Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancer

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
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ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

Bristol-Myers Squibb: clinical trial and research funding

Astra-Zeneca/MedImmune: institutional research funding

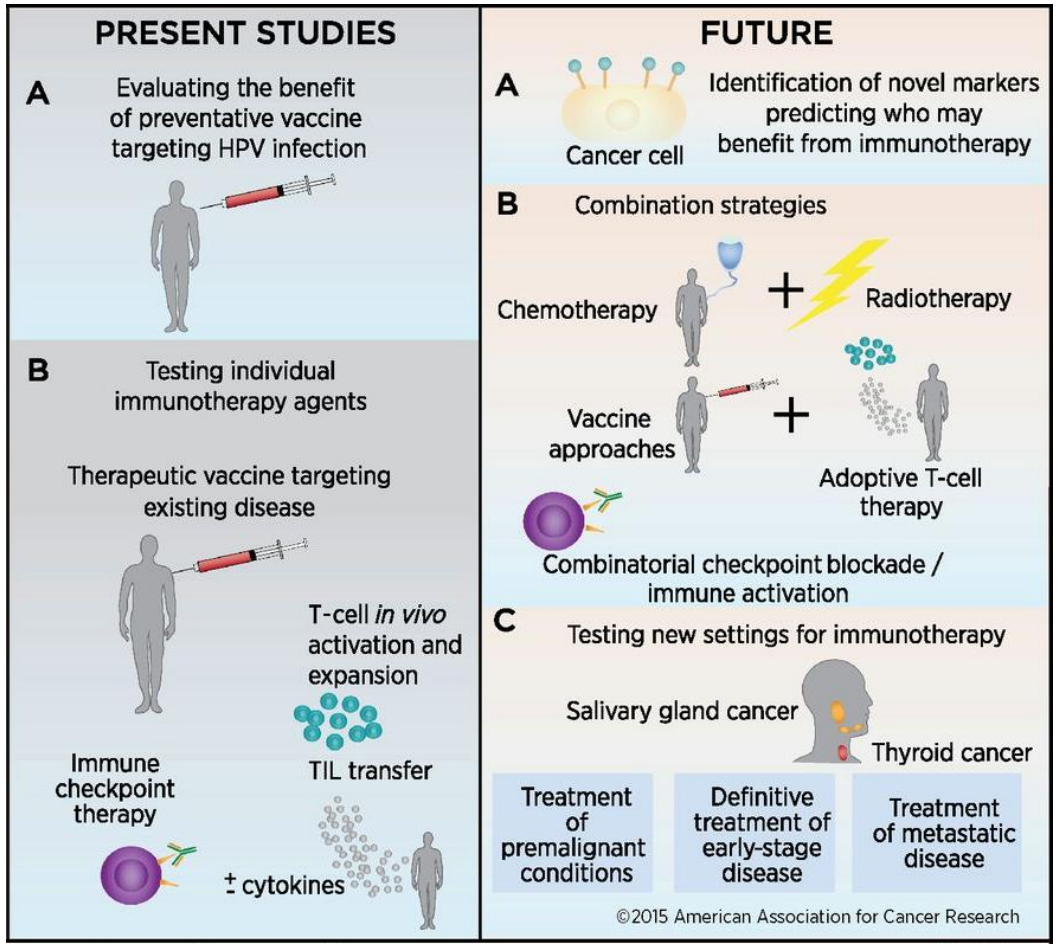
Merck: Consultant

Regeneron: Consultant

I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Head and Neck Cancers

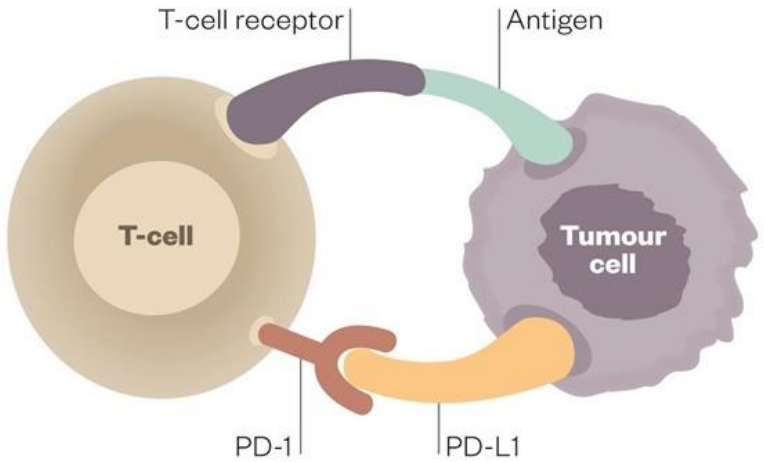
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Expression of immunologic markers to guide treatment
  - Preventive vaccination against virally mediated cancers
  - PD-1 checkpoint inhibitors for the treatment of metastatic disease



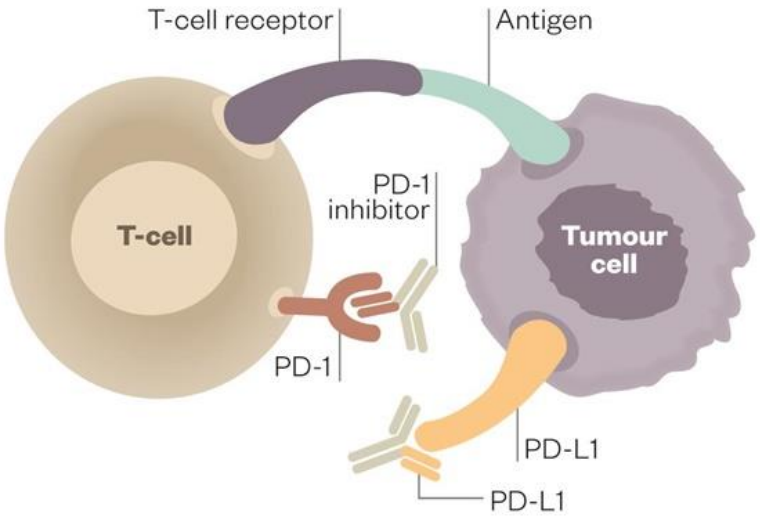
Schoenfeld JD, Cancer Immunol Res, 2015

Immunotherapy for the Treatment of Head and Neck Cancers

Immune Checkpoint Inhibitors (ICI)



PD-1 acts as “off-switch” for T cells, allowing cancer cells to evade immune attack



Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells

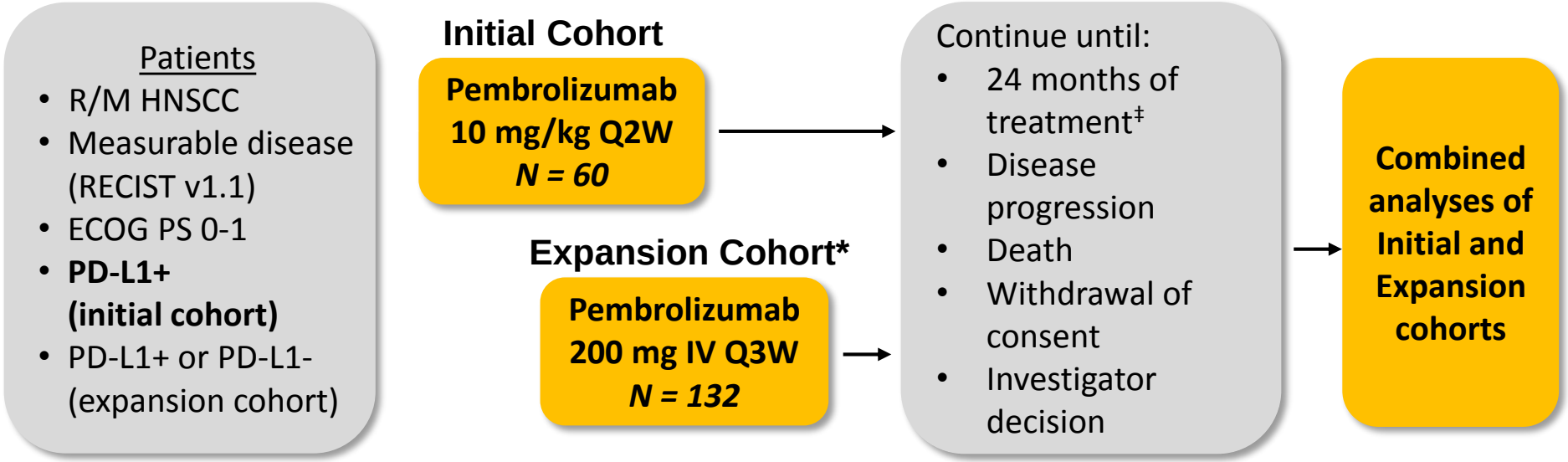
FDA-approved Checkpoint Inhibitors for Use in Head and Neck Cancers

- Pembrolizumab 200 mg IV Q3W(anti-PD-1)
  - KEYNOTE – 012/055: Patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (HNSCC) with disease progression on or after platinum-containing chemotherapy
  - Accelerated Approval by FDA – August 5, 2016

- Nivolumab 240 mg IV Q2W or 480 mg IV Q4W (anti-PD-1)
  - CheckMate – 141: Patients with R/M HNSCC with disease progression on or after a platinum-based therapy
  - Breakthrough Therapy Designation by FDA – April, 2016
  - Approval – November 10, 2016

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2



Response assessment: Every 8 weeks until disease progression

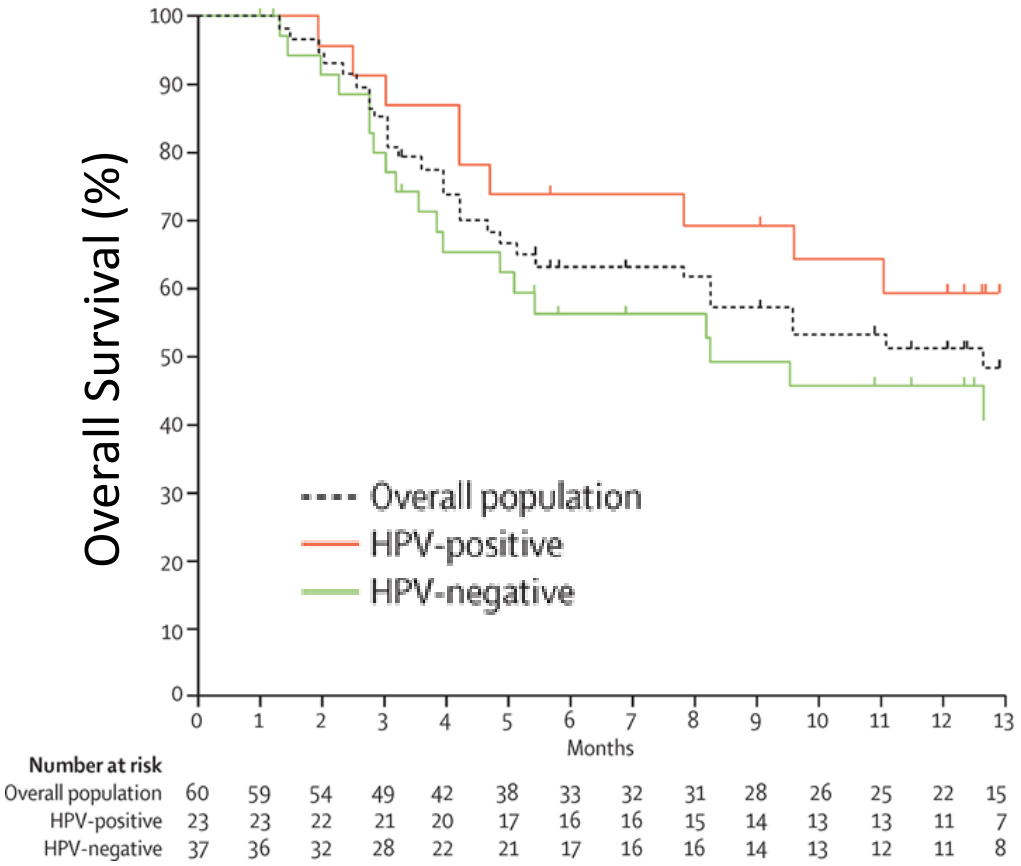
Primary end points: ORR (RECIST v1.1, central imaging vendor review), safety

