Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancer

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ACCC Association of Community Cancer Centers

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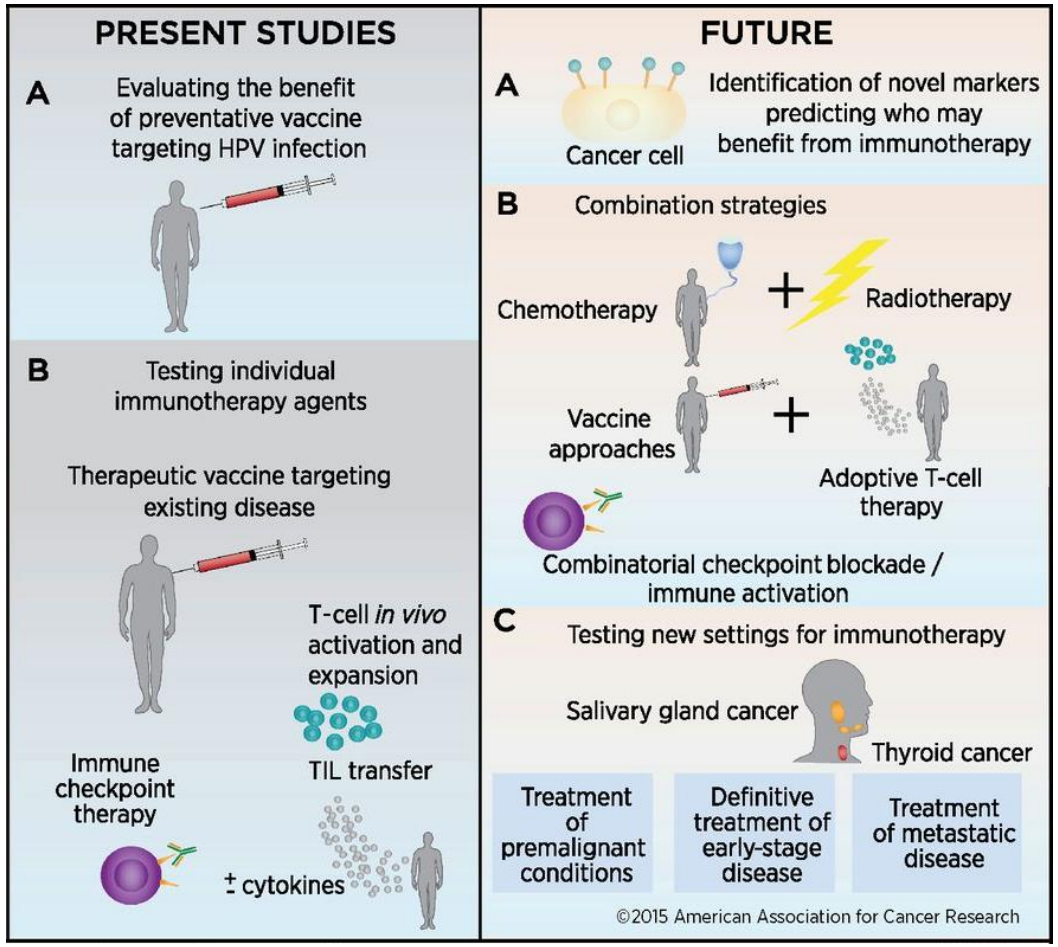
Disclosures

- Research support from Merck, BMS, AstraZeneca for my role as PI for clinical trials.
- I will not be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Head and Neck Cancers

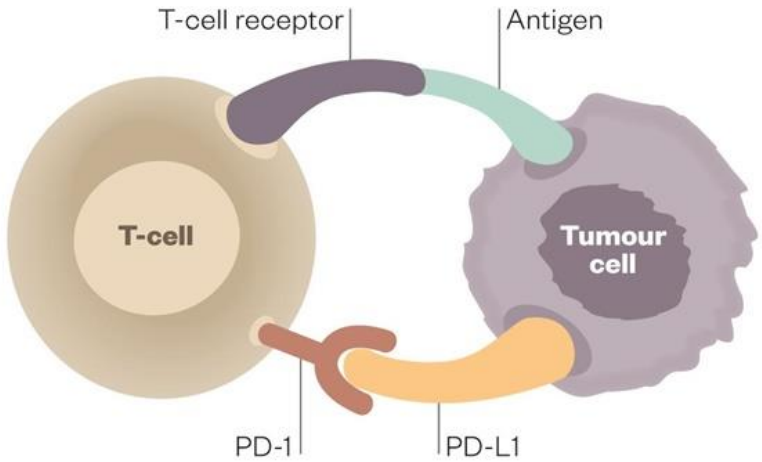
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Expression of immunologic markers to guide treatment
  - Preventive vaccination against virally mediated cancers
  - PD-1 checkpoint inhibitors for the treatment of metastatic disease



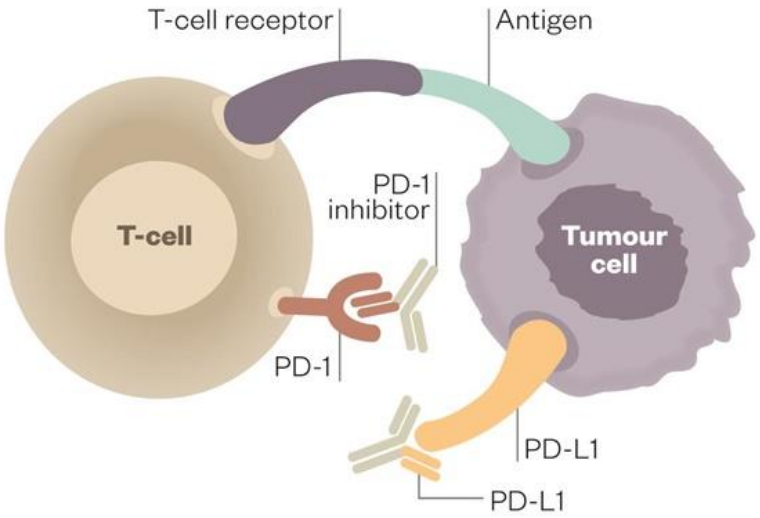
Schoenfeld JD, Cancer Immunol Res, 2015

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

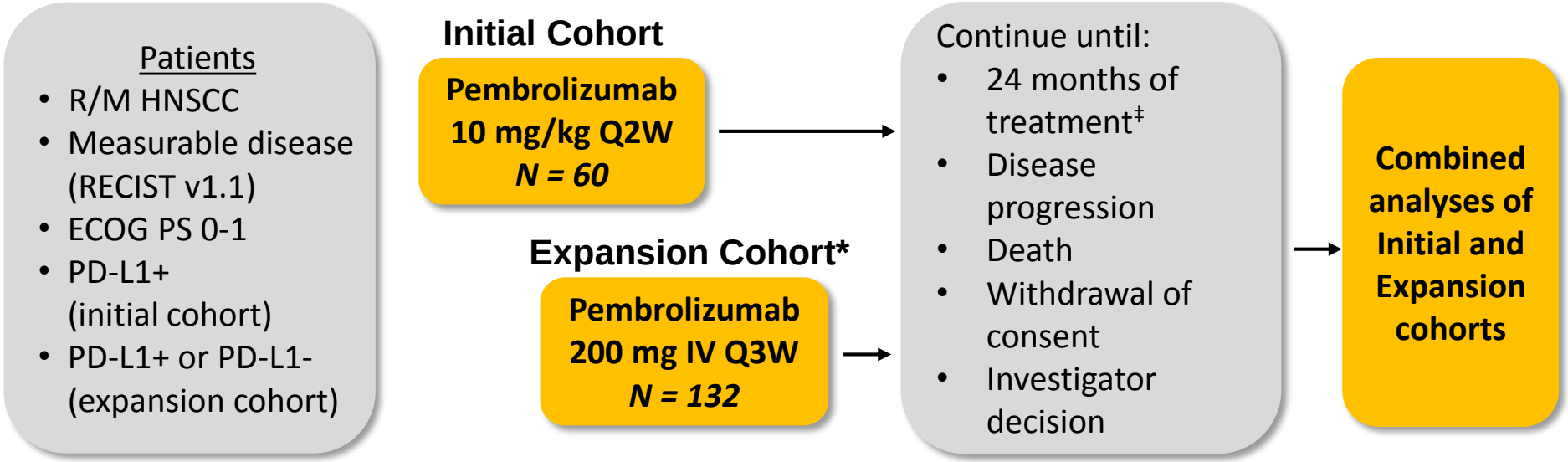
FDA-approved Checkpoint Inhibitors for Use in Head and Neck Cancers

