (0.53–0.96)
Not reported	1	1	—
Previous cetuximab use			
Yes	147	74	0.81 (0.57–1.15)
No	93	47	0.55 (0.35–0.86)
Intended standard therapy			
Cetuximab	33	15	0.47 (0.22–1.01)
Methotrexate	119	52	0.64 (0.43–0.96)
Docetaxel	88	54	0.82 (0.53–1.28)
Site of primary tumor			
Larynx	34	15	0.75 (0.36–1.59)
Oral cavity	108	67	0.73 (0.51–1.07)
Pharynx	92	36	0.71 (0.42–1.19)
Other	6	3	—
No. of previous lines of systemic therapy			
1	106	58	0.72 (0.48–1.07)
2	80	45	0.64 (0.40–1.00)
≥3	54	18	0.77 (0.38–1.57)
Platinum-refractory disease in context of primary therapy			
Yes	52	26	0.63 (0.35–1.12)
No	188	95	0.71 (0.52–0.97)

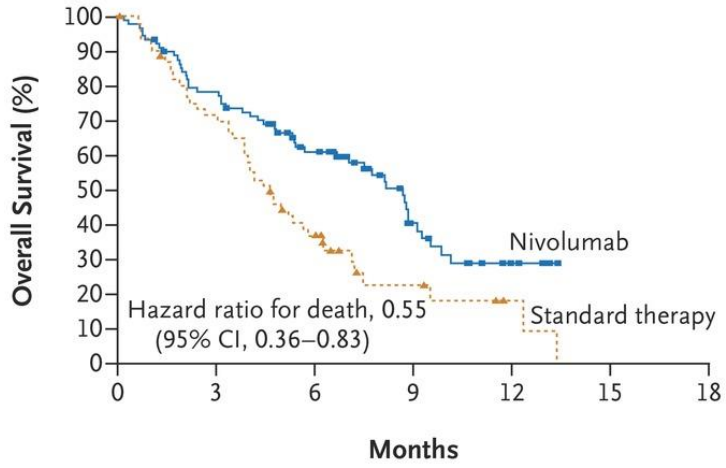


Ferris RL et al. N Engl J Med 2016;375:1856-1867

PD-L1 Staining and Response

A Overall Survival among Patients with Baseline PD-L1 ≥1%

	No. of Patients	No. of Deaths	Median Overall Survival *mo (95% CI)*
Nivolumab	88	49	8.7 (5.7–9.1)
Standard Therapy	61	45	4.6 (3.8–5.8)

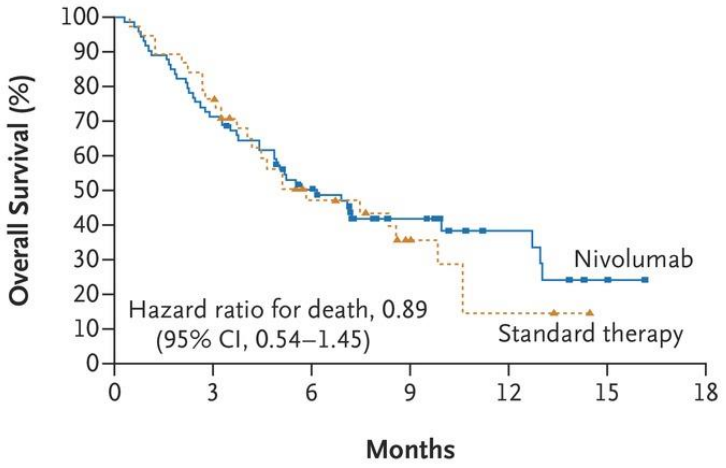


No. at Risk

Nivolumab	88	67	44	18	6	0
Standard therapy	61	42	20	6	2	0

B Overall Survival among Patients with Baseline PD-L1 <1%

	No. of Patients	No. of Deaths	Median Overall Survival *mo (95% CI)*
Nivolumab	73	45	5.7 (4.4–12.7)
Standard Therapy	38	25	5.8 (4.0–9.8)