Secondary end points: ORR (investigator), PFS, OS, duration of response (DOR), ORR in HPV+ patients§

†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

KEYNOTE-012: Pembrolizumab in R/M HNSCC

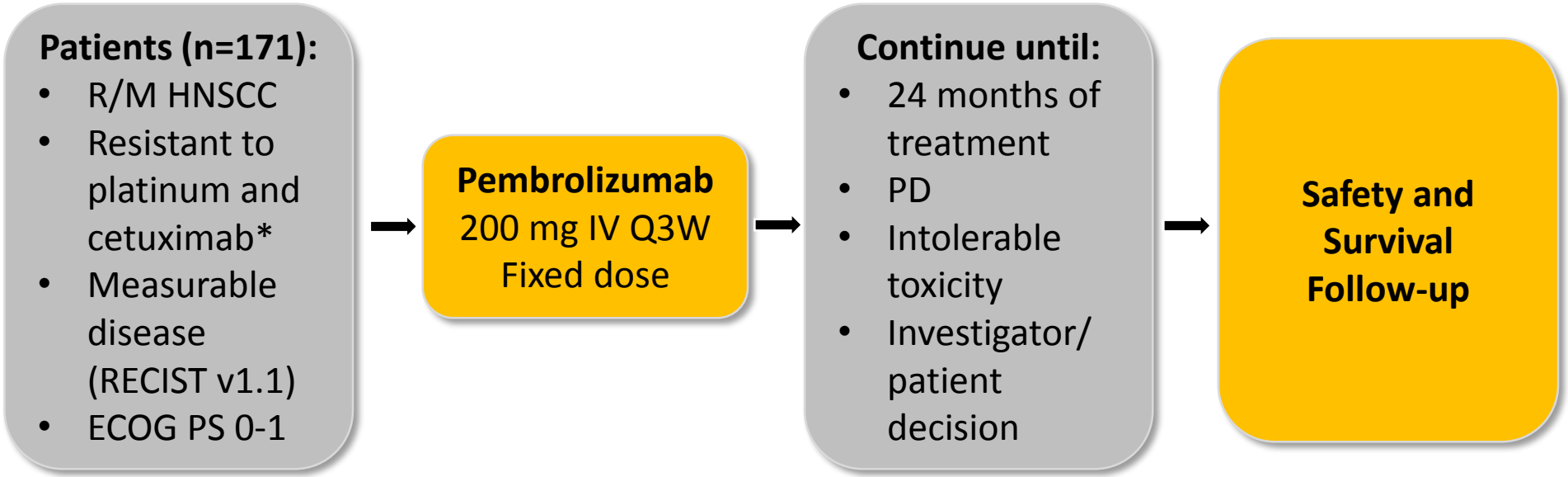
Nonrandomized, Phase 1b Trial, Cohorts† B, B2



- ORR = 18%
  - CR = 4%
  - PR = 14%
- mOS = 8.0 months
- mPFS = 2.2 months

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab

Phase II Trial, Single Arm



Bauml J JCO 2017

Response assessment: Imaging every 6 to 9 weeks (central radiology review)

Primary end points: ORR (RECIST v1.1) by Response Evaluation Criteria in Solid Tumors and safety

Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*75% of patients had ≥ 2 prior lines of therapy for metastatic disease

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab

Phase II Trial, Single Arm

Outcome	All Patients	HPV Status		PD-L1 Status		
	N=171	Positive n=37	Negative n=131	≥1% n=140	<1% n=26	≥50% n=48
ORR, %	16	16	15	18	12	27
mPFS, mo	2.1					
6-mo PFS,%	23	25	21	24	20	31
6-mo OS, %	59	72	55	59	56	60

Bauml J, et al, J Clin Oncol. 2017

- Neither tumor PD-L1 expression or HPV status are sufficiently robust in guiding the use of pembrolizumab at this time.

CheckMate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

Phase III Randomized, Safety and Efficacy Trial

Key Eligibility Criteria

- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status[a]

Stratification factor

- Prior cetuximab treatment

R 2:1

Nivolumab
3 mg/kg IV Q2W

Vs.

Investigator's Choice

- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

Primary endpoint

- OS

Other endpoints

- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

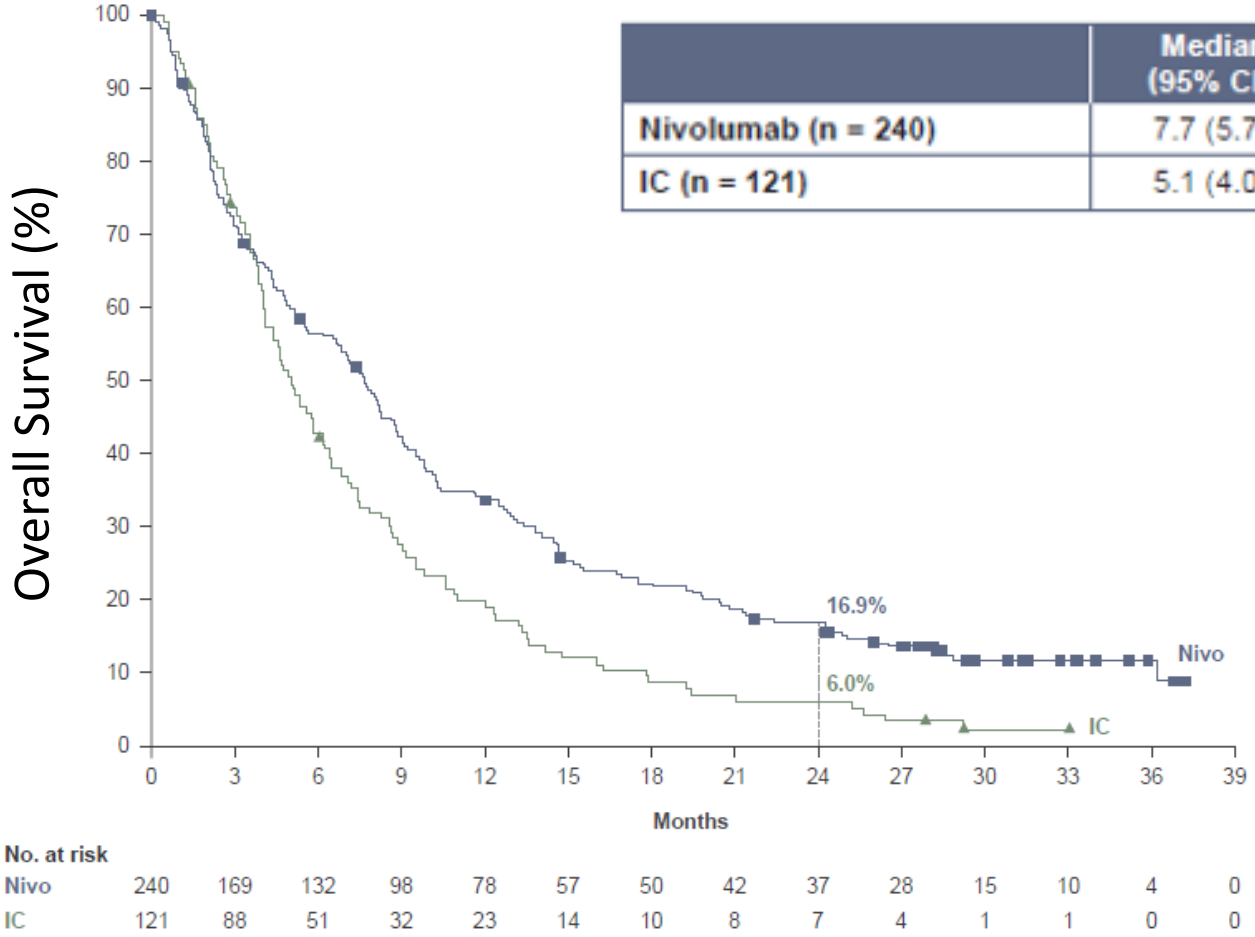
[a]Tissue required for testing

Ferris & Gillison, NEJM, 2016

Checkmate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

Overall Survival: 2 year report

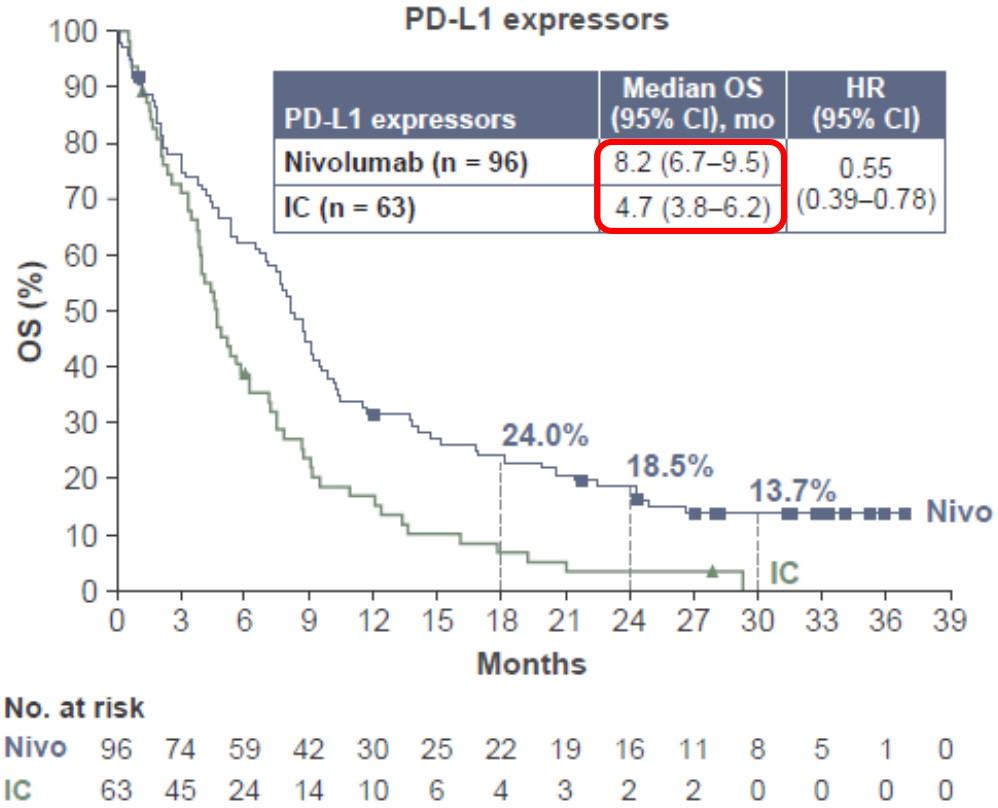
	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 240)	7.7 (5.7–8.8)	0.68 (0.54–0.86)
IC (n = 121)	5.1 (4.0–6.2)	