- 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

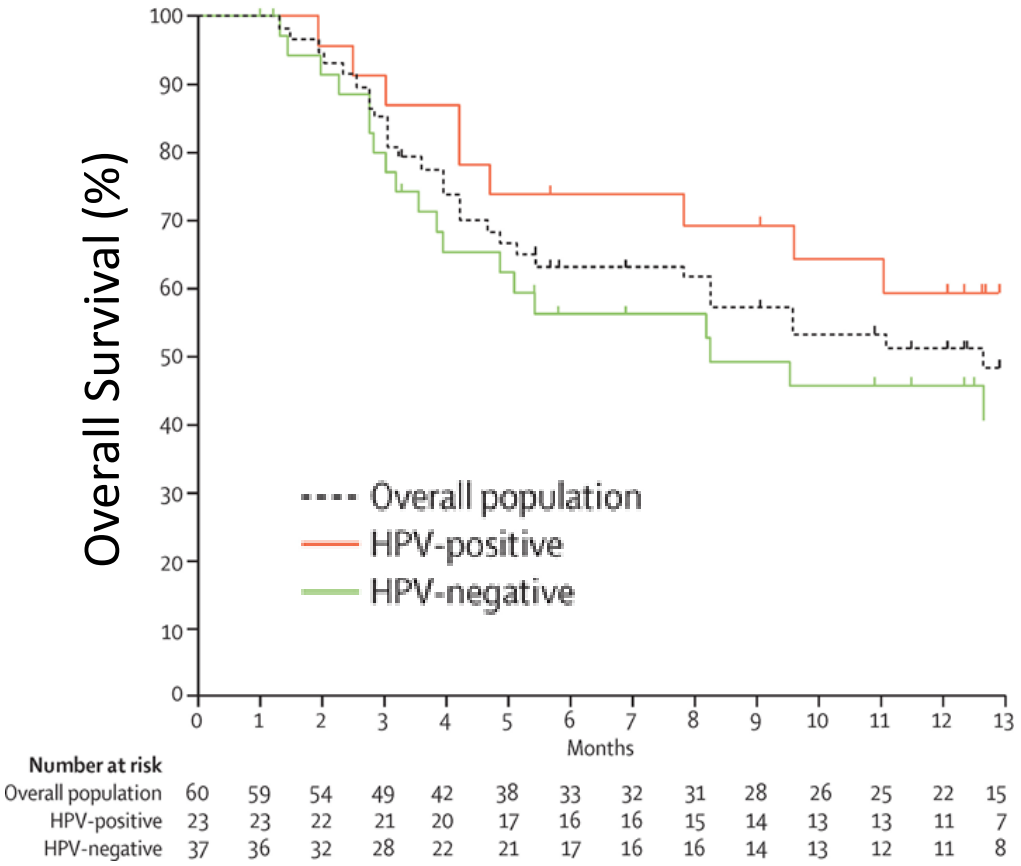
Primary end points: ORR (RECIST v1.1, central imaging vendor review), safety

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

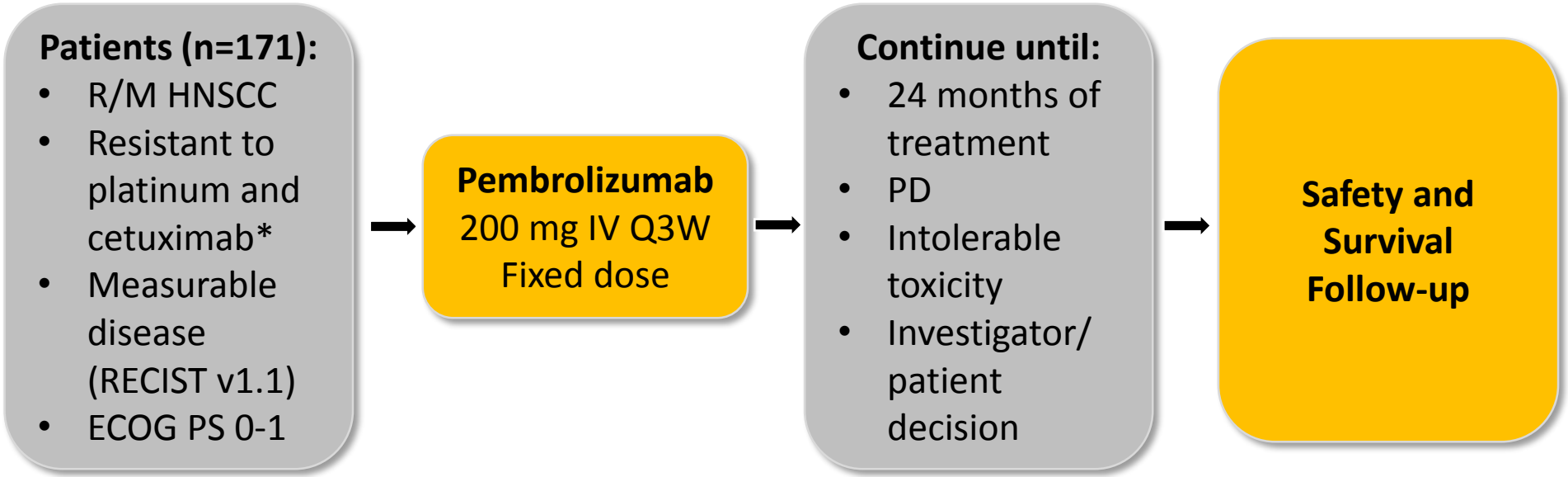
Nonrandomized, Phase 1b Trial, Cohorts† B, B2



- 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.

