SCCHN – Systemic Therapy

Merrill Kies

Current Treatment Approaches

- Surgery
- Radiation therapy

Local / Regional

- Chemotherapy
- Targeted therapy
- Immunotherapy

Distant / MR

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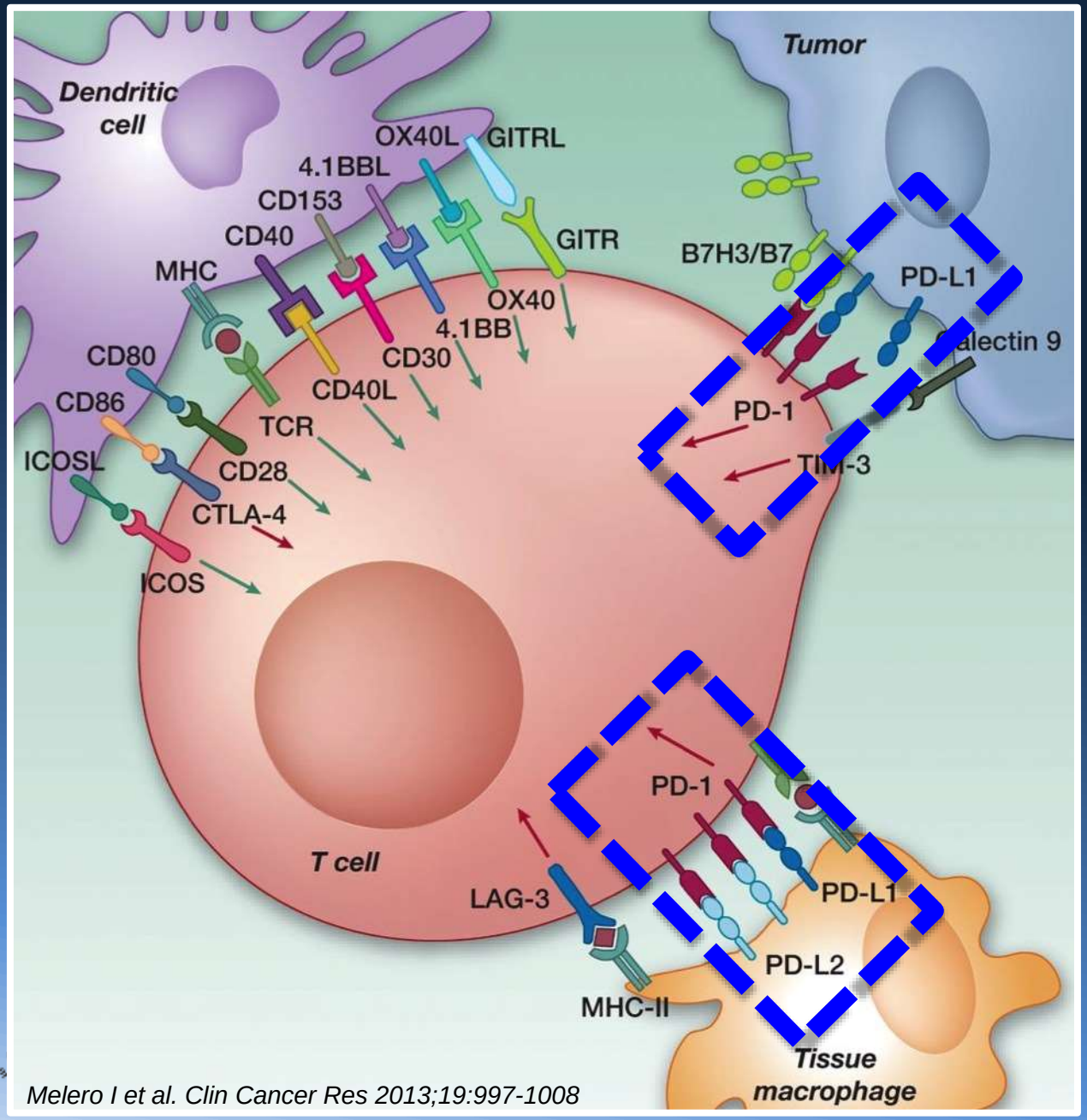
Basis for Immune therapy – Immune Escape