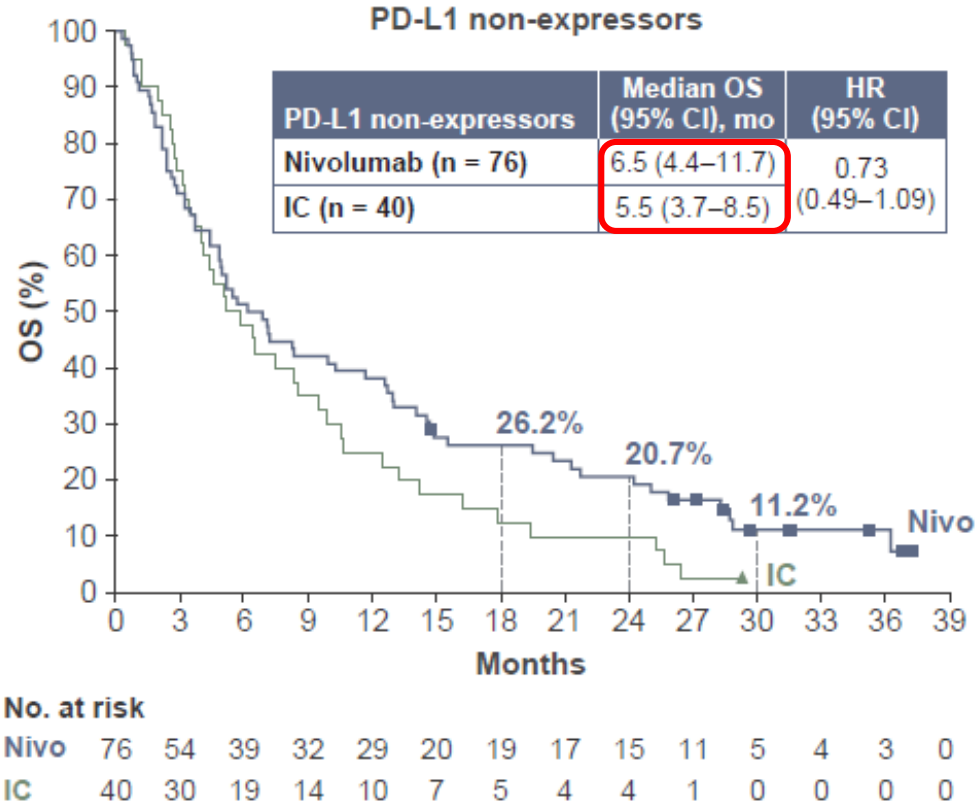


Ferris RL. Oral Oncology, 2018

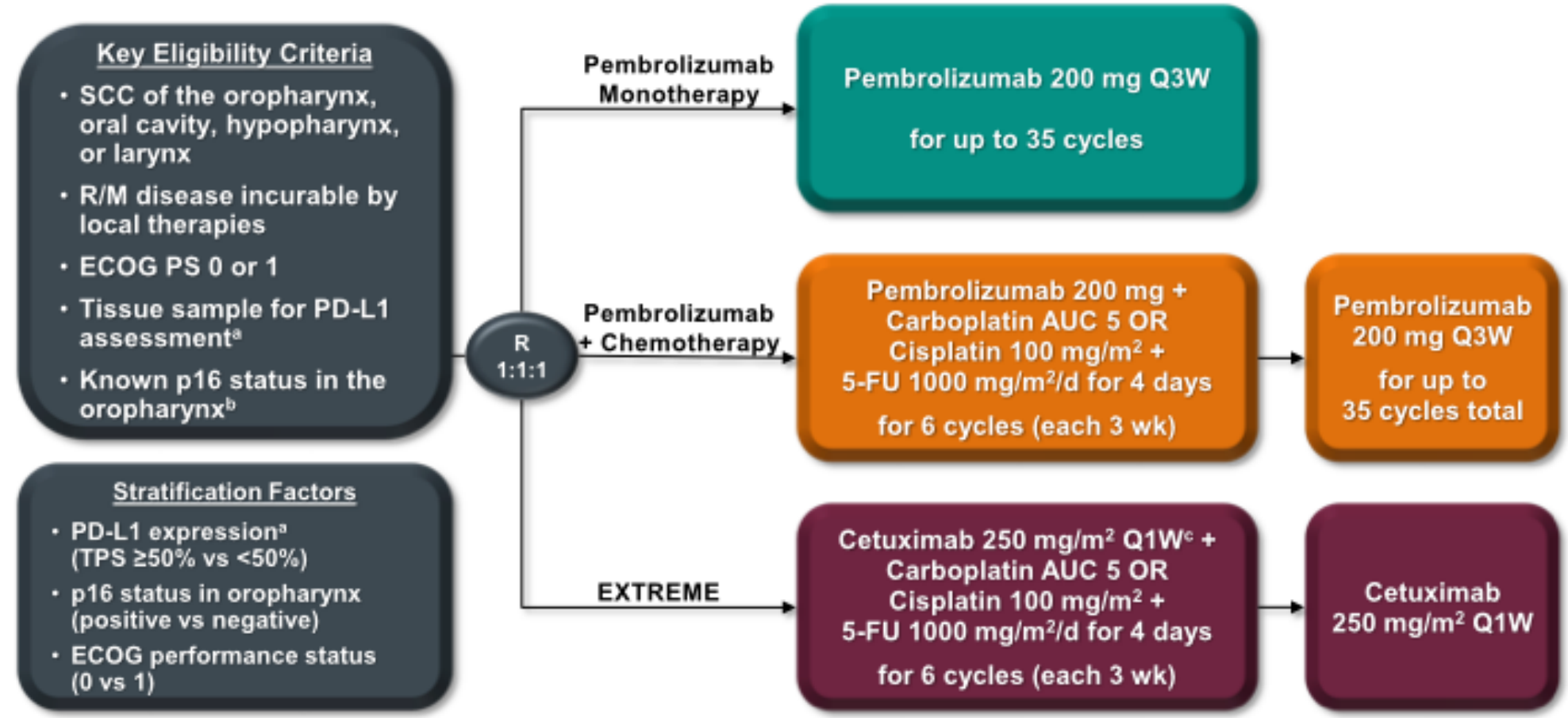
Evaluating Biomarkers in HNSCC

CheckMate 141: 2 year update





In Development: KEYNOTE-048 Pembrolizumab +/- Chemotherapy in Newly diagnosed R/M HNSCC

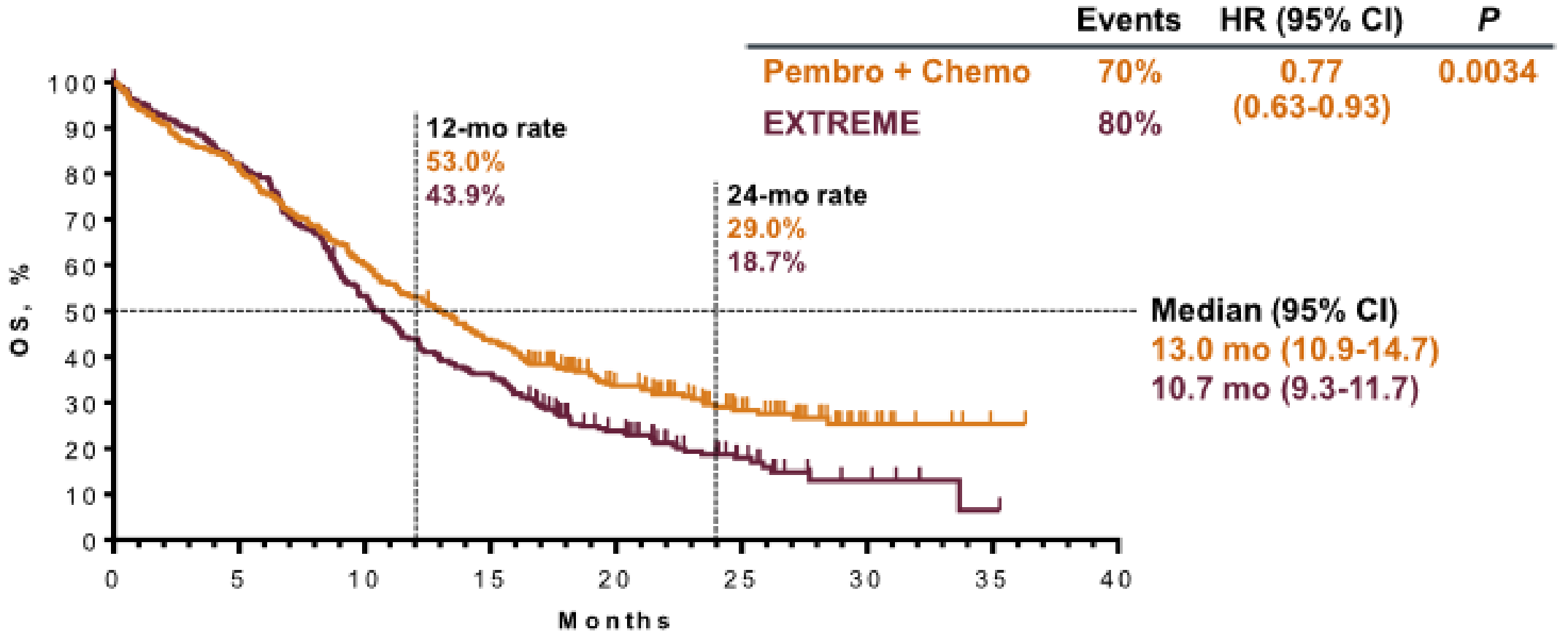


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Burtness et al. ESMO 2018

In Development: KEYNOTE-048 Pembrolizumab +/- Chemotherapy in Newly diagnosed R/M HNSCC

All Patients

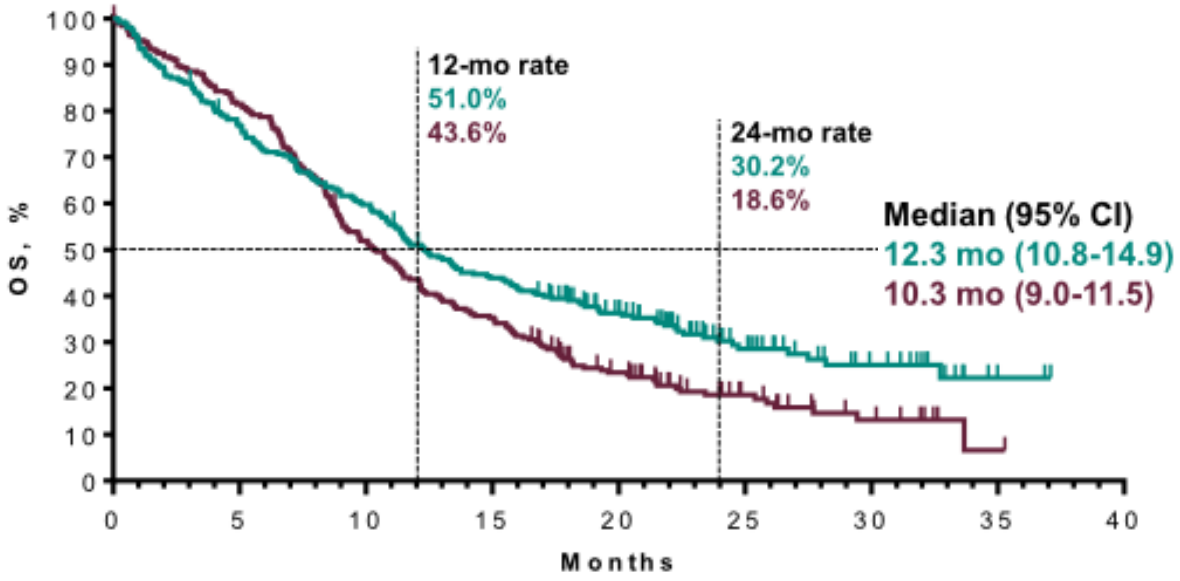


Burtness et al. ESMO 2018

In Development: KEYNOTE-048 Pembrolizumab +/- Chemotherapy in Newly diagnosed R/M HNSCC