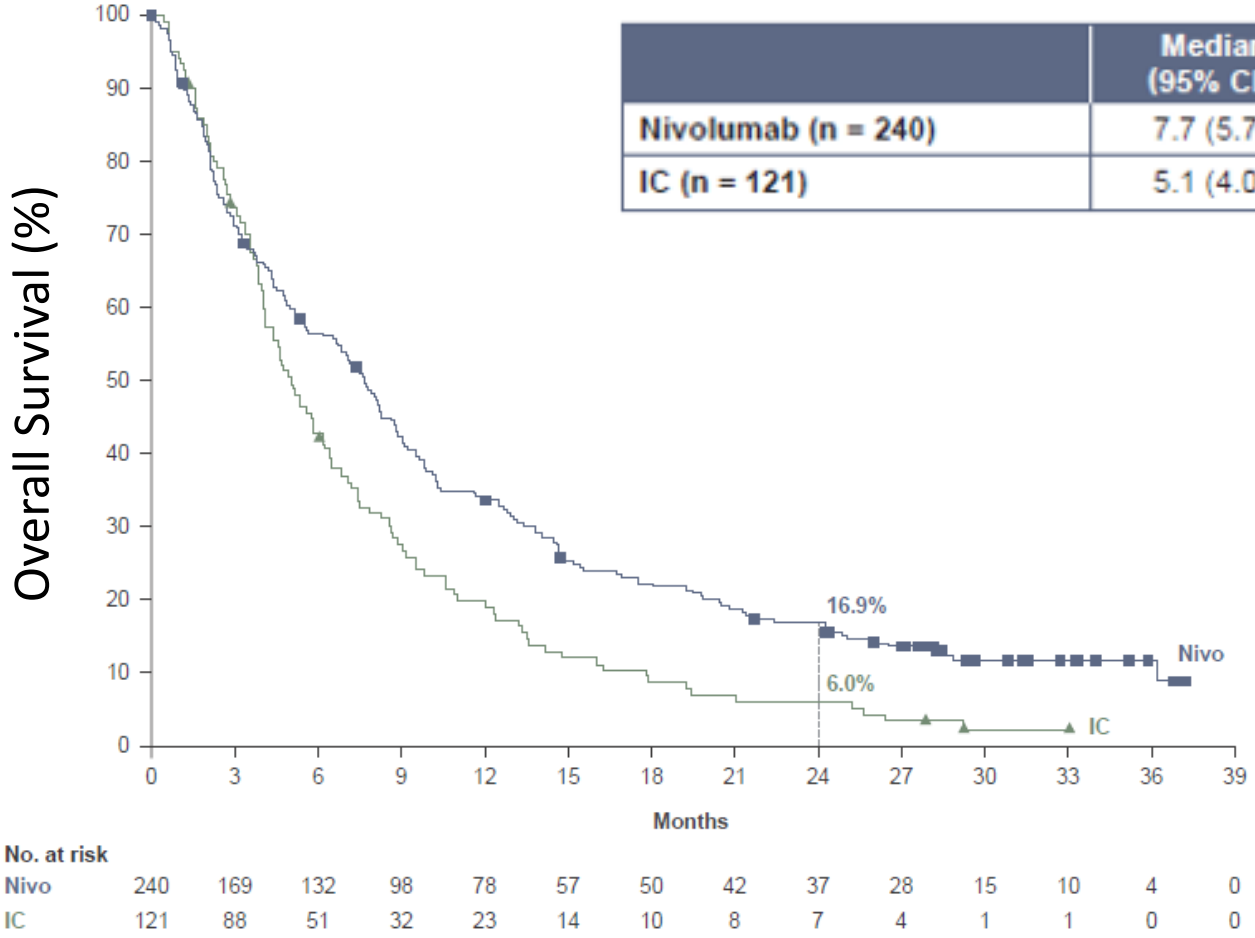
[a]Tissue required for testing

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)	