Melero I et al. Clin Cancer Res 2013;19:997-1008

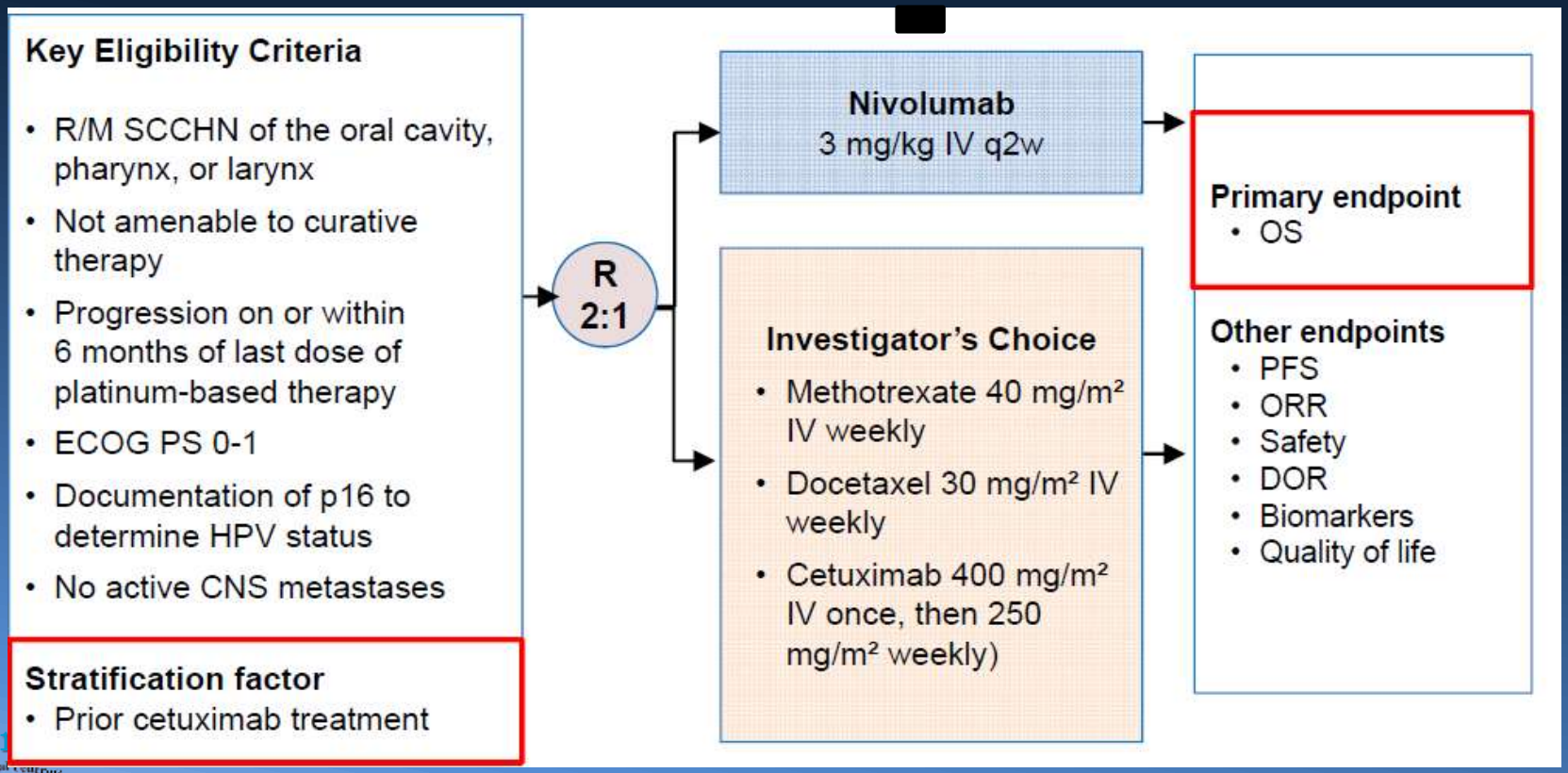
- Expression of PD-L1 on
  a) tumor cells &
  b) macrophages
  can suppress immune surveillance.
- In mouse models antibodies *blocking PD-1 / PD-L1 interaction* lead to <u>tumor rejection</u>
- Clinical prognosis correlates with presence of TILs and PD-L1 expression in multiple cancers.

Current Status

- Nivolumab (CheckMate 141) and Pembrolizumab (KEYNOTE-012) approved in 2016 for R/M HNSCC
- Ongoing trials: First-line recurrent disease, definitive with RT, neoadjuvant and adjuvant settings
- Single agents, combinations + chemotherapy, and biologics