No. at Risk

Nivolumab	73	52	33	17	8	3	0
Standard therapy	38	29	14	6	2	0	0

Ferris RL et al. N Engl J Med 2016;375:1856-1867

ADVANCES IN Cancer IMMUNOTHERAPY™

Side Effects

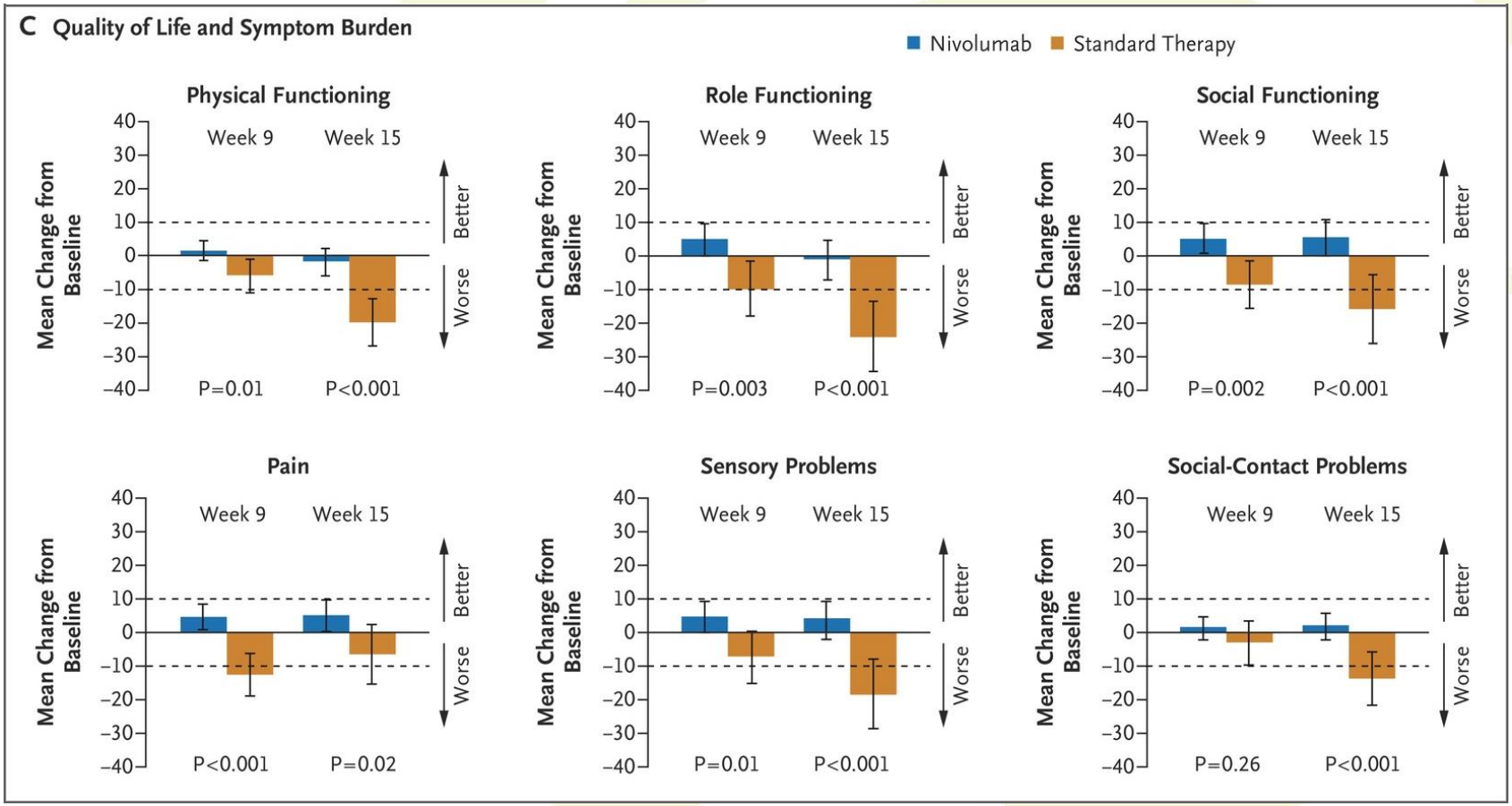
Event	Nivolumab (N=236)		Standard Therapy (N=111)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any event	139 (58.9)*	31 (13.1)	86 (77.5)†	39 (35.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Decreased appetite	17 (7.2)	0	8 (7.2)	0
Pruritus	17 (7.2)	0	0	0
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Vomiting	8 (3.4)	0	8 (7.2)	0
Dry skin	7 (3.0)	0	10 (9.0)	0
Stomatitis	5 (2.1)	1 (0.4)	10 (9.0)	3 (2.7)
Weight loss	4 (1.7)	0	6 (5.4)	0
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Peripheral neuropathy	1 (0.4)	0	7 (6.3)	0
Alopecia	0	0	14 (12.6)	3 (2.7)
Neutropenia	0	0	9 (8.1)	8 (7.2)