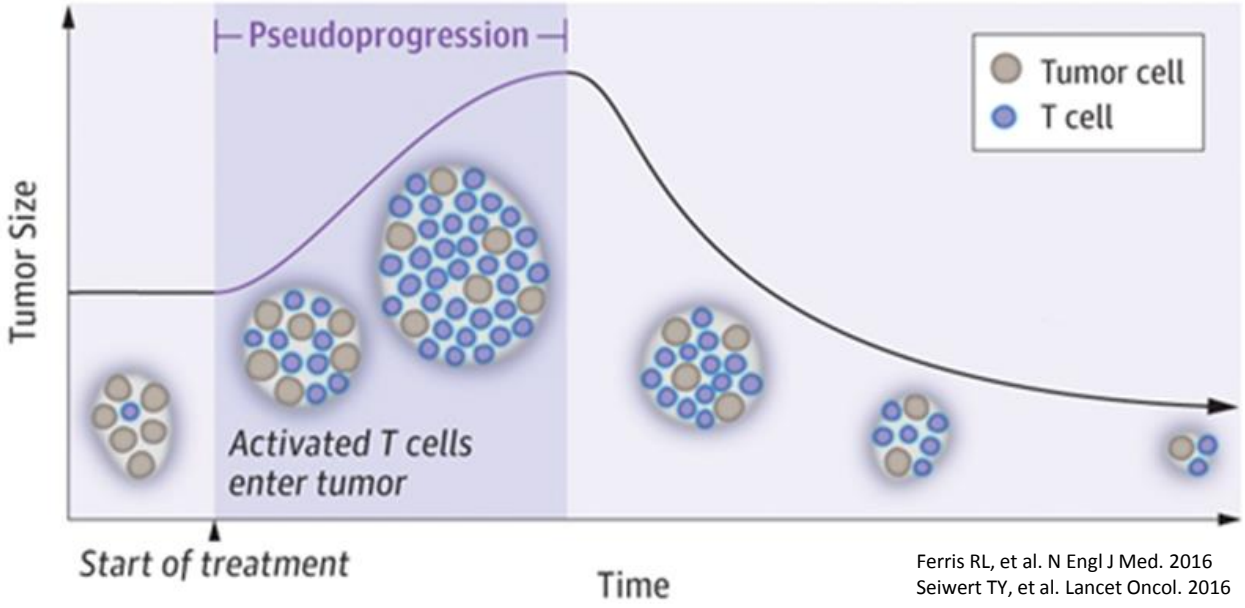


Ferris RL. Oral Oncology, 2018

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

Pseudoprogression

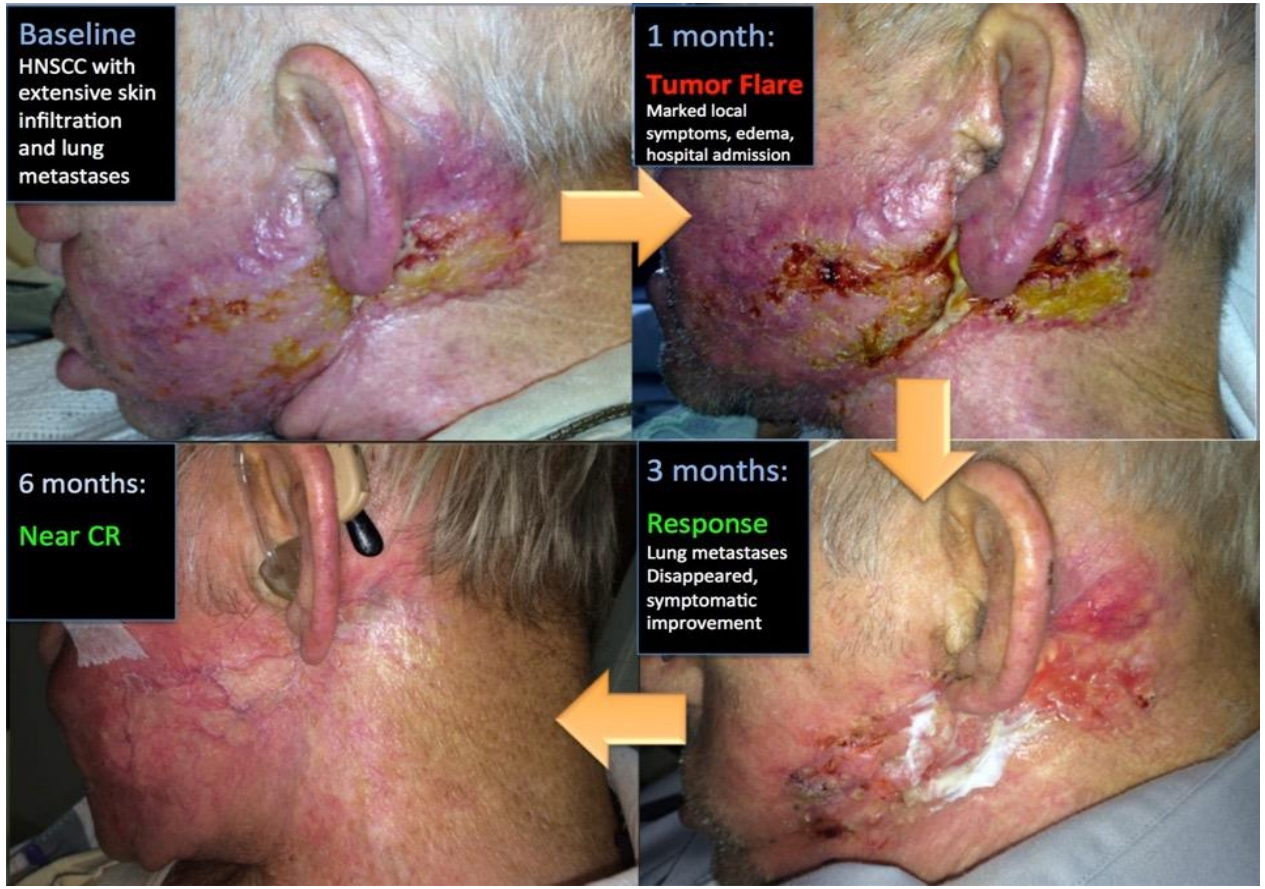
- Early appearance of an increase in tumor burden, subsequently followed by tumor regression
- Initially recognized in the melanoma trials, with incidence up to 10%



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



- KEYNOTE-012 showed an exceedingly rare rate of pseudoprogression with pembrolizumab.

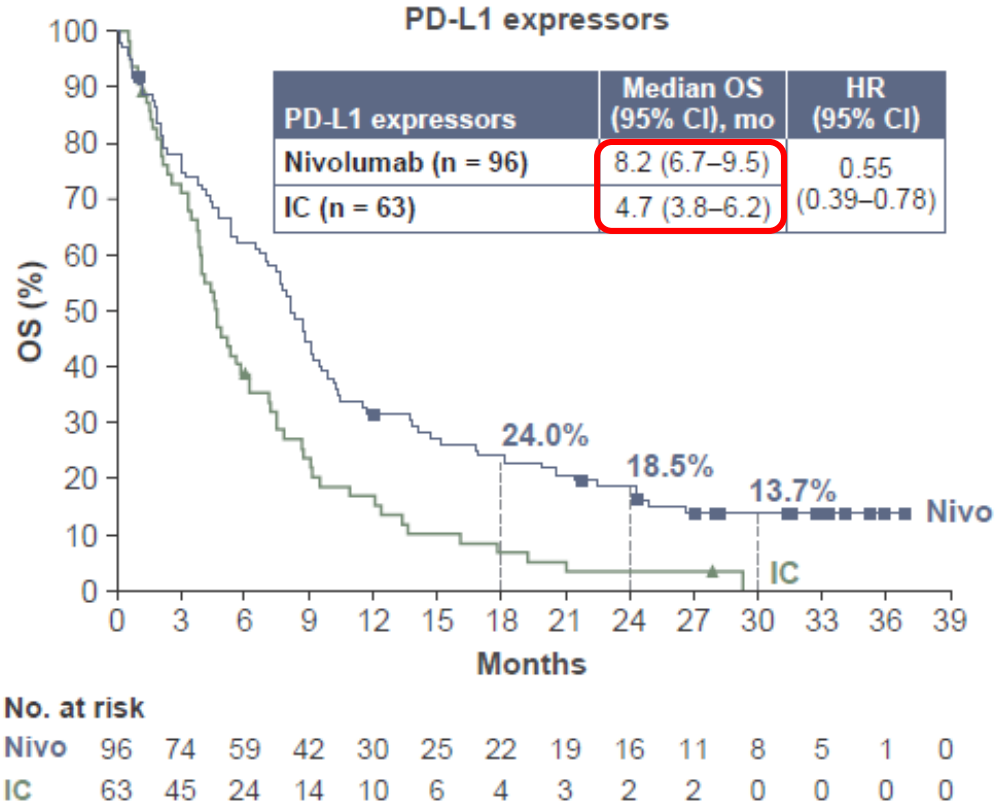
Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

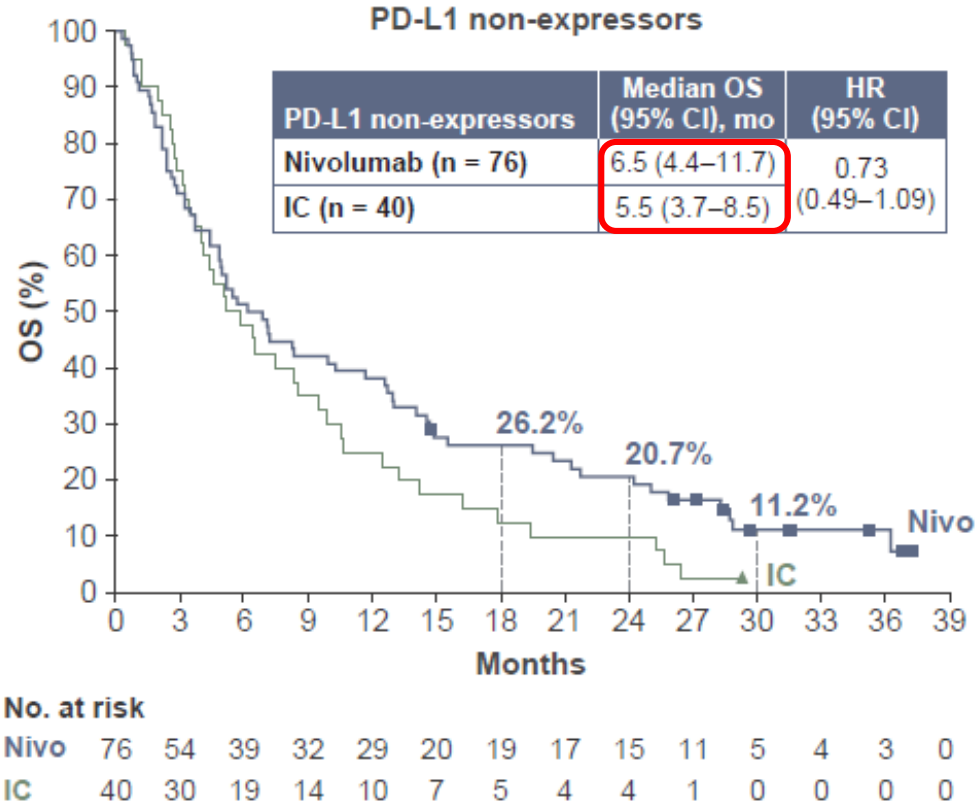
Evaluating Biomarkers in HNSCC

- 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
    - Initially did not meet survival endpoints in total population but improved outcomes in patients with PD-L1 expressing tumor
  - CheckMate 141: More benefit was seen in PD-L1-positive tumors