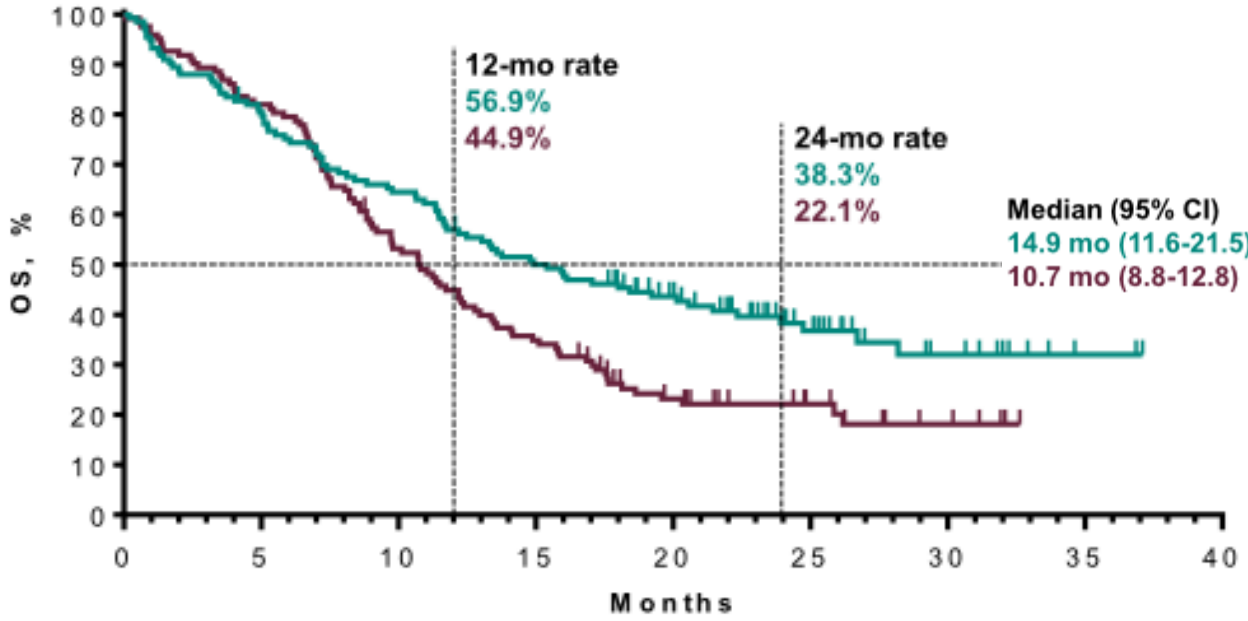
PD-L1 CPS ≥ 1%

	Events	HR (95% CI)	*P*
Pembro alone	69%	0.78 (0.64-0.96)	0.0086
EXTREME	81%		



PD-L1 CPS ≥ 20%

	Events	HR (95% CI)	*P*
Pembro alone	62%	0.61 (0.45-0.83)	0.0007
EXTREME	78%		



Burtness et al. ESMO 2018

Evaluating Biomarkers in HNSCC

- Current FDA approvals of pembrolizumab and nivolumab are NOT contingent upon tumor PD-L1 status
  - KEYNOTE - 012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - KEYNOTE - 040: Phase III pembrolizumab vs. investigator's choice chemotherapy
    - Did not meet survival endpoints in total population but improved outcomes in patients with PD-L1 expressing tumor
  - CheckMate 141: Most benefit was seen in PD-L1-positive tumors

Immune-related Adverse Events

KEYNOTE-012 and CheckMate 141

KEYNOTE 012

Table 2. Treatment-Related Adverse Events by Grade Severity (all-patients-as-treated population; N = 132)

Treatment-Related Adverse Event	Grade 1 or 2 (≥ 10% of patients), No. (%)	Grade 3 (any occurrence), No. (%)	Grade 4 (any occurrence), No. (%)
Patients with ≥ 1 event	70 (53)	8 (6)	4 (3)
Hypothyroidism	14 (11)	0	0
Immune thrombocytopenic purpura	0	0	1 (1)
Abdominal pain	1 (1)	1 (1)	0
Colitis	0	1 (1)	0
Dysphagia	1 (1)	1 (1)	0
Nausea	6 (5)	1 (1)	0
Stomatitis	1 (1)	1 (1)	0
Facial edema	0	1 (1)	0
Fatigue	28 (21)	0	0
Localized edema	0	1 (1)	0
Infection	0	1 (1)	0
Decreased appetite	9 (7)	2 (2)	0
Dehydration	0	1 (1)	0
Diabetic ketoacidosis	0	0	1 (1)
Hyperglycemia	1 (1)	0	1 (1)
Type I diabetes mellitus	0	1 (1)	0
Laryngeal edema	0	0	1 (1)
Pneumonitis	2 (2)	2 (2)	0
Respiratory distress	0	1 (1)	0
Facial swelling	3 (2)	1 (1)	1 (1)

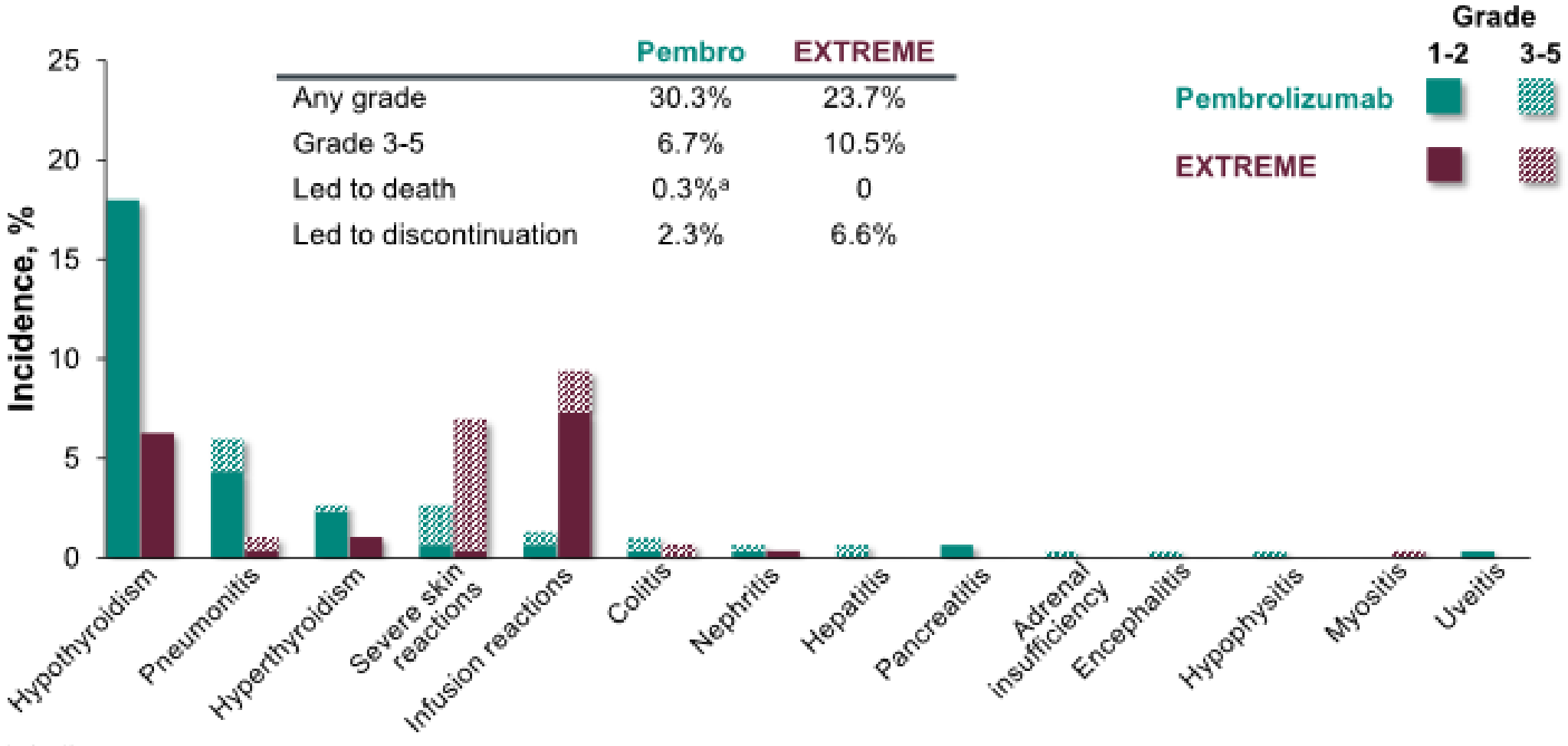
CheckMate 141

Event	Nivolumab (N=236)	
	Any Grade	Grade 3 or 4
Any event	139 (58.9)*	31 (13.1)
Fatigue	33 (14.0)	5 (2.1)
Nausea	20 (8.5)	0
Rash	18 (7.6)	0
Decreased appetite	17 (7.2)	0
Pruritus	17 (7.2)	0
Diarrhea	16 (6.8)	0
Anemia	12 (5.1)	3 (1.3)
Asthenia	10 (4.2)	1 (0.4)
Vomiting	8 (3.4)	0
Dry skin	7 (3.0)	0
Stomatitis	5 (2.1)	1 (0.4)
Weight loss	4 (1.7)	0
Mucosal inflammation	3 (1.3)	0
Peripheral neuropathy	1 (0.4)	0
Alopecia	0	0
Neutropenia	0	0

Immune-related Adverse Events

KEYNOTE-048 – Pembrolizumab monotherapy

	Pembro	EXTREME
Any grade	30.3%	23.7%
Grade 3-5	6.7%	10.5%
Led to death	0.3%[a]	0
Led to discontinuation	2.3%	6.6%