Ferris RL et al. N Engl J Med 2016;375:1856-1867

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Quality of Life



Ferris RL et al. N Engl J Med 2016;375:1856-1867

Treating Head and Neck Cancer

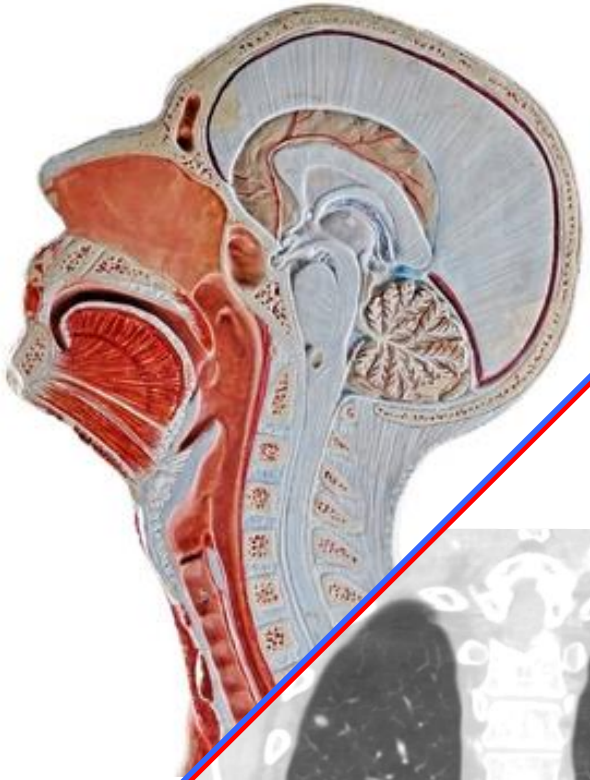
Primary Treatment

Radiation or Chemoradiation

Residual Disease →

← Risk Features

Surgery



Locoregional

Distant Metastases

or No Further Surgery / Radiation

Treatment for Locoregional Recurrence

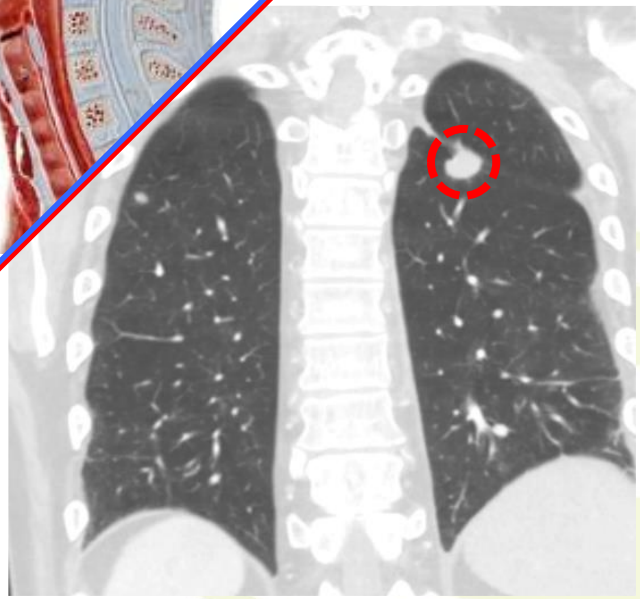
Surgery

If Feasible

Radiation or Chemoradiation