Evaluating Biomarkers in HNSCC

CheckMate 141: 2 year update





Other Biomarkers in HNSCC

- PD-L1 expression on tumor cells + tumor infiltrating immune cells
- Immune Gene Expression
- Mutational Burden

Immune-related Adverse Events

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

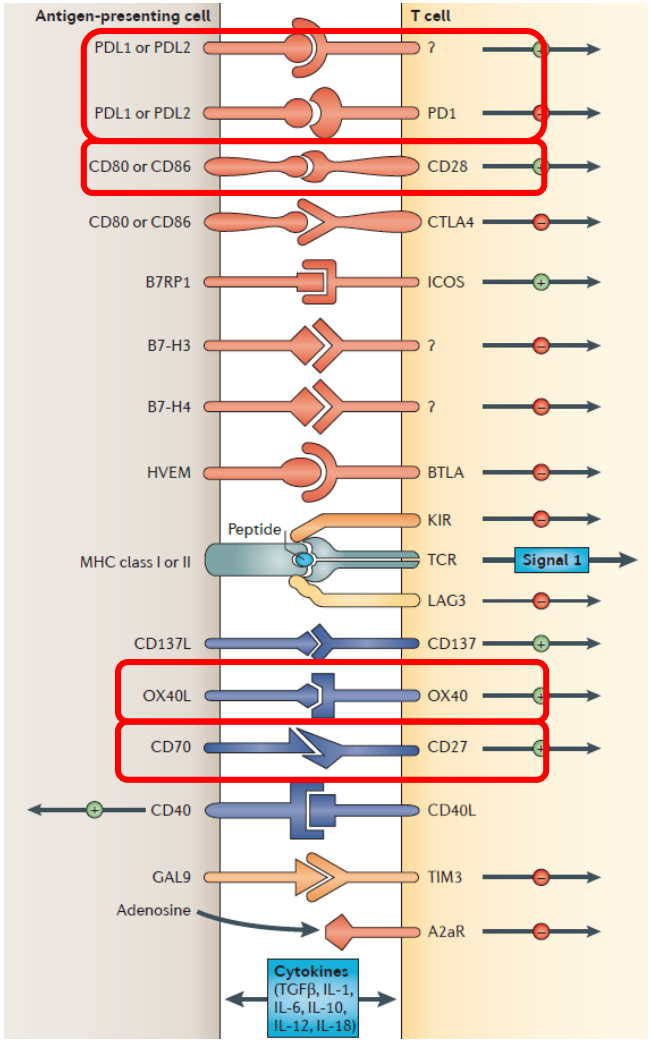
Immune-related Adverse Events

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

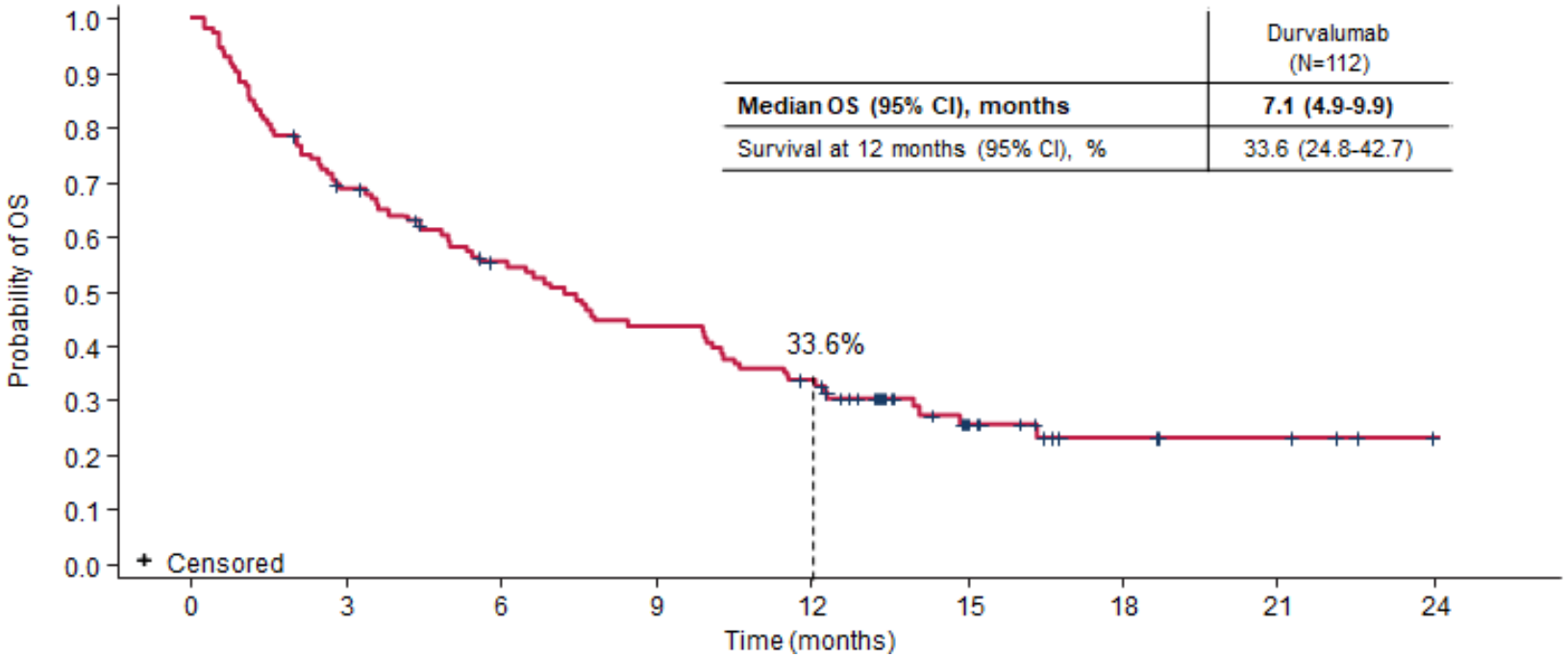
Developmental Immunotherapies for HNSCC



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)

Hawk Trial: Durvalumab in PD-L1 high R/M HNSCC after failure of platinum based therapy *Overall Survival*



	Durvalumab (N=112)
Median OS (95% CI), months	**7.1 (4.9-9.9)**
Survival at 12 months (95% CI), %	33.6 (24.8-42.7)

	N=111
ORR, n (%)	18 (16.2 [95% CI, 9.90-24.41])
DCR at 24 weeks n (%)	26 (23.4)