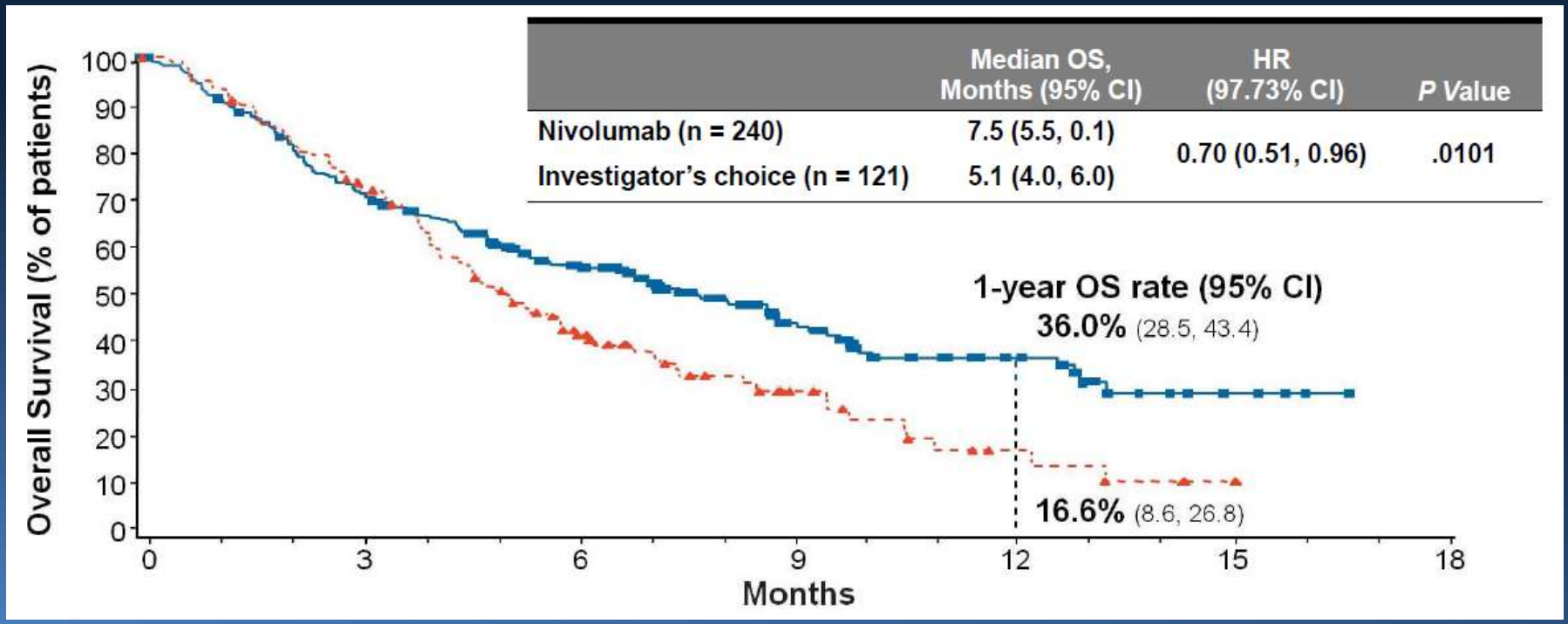
CheckMate 141: Study Design

Randomized, global, phase III trial of the efficacy and safety of nivolumab versus investigator's choice in patients with R/M SCCHN



Ferris R et al, NEJM 2016

CheckMate 141: Overall Survival



	Median OS, Months (95% CI)	HR (97.73% CI)	*P* Value
Nivolumab (n = 240)	7.5 (5.5, 0.1)	0.70 (0.51, 0.96)	.0101
Investigator's choice (n = 121)	5.1 (4.0, 6.0)		

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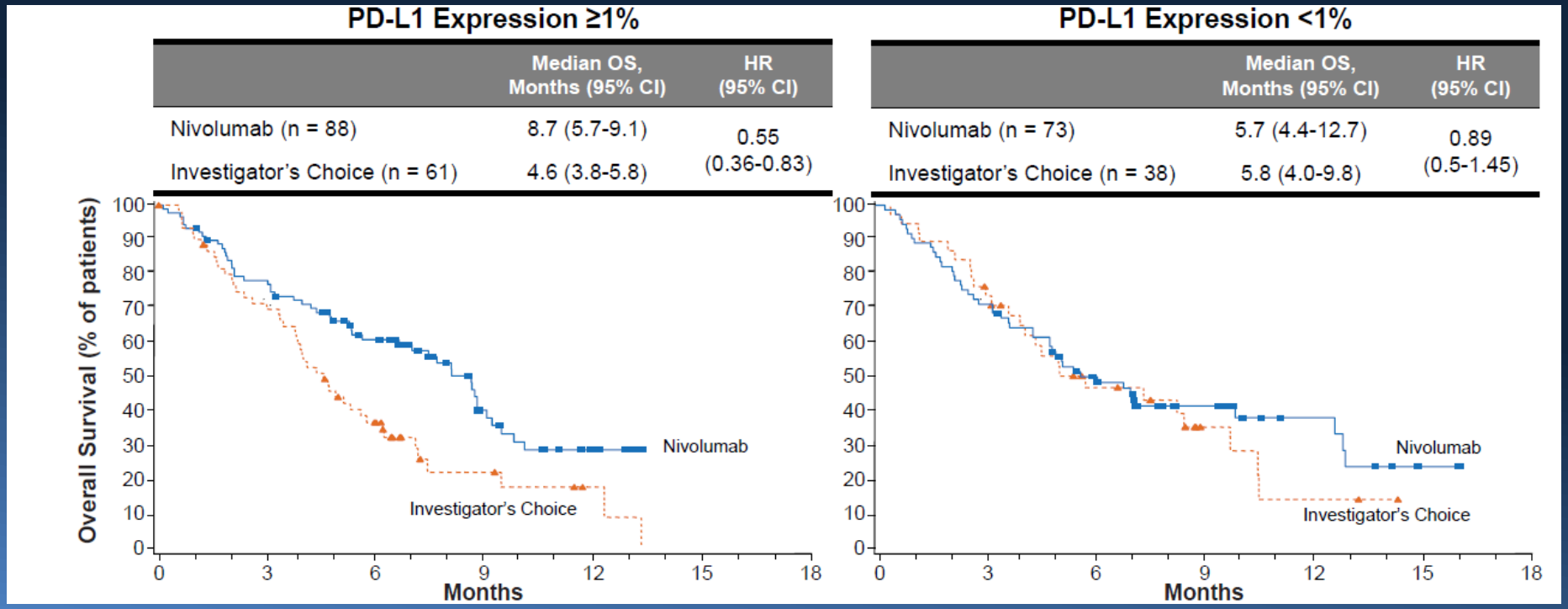
Ferris R et al, NEJM 2016