If Maximum Exposure Not Exceeded and Long Disease Free Interval

Poorer Outcomes
Increased Morbidity



Chemo

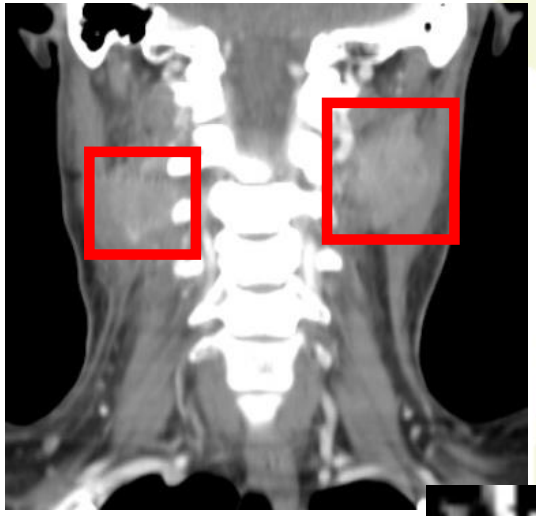
Chemo

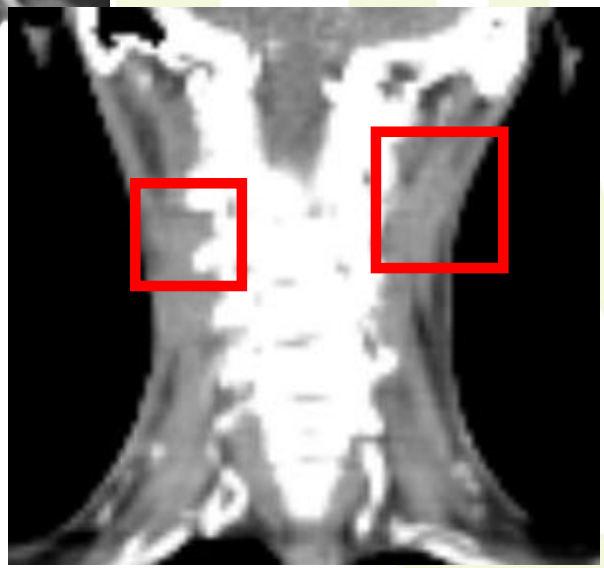
PD1 Abs

Chemo

ADVANCES IN Cancer IMMUNOTHERAPY™

Case 1





51 year old woman with NPC

CR to induction chemotherapy

Consolidated with chemoradition

NED at 4 years

A. Chemoradiation
B. Induction chemotherapy then radiation
C. Surgery
D. Chemotherapy
E. Pembrolizumab or nivolumab
F. Ipilimumab and nivolumab

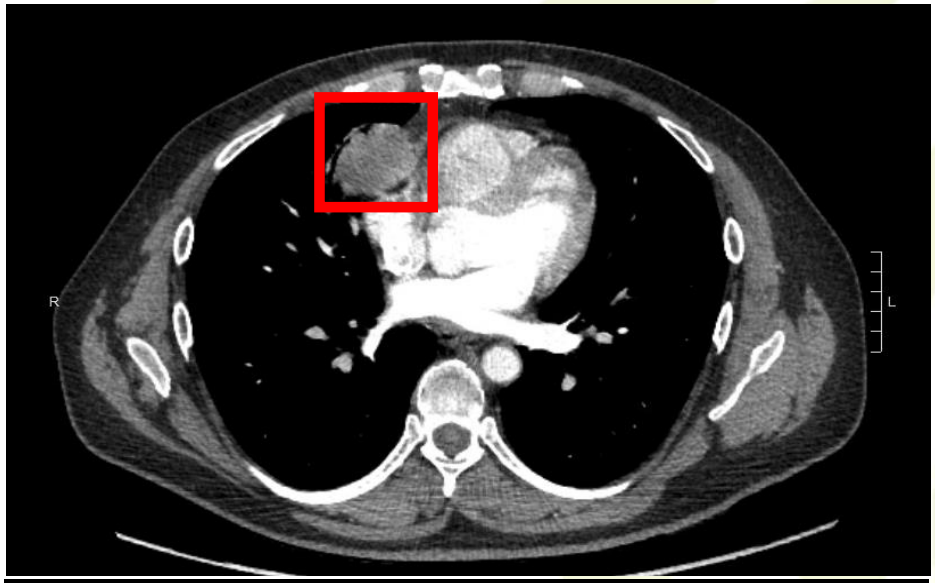
PD-1 Antibodies are NOT approved (yet) for NPC