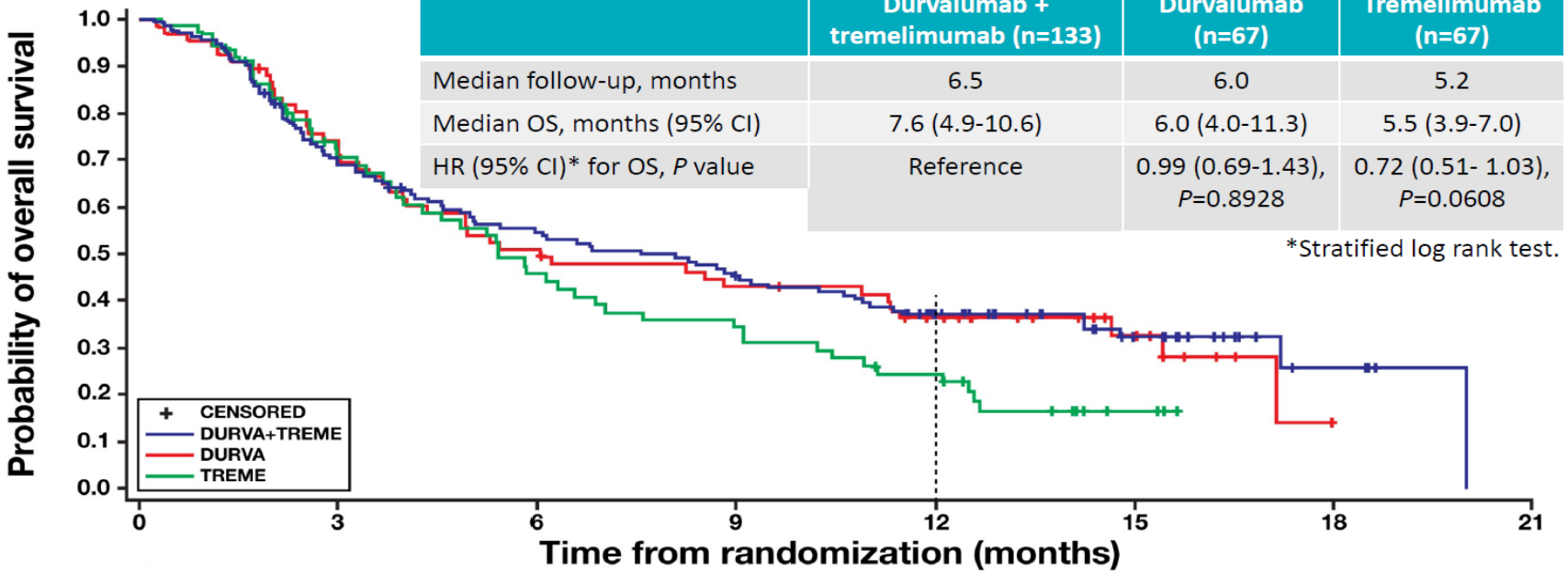
Zandberg et al. ESMO Annual Congress 2017 #1042O

Condor Trial: Durvalumab + Tremelimumab in PD-L1 low R/M HNSCC after failure of platinum based therapy: *Overall Survival*

Overall Survival

	Durvalumab + tremelimumab (n=133)	Durvalumab (n=67)	Tremelimumab (n=67)
Median follow-up, months	6.5	6.0	5.2
Median OS, months (95% CI)	7.6 (4.9-10.6)	6.0 (4.0-11.3)	5.5 (3.9-7.0)
HR (95% CI)* for OS, *P* value	Reference	0.99 (0.69-1.43), *P*=0.8928	0.72 (0.51- 1.03), *P*=0.0608

*Stratified log rank test.



	Durvalumab + tremelimumab (n=129)	Durvalumab (n=65)	Tremelimumab (n=63)
ORR, % (n) [95% CI]	**7.8 (10)** [3.8–13.8]	**9.2 (6)** [3.5–19.0]	**1.6 (1)** [0.04–8.5]
Odds ratio (95% CI), *P*-value	Reference	0.83 (0.29–2.53), *P*=0.728	5.21 (0.96–96.70), *P*=0.056
Complete response, n	0	0	0
Partial response, n	10	6	1