CheckMate 141: Treatment Administration

	Nivolumab (n = 240)	Investigators Rx (n = 121)	Total (n = 361)
Pts receiving ≥ 1 dose, n (%)	236 (98.3)	111 (91.7)	347 (96.1)
Investigator's therapy, n (%)			
Methotrexate	-	46 (38.0)	-
Docetaxel	-	52 (43.0)	-
Cetuximab	-	13 (10.7)	-
Median time on Rx, mo (95% CI)	1.9 (1.6-2.3)	1.9 (1.6-2.0)	-
Median follow-up, mo (range)	5.3 (0-16.8)	4.6 (0-15.2)	-
Number of deaths, n (%)	133 **(55.4)**	87 **(70.2)**	218 (60.4)
Ongoing treatments, n (%)	41 (17.4)	3 (2.7)	44 (12.7)

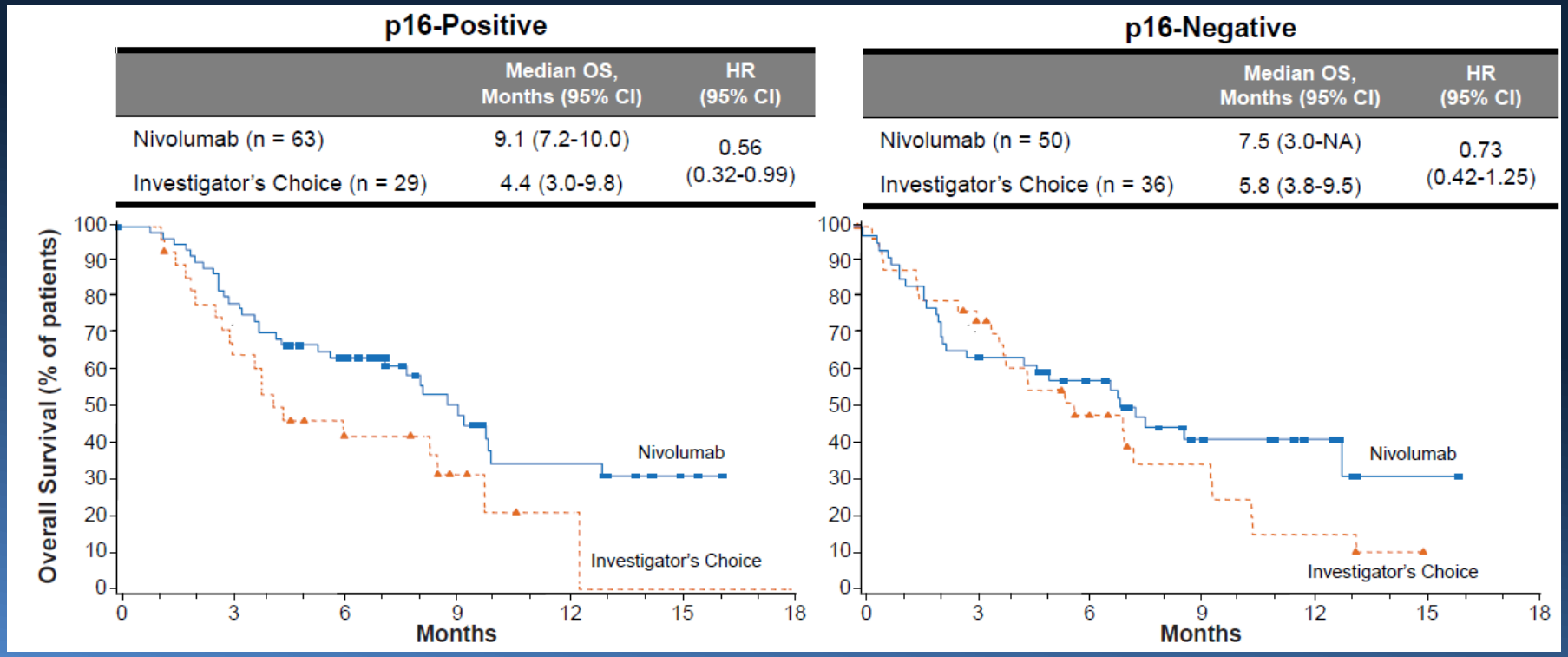
Ferris R et al, NEJM 2016

Overall Survival by PD-L1 Expression



Ferris R et al, NEJM 2016

Overall Survival by p16 Status



Ferris R et al, NEJM 2016

Treatment-Related Select AEs

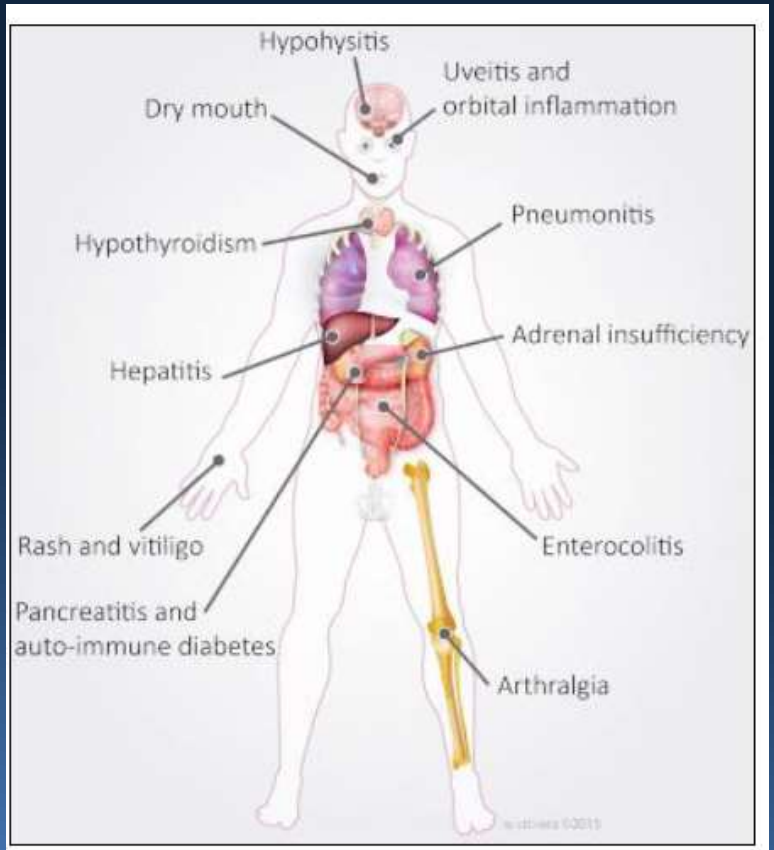
Event	Nivolumab (n = 236)		Investigator's Choice (n = 111)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/infusion reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)