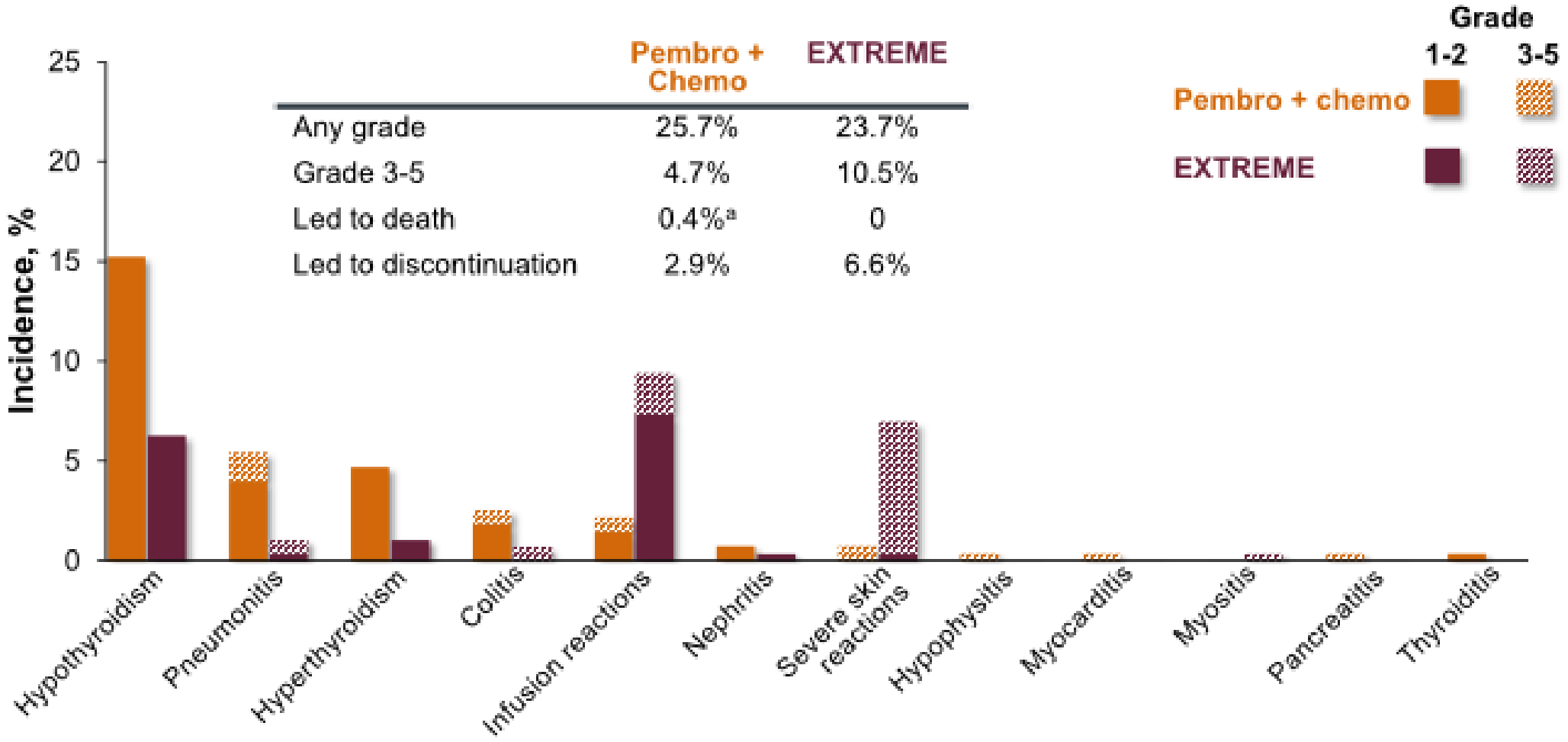


Burtness et al. ESMO 2018

Immune-related Adverse Events

KEYNOTE-048 – Pembrolizumab + Chemotherapy

	Pembro + Chemo	EXTREME
Any grade	25.7%	23.7%
Grade 3-5	4.7%	10.5%
Led to death	0.4%[a]	0
Led to discontinuation	2.9%	6.6%



Burtness et al. ESMO 2018

Immune-related Adverse Events

Table 2 General guidance for corticosteroid management of immune-related adverse events

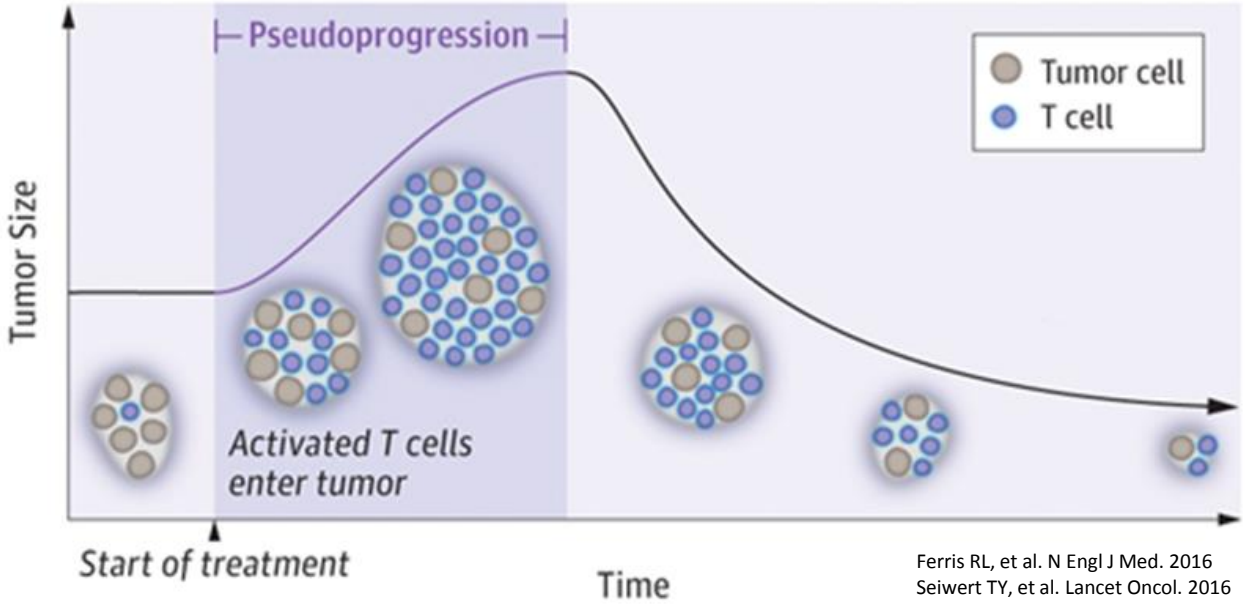
Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Puzanov Journal for ImmunoTherapy of Cancer 2017

Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

Pseudoprogression

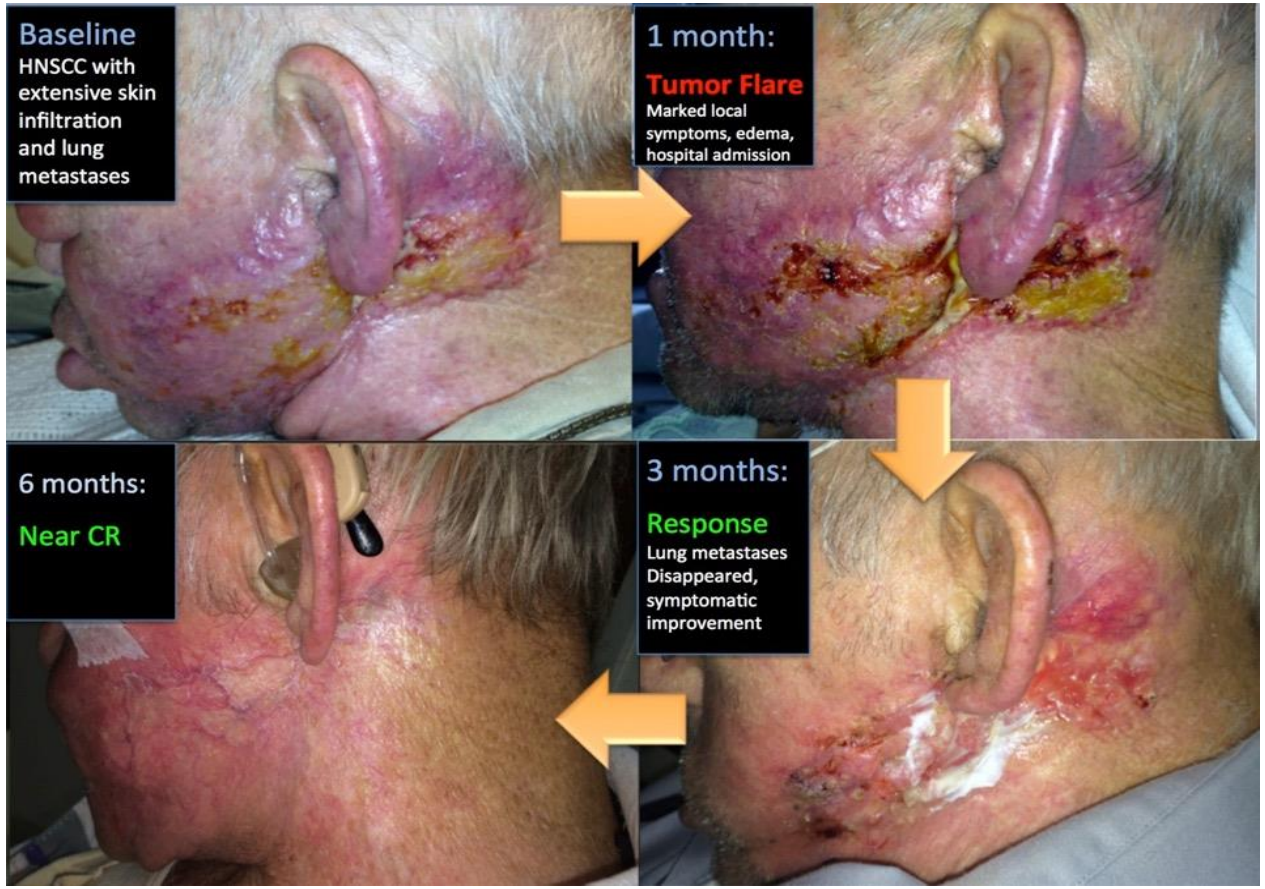
- Early appearance of an increase in tumor burden, subsequently followed by tumor regression
- Initially recognized in the melanoma trials, with incidence up to 10%



Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

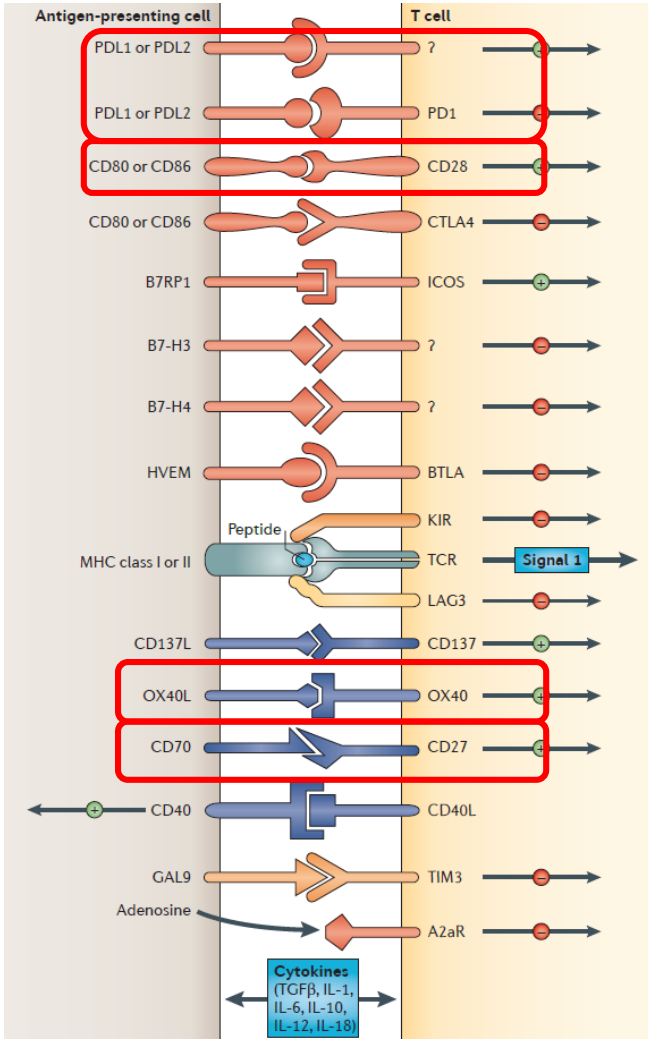
Case Report – KEYNOTE-012



- Both KEYNOTE-012 and CheckMate 141 trials showed an exceedingly rare rate of pseudoprogression with pembrolizumab and nivolumab, respectively.

Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

Developmental Immunotherapies for HNSCC



Pardoll DM Nature 2012

- Durvalumab, atezolizumab, avelumab, CK-301 (anti-PD-L1)
- Cemiplimab (anti-PD-1)
- Ipilimumab, tremelimumab (anti-CTLA-4)
- Varlilumab (anti-CD27)
- PF-04518600, tavolimab (anti-OX40)

Developmental Immunotherapies for HNSCC

MASTERKEY 232/KEYNOTE-137

- Talimogene laherparepvec (T-Vec)
  - Genetically engineered herpes virus
- T-Vec 10^6 PFU/mL intratumoral injection followed by 10^8 PFU/mL Q3W
- Pembrolizumab 200 mg IV Q3W
- Eligibility:
  - R/M HNSCC not suitable for curative therapy
  - Progressed after platinum treatment
  - At least 1 injectable cutaneous, subcutaneous, or nodal tumor ≥ 10 mm in longest diameter

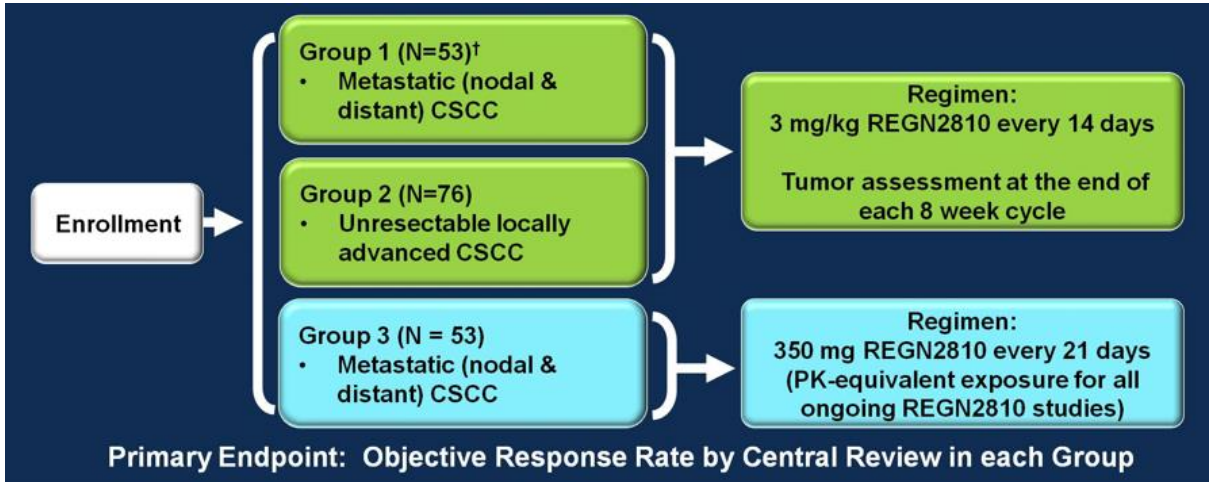
Developmental Immunotherapies for HNSCC

Cemiplimab (REGN2810) for treatment of patients with cutaneous squamous cell carcinoma (cSCC)

FDA approved – 09/28/2018

- Patients with metastatic cSCC
- Patients with locally advanced cSCC who are not candidates for radiation or surgery

NCT02760498

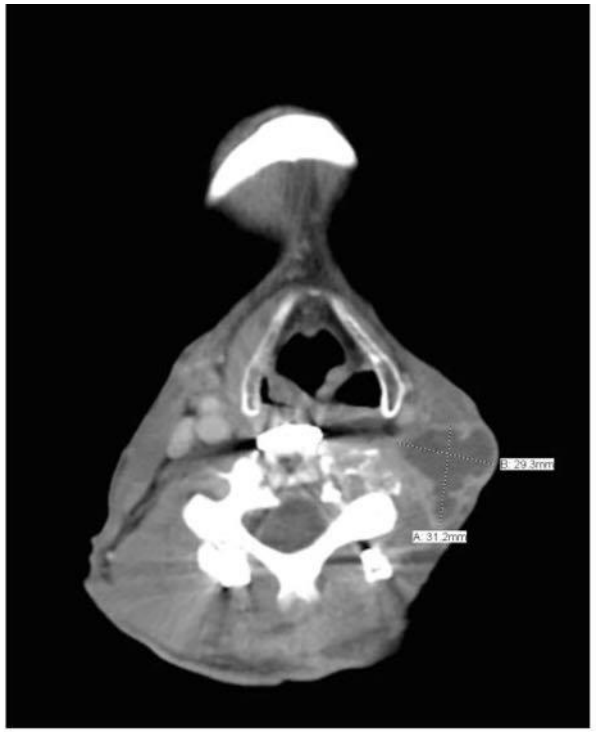


- ORR 46% in 82 patients in study
- Responses durable, median DOR not reached

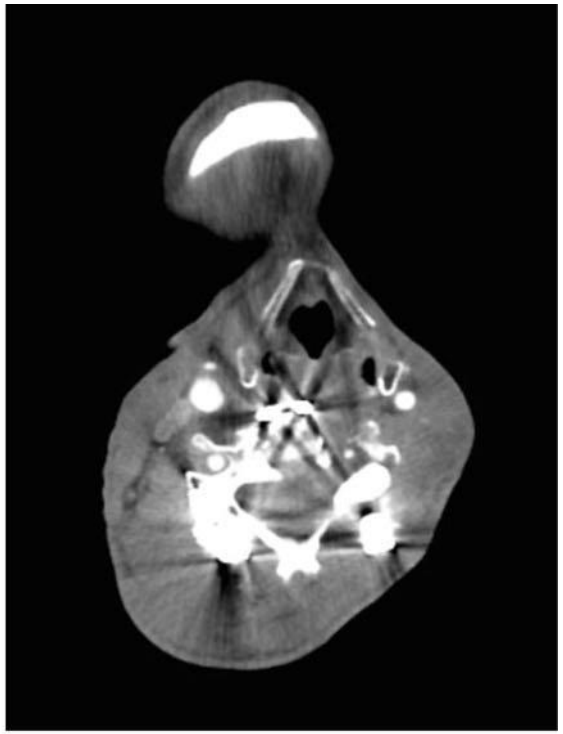
Conclusions

1. Chemotherapy offers short survival with many side effects
2. PD-1 antibodies nivolumab and pembrolizumab are approved in *platinum-refractory* recurrent / metastatic HNSCC.
3. Most patients have fewer side effects on PD-1 Abs than on chemotherapy
4. Clinical trials are underway to improve immunotherapy response rates and testing immunotherapy in other settings

Case Study 1a: success cSCC



Baseline



Week 16

Neck mass in cSCC patient at baseline (3.1 cm) *left*, and at Week 16 (1.6 cm) *right*.

13 year cSCC disease course

Falchook, Leidner et al. *JITC*, Nov 2016

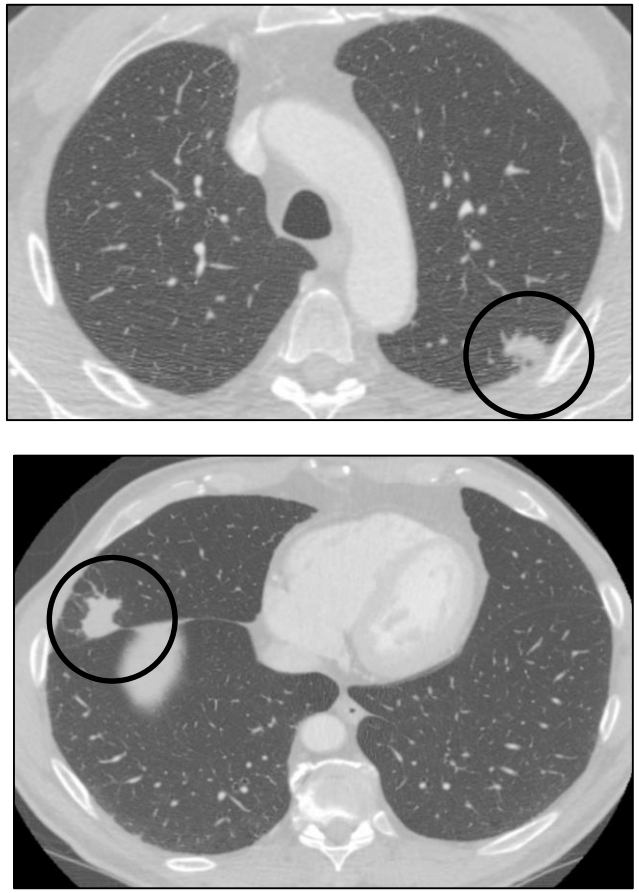
- *MOHS* x10, starting 2002
- *Adjuvant RT* left cheek (2005)
  left mandible (2006)
  left neck w/ Cetuximab (2008)
  bilateral neck w/ Carbo (2010)
- *Systemic Therapy* Capecitabine (2008)
  Cisplatin + Docetaxel (2010)
- 2012 in-scar recurrence L neck s/p excision
- Feb 2015 urgent decompression s/p C4-C5 corpectomy
- March 2015 REGN2810 (cemiplimab, FIH)
  *first dose cohort 1mg/kg q2w IV

CR after 1 year Tx = Feb 2016

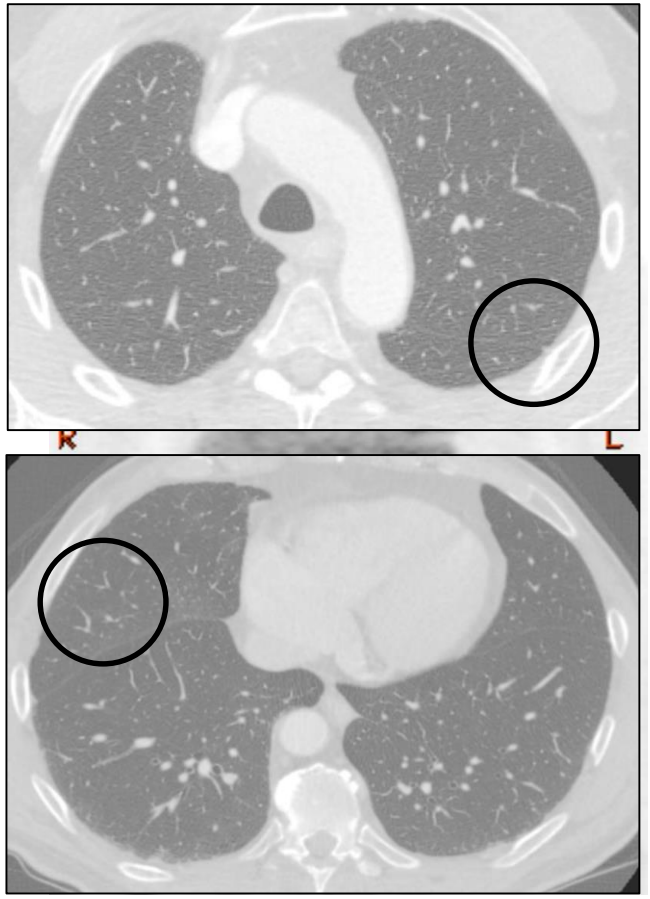
Remains in CR, now 36 months off-treatment

Case Study 1b: success HNC

3 months post ChemoRT



7 months post ChemoRT



HPV+ OPC Stage IVA (T3 N2b M0)

AJCC 8th clinical stage II

- 2013 Definitive ChemoRT (70 Gy + Cis 100 x2)
  - Zoster V3 ipsilateral left at 3 months post.