Siu et al. MTD HN Symposium 2018

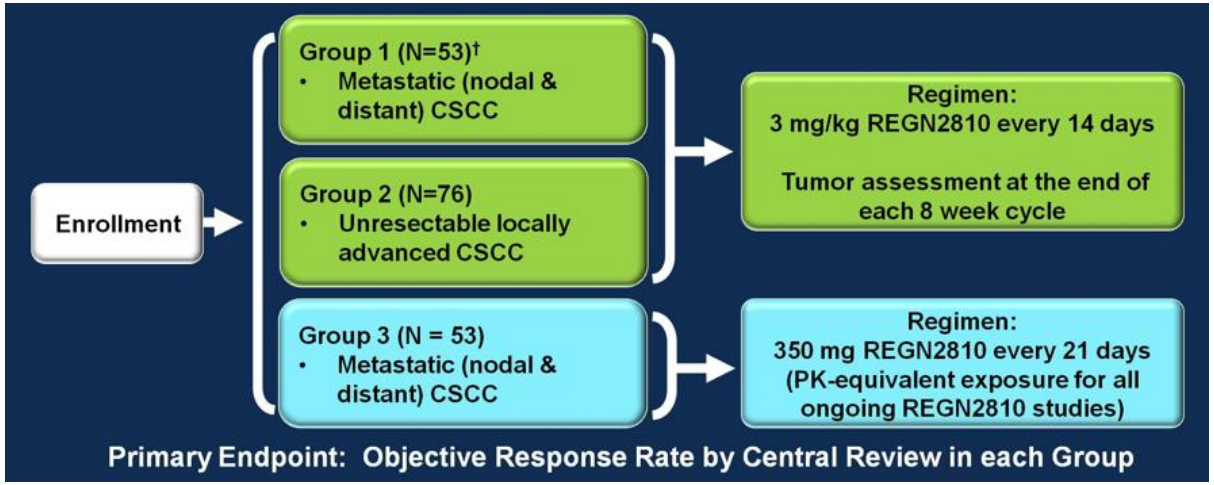
Developmental Immunotherapies for HNSCC

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

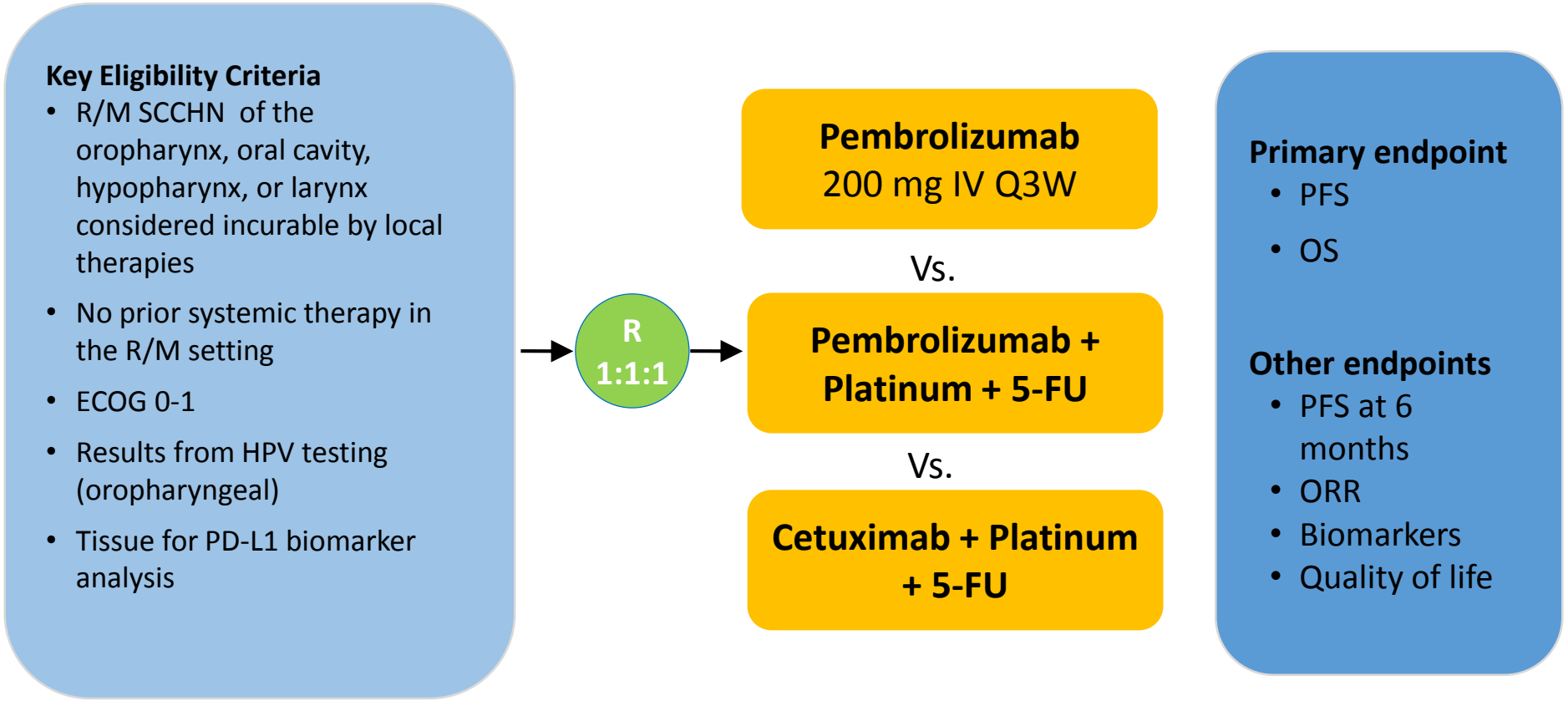
NCT02760498



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

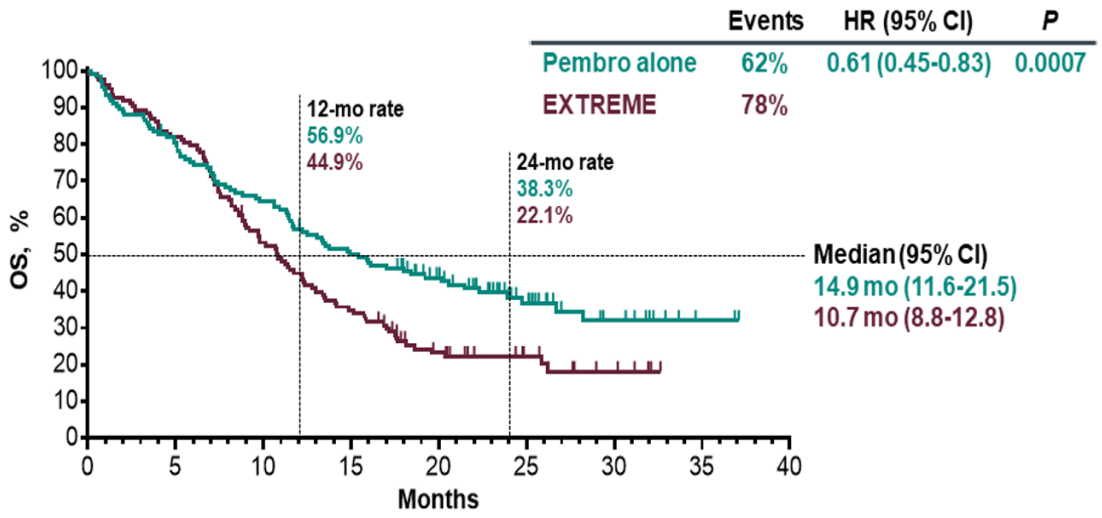
Developmental Immunotherapies for HNSCC

KEYNOTE – 048 (NCT02358031)