Select AEs: AEs with potential immunologic etiology that requires monitoring/intervention

Ferris R et al, NEJM 2016

Immune-Related Adverse Events (IRAEs)

- Skin: Exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, vitiligo, alopecia
- Eyes: Uveitis, iritis
- Endocrine: Hypothyroidism, adrenal, insufficiency, hypophysitis
- Pulmonary: Pneumonitis, interstitial lung disease, acute interstitial pneumonitis
- Gastrointestinal: Colitis, enterocolitis, necrotizing colitis, gastrointestinal perforation
- Hepatic: Autoimmune hepatitis
- Renal: Autoimmune nephritis, renal failure
- Neurologic: Autoimmune neuropathy, demyelinating polyneuropathy, Guillain-Barre, myasthenia gravis



Michot JM, et al. *Eur J Cancer*. 2016;54:139-144.

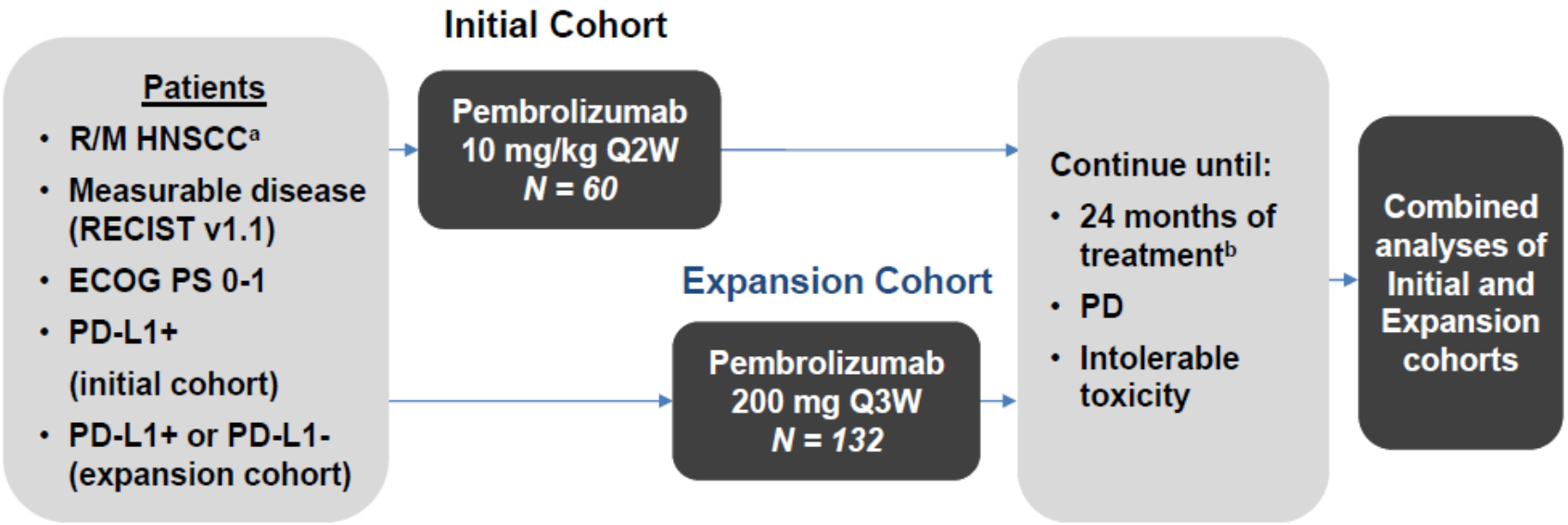
Weber JS et al, JCO 2015

CheckMate 141: Nivolumab Beyond Progression

- Of the 236 nivolumab-treated patients, 139 (59%) progressed and of these patients, 57 (41%) were treated with nivolumab beyond RECIST-defined progression
- Patients treated beyond progression received a median of 9 doses (range: 3, 33) of nivolumab
- Of 57 patients treated beyond progression, 13 (23%) had a reduction in target lesion size and 14 (25%) had stable lesion size post-progression
  - Of the 13 patients with reductions, 7 were p16 positive, 3 had PD-L1 expression ≥1%, and 4 had ≥20% tumor size increase at first progression
  - Two patients had post-progression reduction in target lesions of >30%
- Median OS was 12.7 months for patients treated beyond progression and 6.1 months for those not treated beyond progression