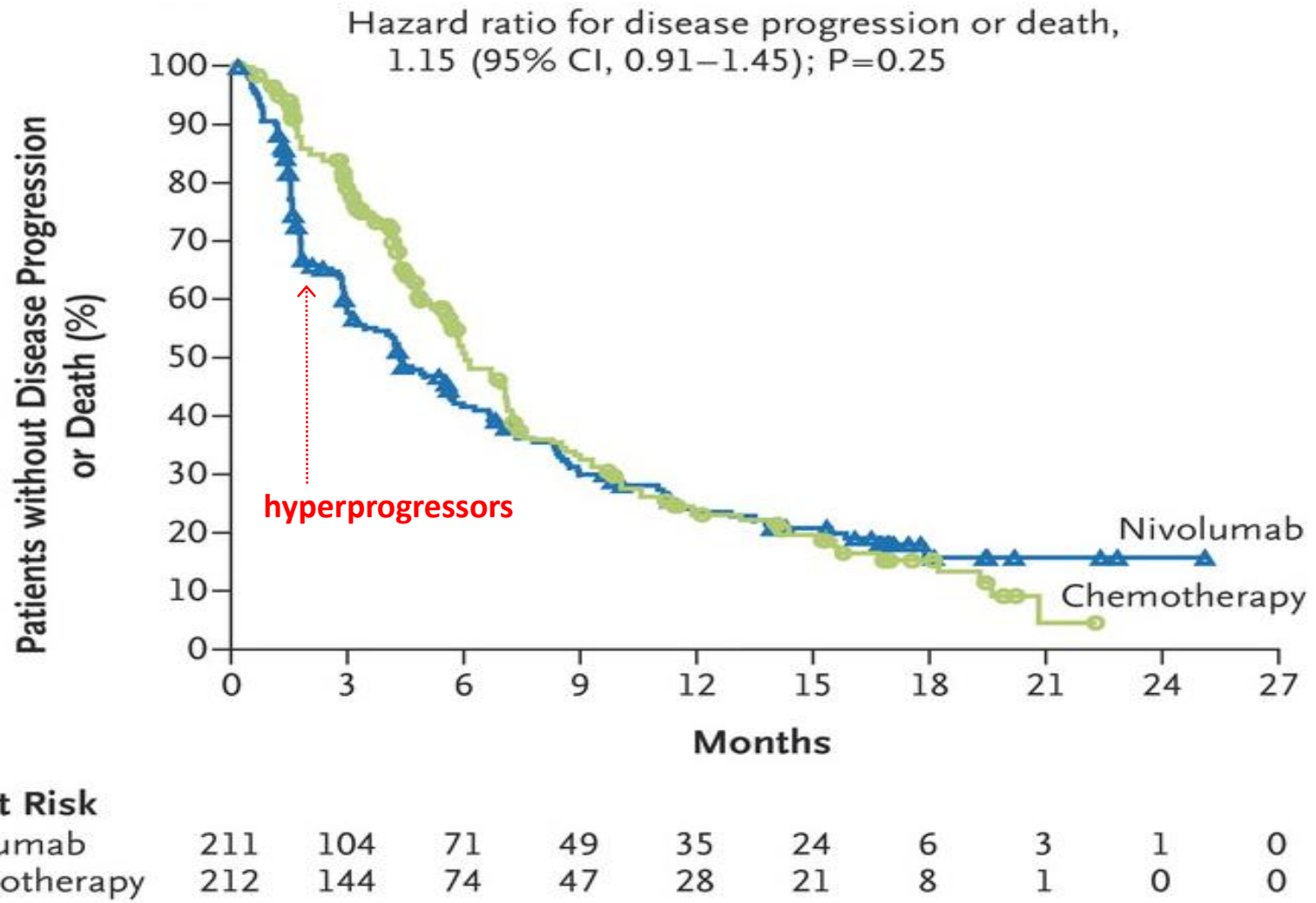
- Lung mets @ 3 months post-CRT
- April 2014 Phase I trial: anti-KIR/anti-PD-1

CR after 6 months Tx = Nov 2014

Remains in CR, now 50+ months off-treatment

Case study 2a: failure Oral SCC

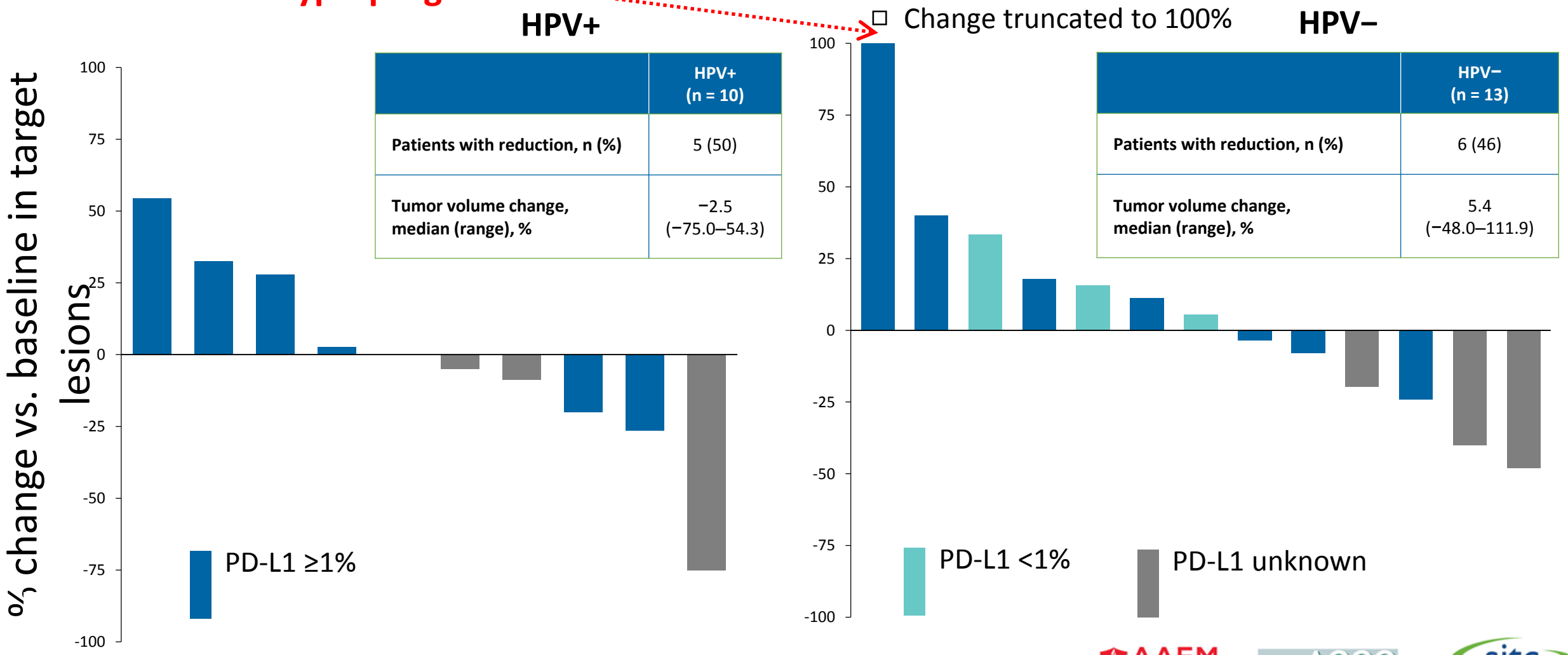
Checkmate 026:
1st line Lung
Nivo v. Platin-couplet
(NSCLC, any histology)



Carbone DP et al. N Engl J Med 2017;376:2415-2426.

Case study 2a: failure Oral SCC

Hyperprogressor

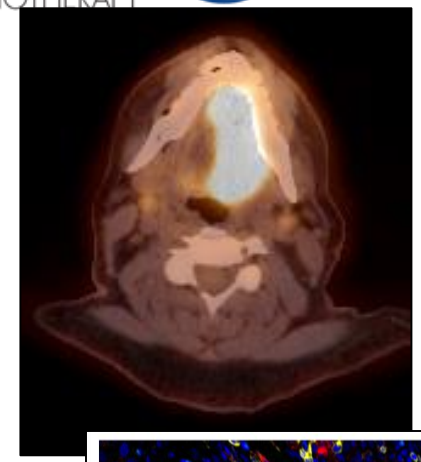


	HPV+ (n = 10)
Patients with reduction, n (%)	5 (50)
Tumor volume change, median (range), %	−2.5 (−75.0–54.3)

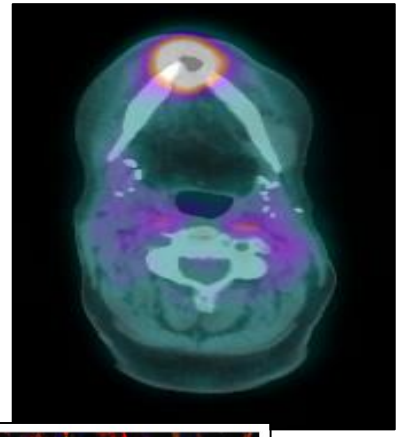
	HPV− (n = 13)
Patients with reduction, n (%)	6 (46)
Tumor volume change, median (range), %	5.4 (−48.0–111.9)