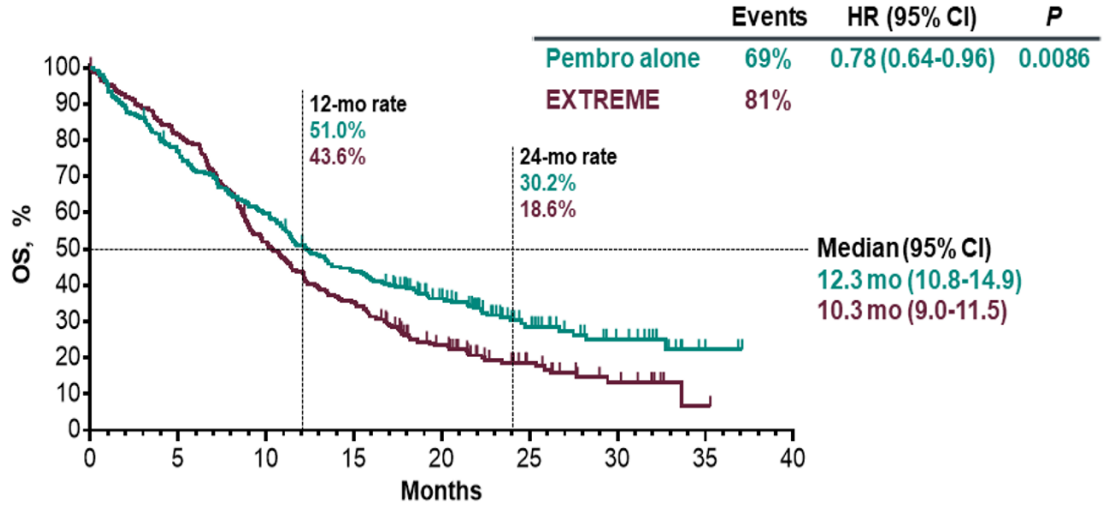


Keynote 048: Overall Survival

Overall Survival: P vs E, CPS ≥20 Population



Overall Survival: P vs E, CPS ≥1 Population

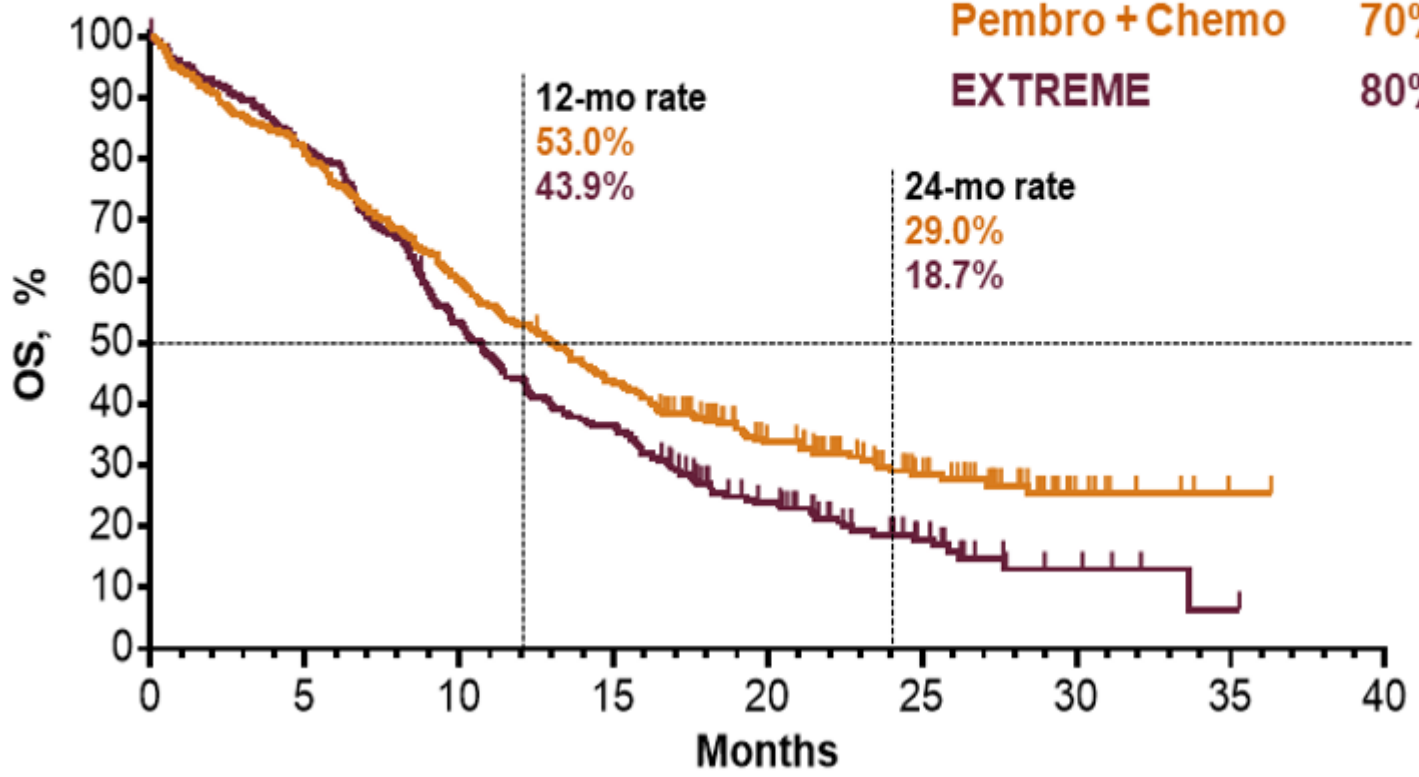


Burtness et al. ESMO 2018

Keynote 048: Overall Survival

Overall Survival: P+C vs E, Total Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	70%	0.77 (0.63-0.93)	0.0034
EXTREME	80%		



Median (95% CI)
13.0 mo (10.9-14.7)
10.7 mo (9.3-11.7)

Burtness et al. ESMO 2018

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

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 1

- The patient is a 65 yo W male with pmh for Htn and DM presents for recurrent/metastatic oral cavity SCC.
  - Initial presentation with T2N2bM0 SCC of the right oral tongue s/p resection and adjuvant CRT (+ENE) completed in Feb 2016
  - Presents in June of 2018 with recurrence in the left neck and pulmonary metastasis
  - Started on Carbo/5FU/Cetuximab s/p 6 cycles with progression of disease
- What would you recommend as the best next therapy?
  - A. Pembrolizumab plus paclitaxel
  - B. Nivolumab
  - C. Cetuximab plus Nivolumab
  - D. Docetaxel

Case Study 1 (continued)

- Patient is initiated on Nivolumab with imaging showing response after 3 months of therapy. The patient continues on Nivolumab and then presents for his 5th dosage with complaints of diarrhea
  - 8 loose BMs per day
  - Possible sick contact at a family get together a week before
  - Some lightheadedness/dizziness
  - BP 90/60 (normally 130-140/80), P: 110
  - PE: Gen- NAD, Abd – soft, mild LLQ tenderness, +BS, ND
  - Labs: K= 2.7, Cr = 2.2

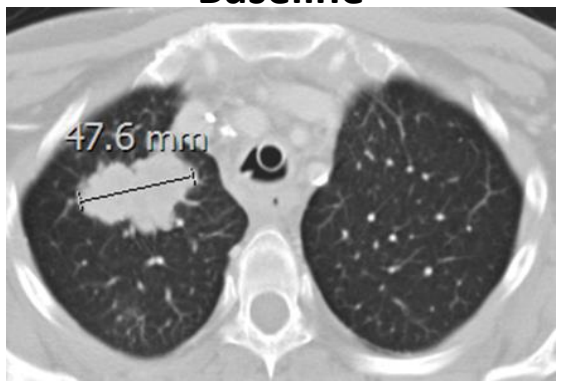
Case Study 1 (continued)

- What would you recommend as the next step for this patient

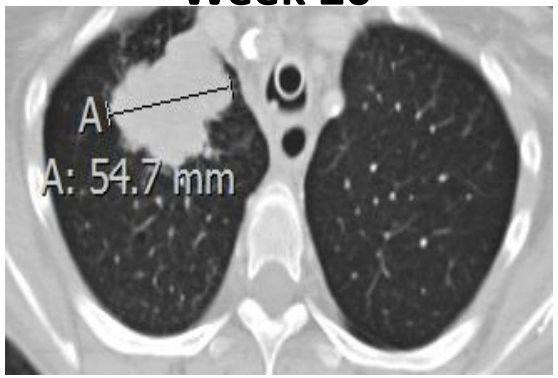
  - A. Give Nivolumab as an outpatient then admit for IVF and work up for diarrhea
  - B. Give Nivolumab as an outpatient then admit for work up for diarrhea and start steroids 1mg/kg daily.
  - C. Hold Nivolumab as an outpatient, admit for IVF and work up, start steroids 1mg/kg daily
  - D. Hold Nivolumab as an outpatient, admit for IVF and work up, start steroids 1mg/kg daily and then give Nivolumab as an inpatient with close monitoring.

Patient Case Study 2
Durvalumab in HNSCC

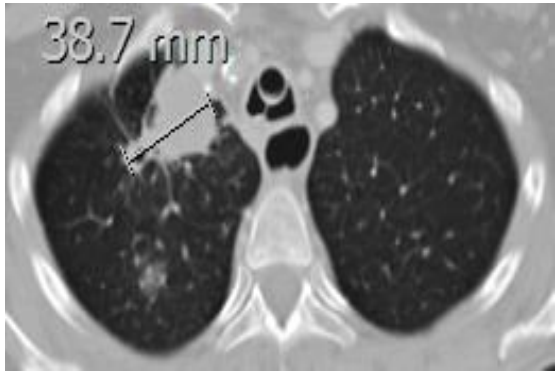
Baseline



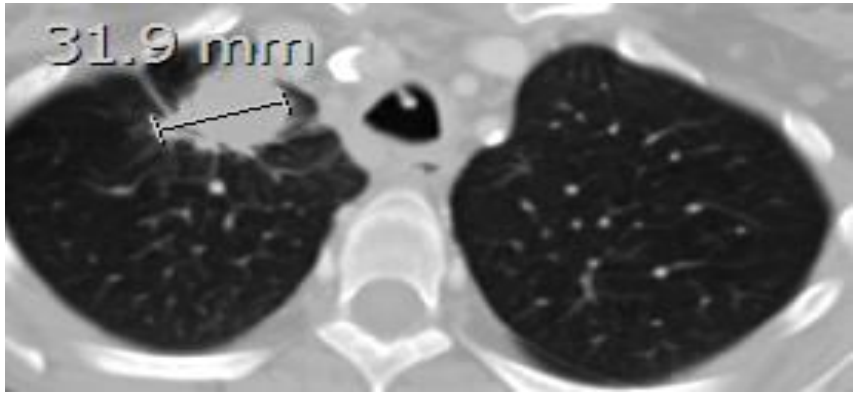
Week 20



End of Treatment - Month 12



Post Treatment – Month 27



Post Treatment – Month 43