Haddad R /abstr, Proc AACR 2017

KEYNOTE-012: Study Design



Response assessment: Every 8 weeks

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

Secondary end points: ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients[c]

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Chow LQ et al, JCO 2016

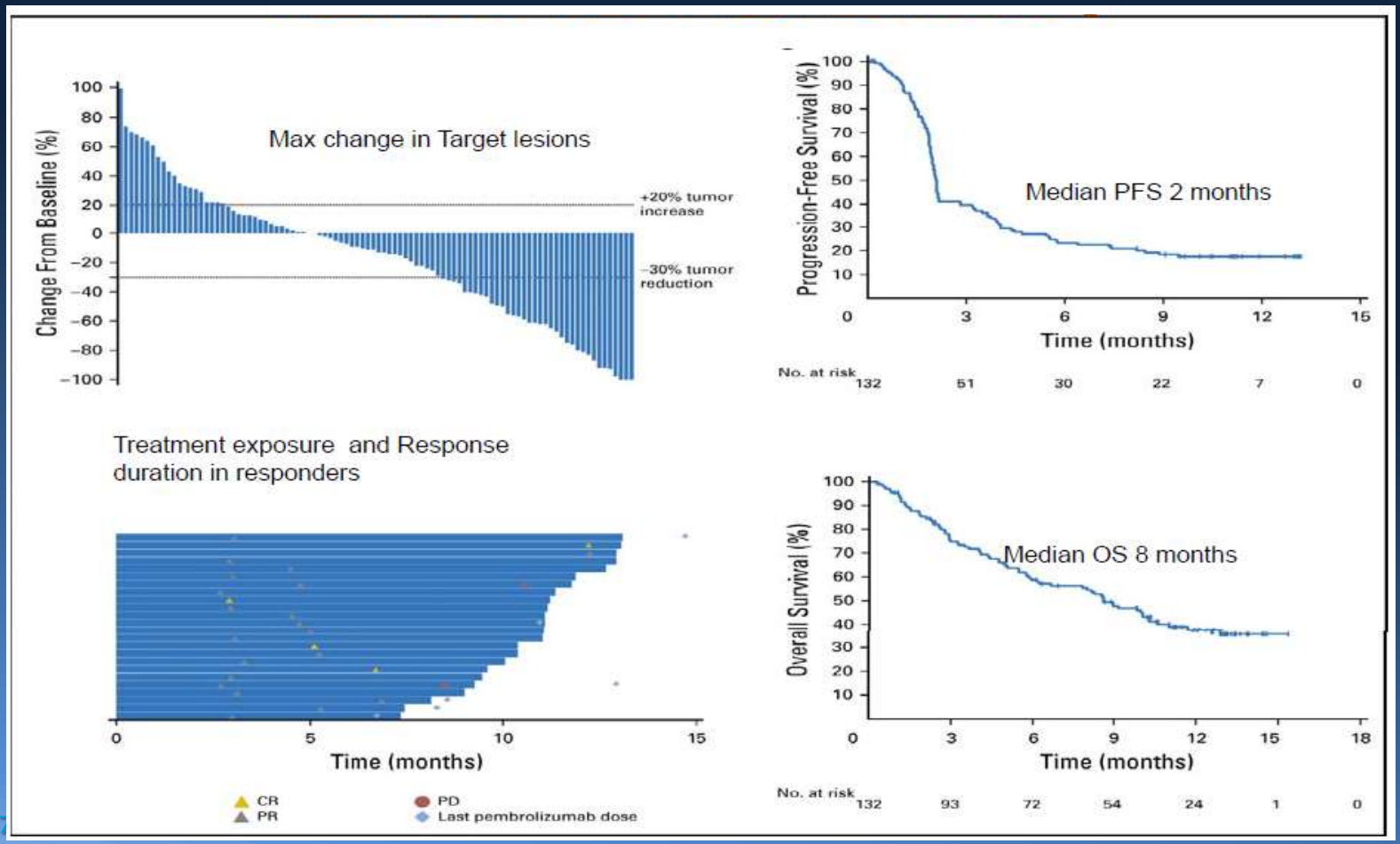
Baseline Demographics and Patient Characteristics

Characteristic	All Patients (N = 132)
Median age (range), years	60 (25-84)
Male	110 (83)
Race	
White	95 (72)
Asian	29 (22)
Other	8 (6)
ECOG PS	
0	38 (29)
1	94 (71)
Smoking status	
Smoked	81 (61)
Never smoked	51 (39)
HPV status	
HPV-associated	28 (21)
Non–HPV associated	104 (79)

Characteristic	All Patients (N = 132)
Sum of target lesions at baseline, median (range), mm	99 (16-664)
Primary location	
Oropharynx	60 (45)
Oral cavity	17 (13)
Larynx	16 (12)
Hypopharynx	12 (9)
Nasal cavity	8 (6)
Nasopharynx	5 (4)
Sinus	3 (2)
Other	9 (7)
Previous adjuvant and/or neoadjuvant therapy	53 (40)
Number of previous lines of therapy for recurrent of metastatic diseases	
0	24 (18)
1	33 (25)
2	27 (21)
3	20 (15)
4	15 (11)
≤5	13 (10)