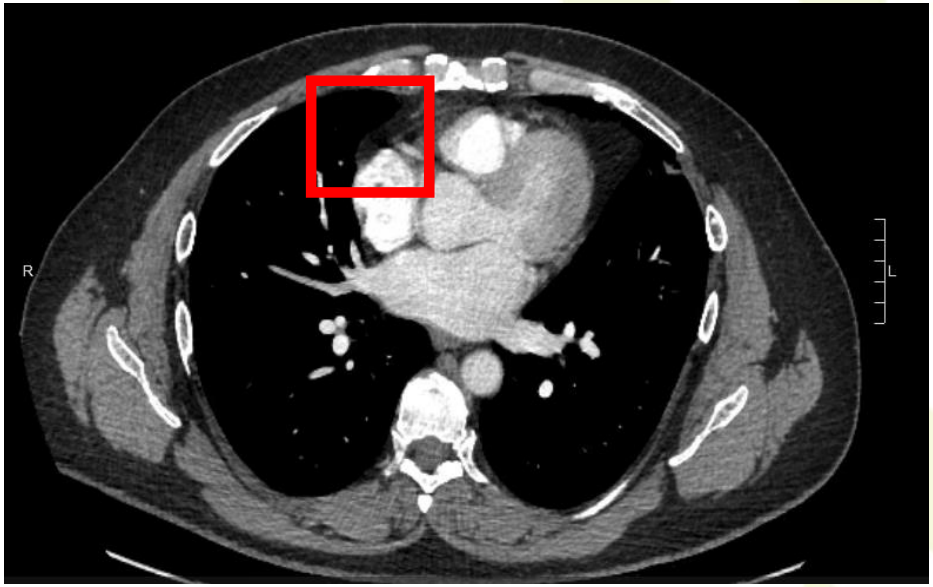
ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Case 2





51 year old man with p16+ OPC

Considered platinum-refractory due to PD within 6 months of chemoXRT

Received PD-1 Ab

Patient is in complete response at 1 year

No significant treatment-associated side effects

A. Chemoradiation
B. Induction chemotherapy then radiation
C. Surgery
D. Chemotherapy
E. Pembrolizumab or nivolumab
F. Ipilimumab and nivolumab

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

I/O Studies in HNSCC at UCSF

Combination	Targets
Durvalumab + tremelimumab	PDL1 + CTLA4
Nivolumab + / - ipilimumab	PD1 + CTLA4
Pembrolizumab + SD-101	PD1 + TLR
Pembrolizumab + ACP-196	PD1 + BTK
Pembrolizumab + PLX3397	PD1 + CSF1
Nivolumab + FPA008	PD1 + CSF1
Nivolumab + epacadostat	PD1 + IDO
Durvalumab + epacadostat	PDL1 + IDO
Nivolumab + lirilumab	PL1 + KIR1
Nivolumab + varilumab	PD1 + CD27

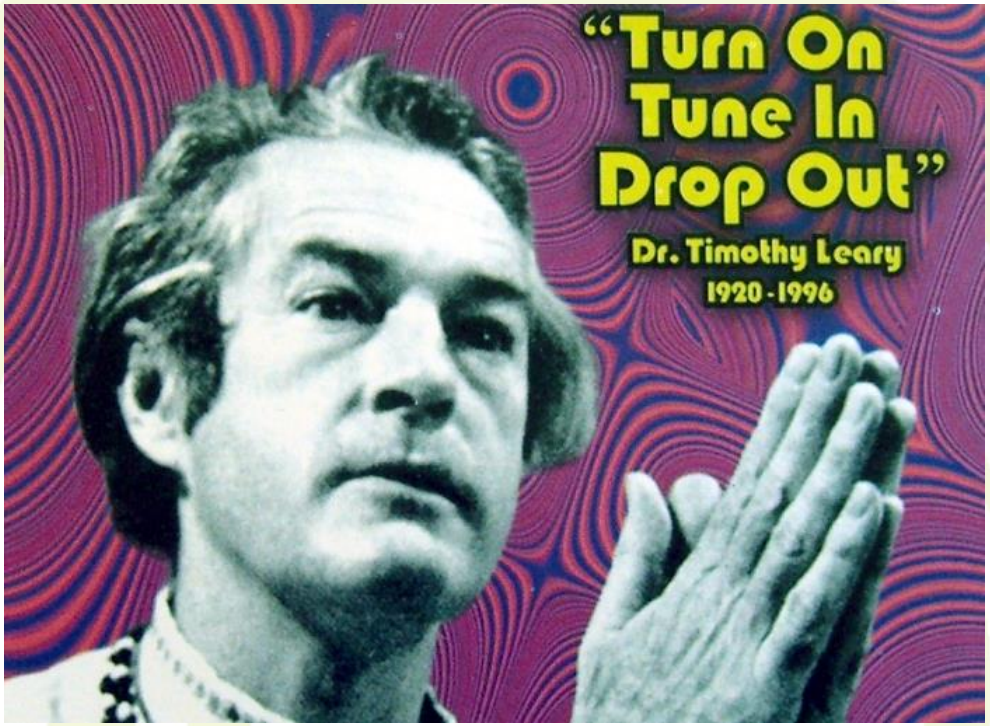
PD-1 Abs alone

- Favorable side effects
- Low response rate
- Durable

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™



Steps to an effective anti-tumor immune response

Learyism	"Tune in"	"Turn on"	"Drop out"
Description	• Bring immune cells into tumor • Make chemicals to activate immune response	Activate immune cells in tumor	Get rid of "regulatory" cells that get in the way of immune response
Examples of agents	1. CTLA4 Ab 2. pIL12-EP 3. TVEC 4. TLR agonists	1. PD-1 Abs	1. IDO inhibitors 2. CSF-1 inhibitor