Ferris et al., Checkmate 358 (ESMO 2017 LBA46): % Δ after Nivo x2

Case study 2a: failure Oral SCC

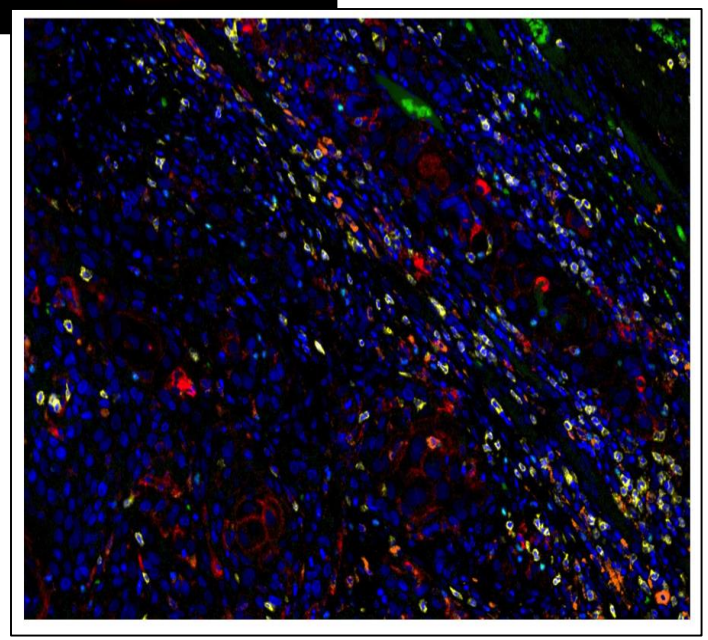


Oral SCCa, stage IVA (T4a N2c M0)
*local Recurrence at 9 months ➔

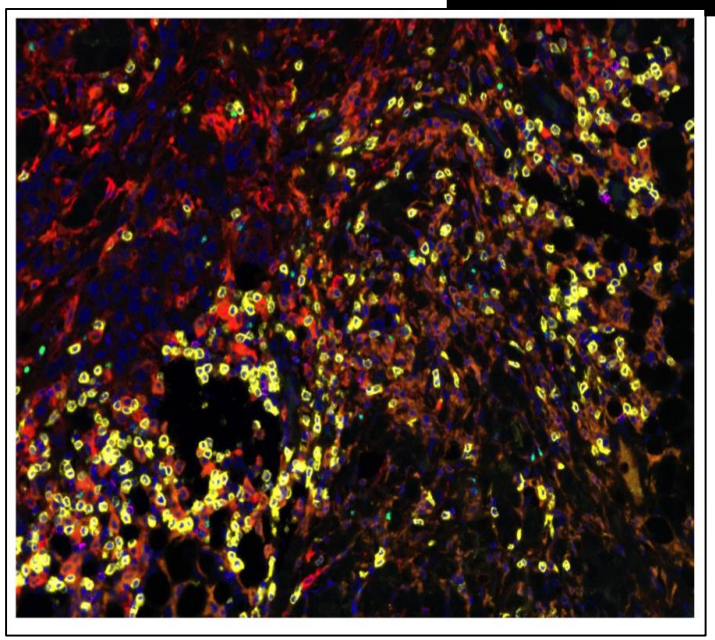


PD-L1 CD8 CD3 FoxP3 CD163 DAPI

PD-1



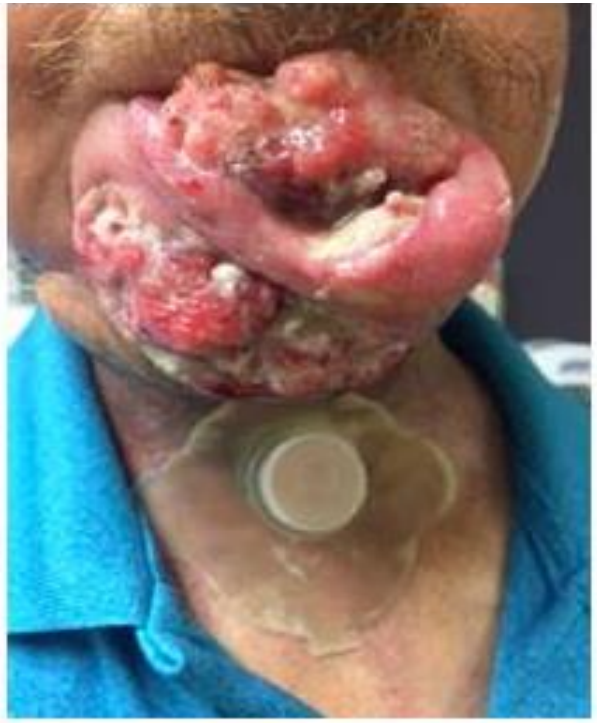
Adjuvant ChemoRT ➔9 months➔



How to treat now?

Case study 2a: failure Oral SCC

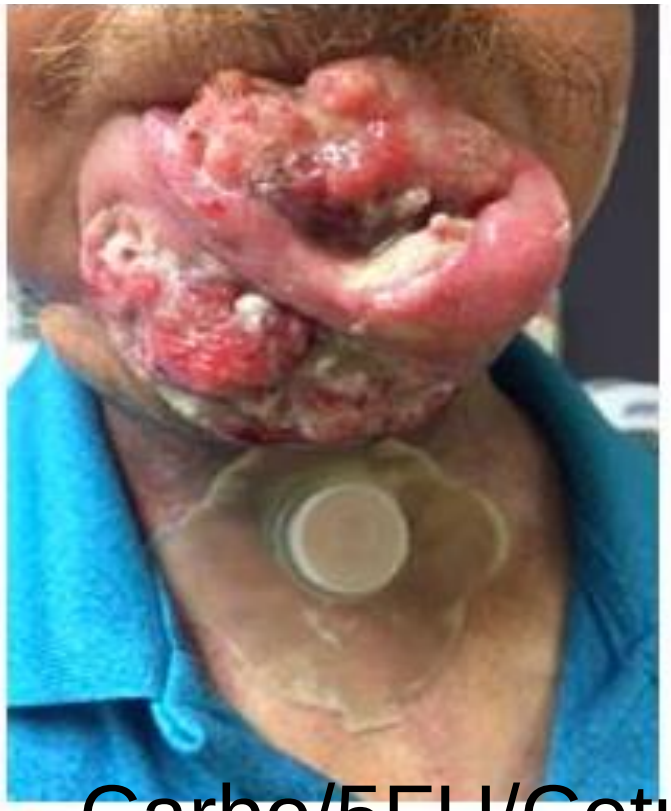
← 6 weeks →



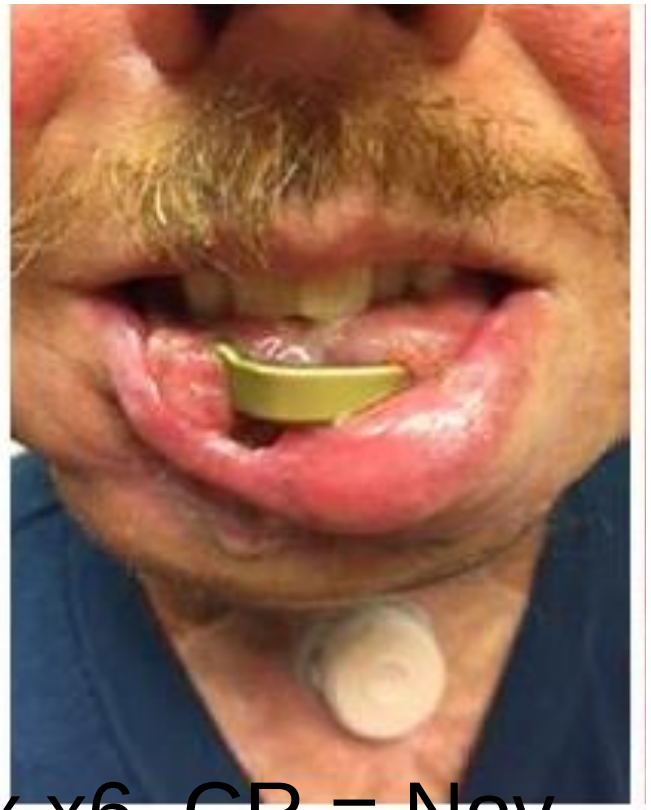
PD-1 re-challenge = hyperprogression

Case study 2a: failure Oral SCC

Week 0



Week 24



CHEK2 c.470T>C:p.Ile157Thr (germline)

TP53 c.782+1G>T

Unknown Clinical Significance:
EGFR c.1295A>G:p.Gln432Arg
ERBB3 c.170A>G:p.Glu57Gly
GNAQ c.907_919del: p.Gln303fs
LRP1B c.10974T>G:p.Cys3658Trp

Primary cell line

80-90e^6 TIL in cyro

All 6 clones recognize autologous tumor but not allo tumor (523 -728 pg/ml IFNγ)

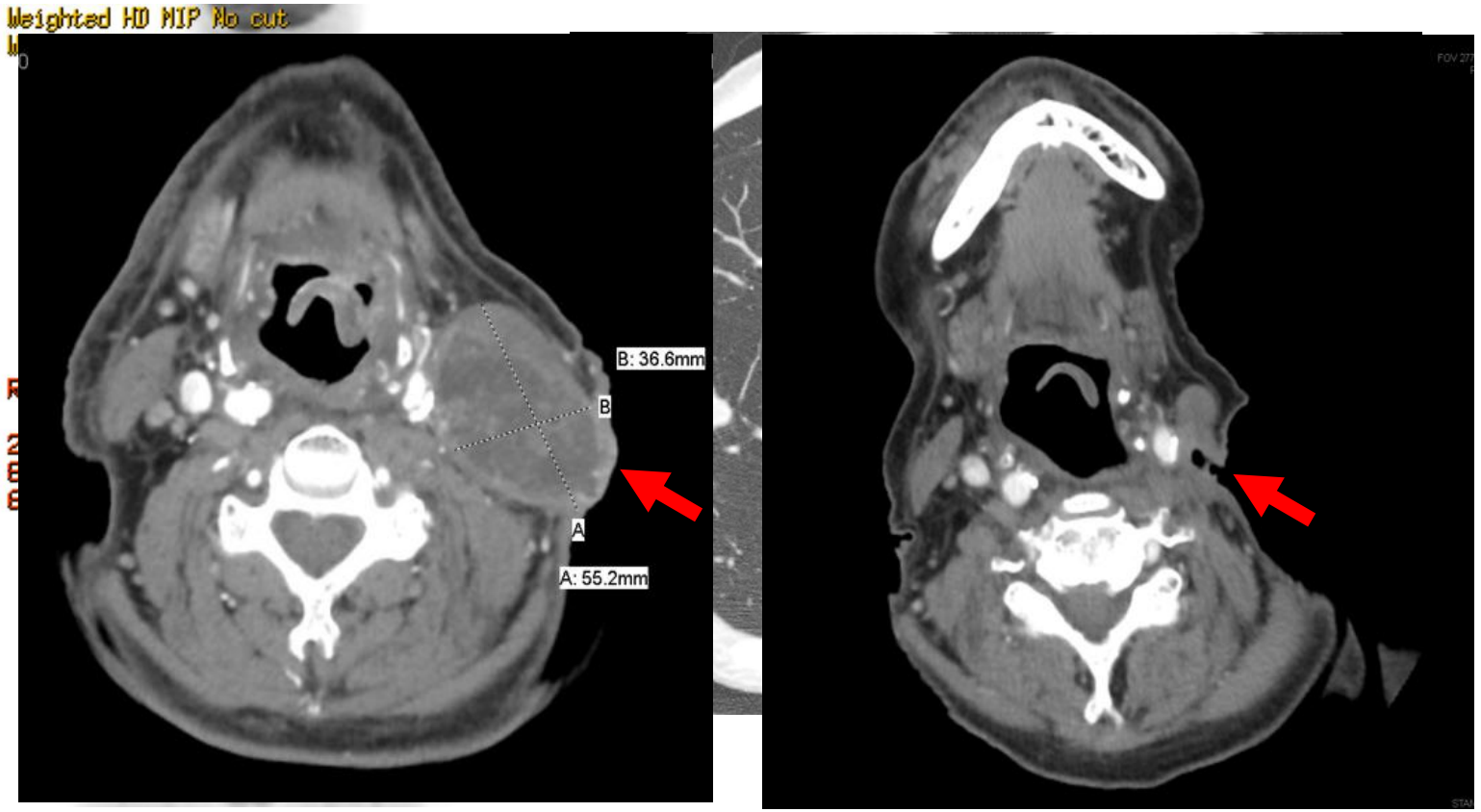
Carbo/5FU/Cetux x6, CR = Nov 2017
*stable CR, now 14 months off treatment

Kato et al., *Clin Cancer Res.* 2017 Aug 1

Case study 2b: success(?) HNC

Baseline 36 mm

6 months: 0 mm



Larynx Stage IVC (T4 N2c M1)

- Jan 2014 urgent tracheostomy, PEG
  - TPF induction x2 cycles
  - Consolidative Quad Shot GTV x3 (44.4 Gy)
- July 2014 Phase I trial: anti-KIR/anti-PD-1
  - CR after 6 months Tx = Jan 2015
  - 21 months withdrew d/t UGIB (Apr 2016)
- Sep 2016 recurred in oral cavity & lungs
  - Nivo rechallenge, salvage RT, both failed.
  - Died in hospice 3.5 years after M1 Dx (July 2017)

Do differently in future?

Thank You

Developmental Immunotherapies for HNSCC

KEYNOTE – 048 (NCT02358031)