Chow LQ et al, JCO 2016

KEYNOTE-012: Efficacy



Chow LQ et al, JCO 2016

KEYNOTE-012: PDL-1, PFS and OS

PD-L1 Status	Tumor and Immune Cells			Tumor Cells Only		
	Nonresponders, No.	Responders, No.	Response, % (95% CI)	Nonresponders, No.	Responders, No.	Response, % (95% CI)
Negative (< 1%)	24	1	4 (0.1 to 20)	36	7	16 (7 to 31)
Positive (≥ 1%)	84	23	22 (14 to 31)	72	17	19 (12 to 29)

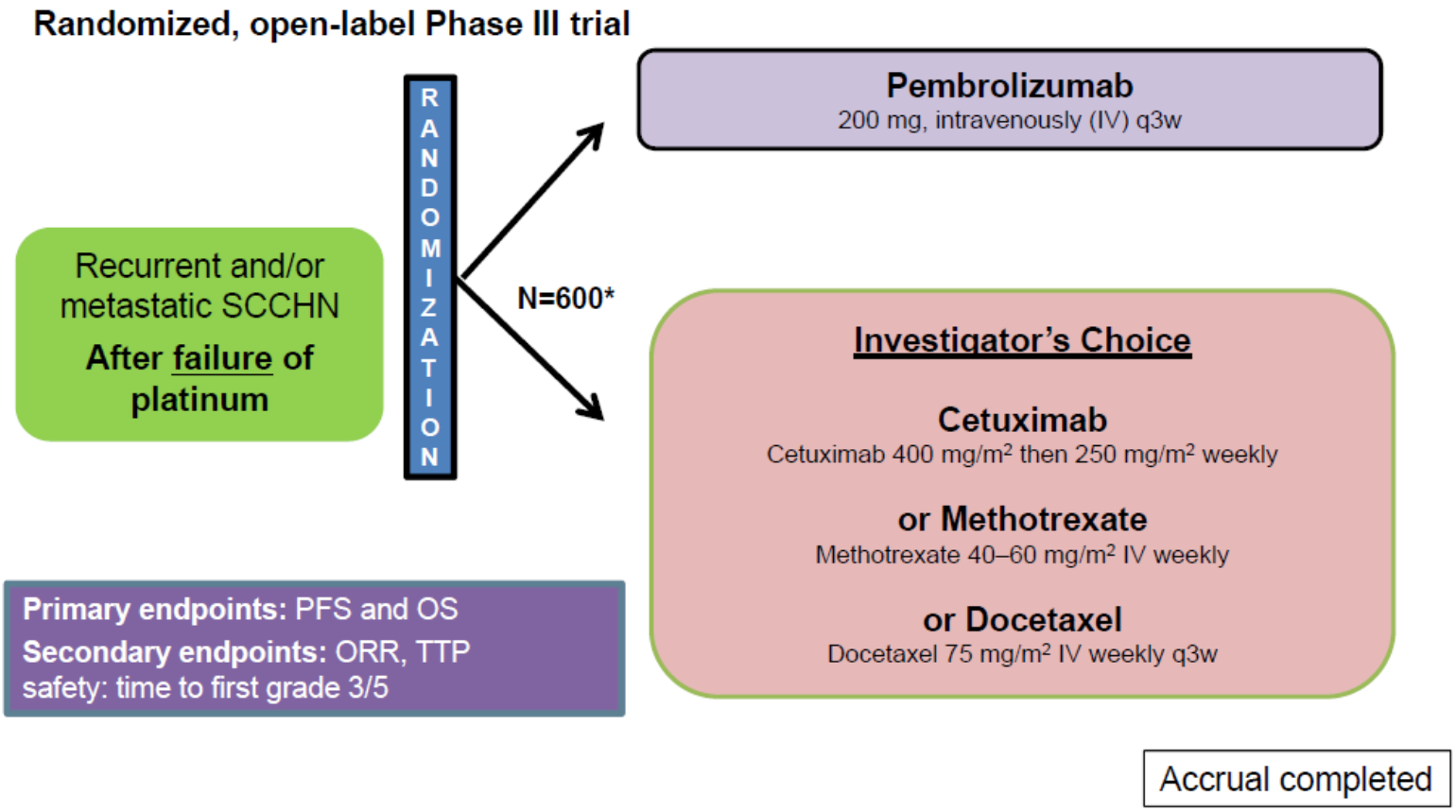
Chow LQ, et al, JCO 2016

STUDIES WITH CHECKPOINT INHIBITORS IN R/M HNSCC

Trial	Ph	N	Eligibility	Treatment	1ry EP	ORR	DOR	PFS	OS
Check Mate-141[1]	III (R)	361	Platinum refractory within 6m	Nivolumab SOC (MTX, Doc, Cet)	OS	13% 6%	-	2.0m 2.3m	7.5 m 5.1 m
KEYNOTE-055[2]	II	171	Platinum and cetuximab refractory	Pembrolizumab	ORR	16%	8m	2.1m	8m
KEYNOTE-012[3]	Ib	132	Any N of prior lines	Pembrolizumab	Safety ORR	18%	NR	2.0m	8m
KEYNOTE-012[4]	Ib	60	PD-L1 positive (≥ 1%), any N of prior lines	Pembrolizumab	Safety ORR	18%	53w	2.0m	13m

Courtesy of Ferrarotto R.