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Treating Head and Neck Cancer

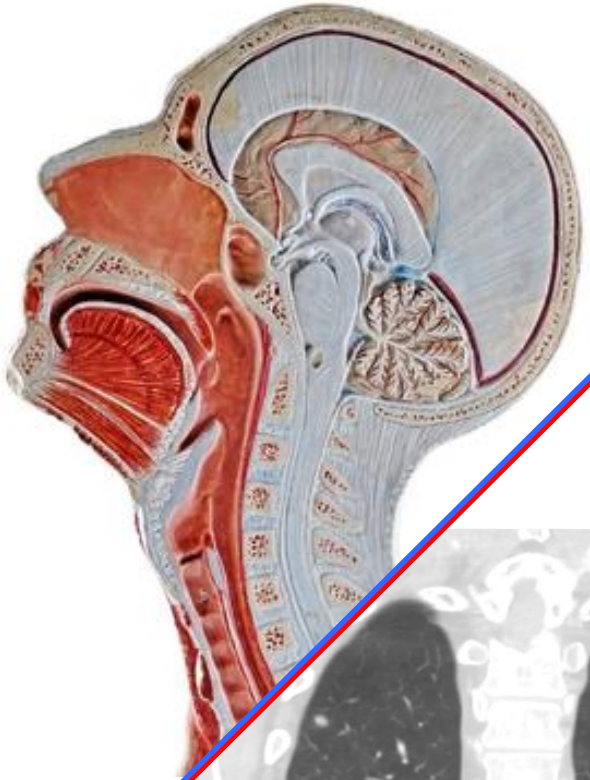
Primary Treatment

Radiation or Chemoradiation

Residual Disease →

← Risk Features

Surgery



Locoregional

Distant Metastases

or No Further Surgery / Radiation

Treatment for Locoregional Recurrence

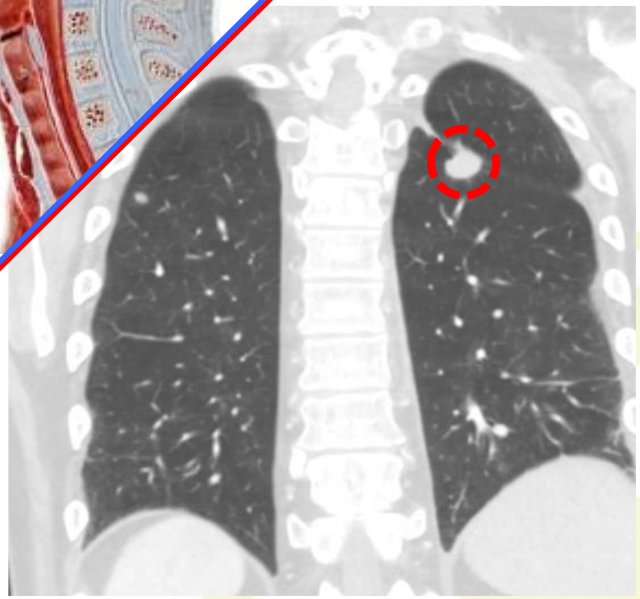
Surgery

If Feasible

Radiation or Chemoradiation

If Maximum Exposure Not Exceeded and Long Disease Free Interval

Poorer Outcomes
Increased Morbidity



Chemo → Chemo → Chemo

Chemo → PD1 Abs

Trials → Trials → Trials

Conclusions for Head and Neck Cancer

1. Chemotherapy offers short survival with many side effects

2. PD-1 antibodies nivolumab and pembrolizumab are approved in *second line recurrent / metastatic HNSCC:*

- Oral cavity
- Oropharynx
- Larynx
- Hypopharynx

3. Most patients have fewer side effects on PD-1 Abs than on chemotherapy

4. Clinical trials are underway to improve immunotherapy response rates