KEYNOTE 040: Pembrolizumab vs Standard Treatment (methotrexate, docetaxel, or cetuximab) in R/M SCCHN

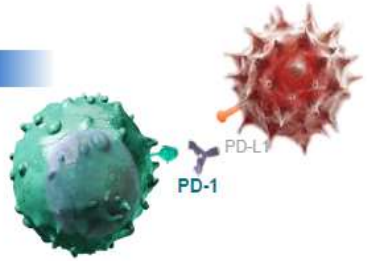


National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT02105636. Accessed: April 19, 2017.

KEYNOTE-048: Study Design

- Phase III, randomized, open-label, clinical trial of pembrolizumab in first-line treatment versus active comparator in patients with R/M HNSCC without prior systemic chemotherapy[1]

Platinum Sensitive



Adapted from Mellman I et al 2011.[2]

Start Date: March 2015

Primary Endpoint: PFS
Other Endpoints: OS, PFS (by immune-related response), ORR

Key Eligibility Criteria
- No prior systemic therapy in R/M setting, except if completed >6 months prior to locally advanced disease
- Available tumor biopsy for PD-L1 analysis
- Have results for HPV status for oropharyngeal cancer (OPC)

Randomized

- Pembrolizumab
- Pembrolizumab + Platinum + 5FU
- Active Comparator (Cetuximab + Platinum + 5FU)

HPV, human papillomavirus; ORR, overall response rate; PD-1, programmed cell death protein 1PFS, progression-free survival; R/M, recurrent or metastatic

1. National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/ NCT02358031. Accessed: April 10, 2017. 2. Mellman I, et al. *Nature.* 2011;480(7378):480-489.

Durvalumab (Study 1108): Tumor Response Overall and by PD-L1 and HPV Status

Patients with R/M HNSCC, progressive disease at study entry, an ECOG PS of 0 or 1, and no prior anti-PD-1/PD-L1 exposure

	Durvalumab 10 mg/kg q 2 w				
	All Patients	PD-L1+	PD-L1-	HPV+	HPV-
ORR by RECIST, % (n/N)	**11** (7/62)	**18** (4/22)	**8** (3/37)	**4** (1/25)	**16** (4/25)
DCR at 12 weeks, % (n/N)	29 (18/62)	32 (7/22)	27 (10/37)	24 (6/25)	24 (6/25)

- Most responses (all PRs) occurred in the first 16 weeks
- Among 7 responders, 6 had duration of response ≥12 months
- Median OS was 8.4 months for PD-L1 high and 8.9 for PD-L1 low/negative
- Treatment related grade 3-4 AEs were reported in 8% of patients; no grade 3-4 pneumonitis, no drug-related colitis of any grade)

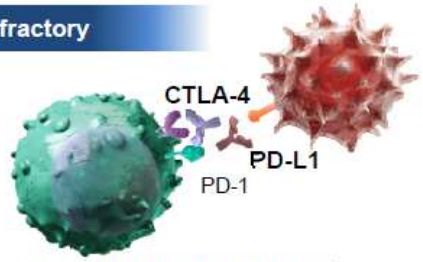
DCR, disease control rate

Segal NH, et al. *Ann Oncol.* 2016;27(Suppl 6):Abstract 949O.

EAGLE: Study Design

- EAGLE: Phase III, randomized, open-label study of efficacy and safety of durvalumab +/- tremelimumab versus standard of care in patients with R/M SCCHN after failure of platinum-based treatment1

Platinum Refractory



Adapted from Mellman I et al 2011.[2]

Start Date: September 2015

Primary Endpoint: OS

Other Endpoints: OS (PD-L1+), OS (PD-L1-), PFS, ORR, DOR, DCR, APF, safety and tolerability

Key Eligibility Criteria

- PD-L1+/- as determined by Ventana SP263 (cutoff: 25%)
- Failure of exactly one Pt-tx for recurrent/metastatic disease, or progression within 6 months of completing platinum-containing multimodality therapy with curative intent
- No prior exposure to immune-mediated therapy

Randomized (1:1:1)
Stratification factor: PD-L1, HPV, and smoking status

Durvalumab	Durvalumab + Tremelimumab	Active Comparator

APF, alive & progression-free; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Pt-tx, platinum-based treatment

1. National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/ NCT02369874. Accessed: April 10, 2017. 2. Mellman I, et al. *Nature.* 2011;480(7378):480-489.

KESTREL: Study Design

Phase III randomized, open-label efficacy and safety of durvalumab +/- tremelimumab versus active comparator in the treatment of first-line R/M HNSCC[1]

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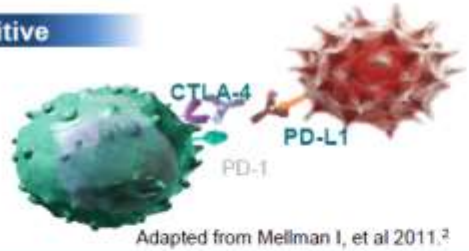


Adapted from Mellman I, et al 2011.[2]

Start Date: October 2015

Primary Endpoint: PFS, OS (durvalumab + tremelimumab vs. SOC)

Other Endpoints: ORR, PFS2, DoR, APF12, OS24, PFS (durvalumab vs. SOC), OS (durvalumab vs SOC), PK, immunogenicity, quality of life

Key Eligibility Criteria

- No prior systemic chemotherapy for recurrent or metastatic disease
- No progression or recurrence ≤6 months since last Pt therapy
- Fresh or archival tumor biopsy

Randomized (2:1:1)

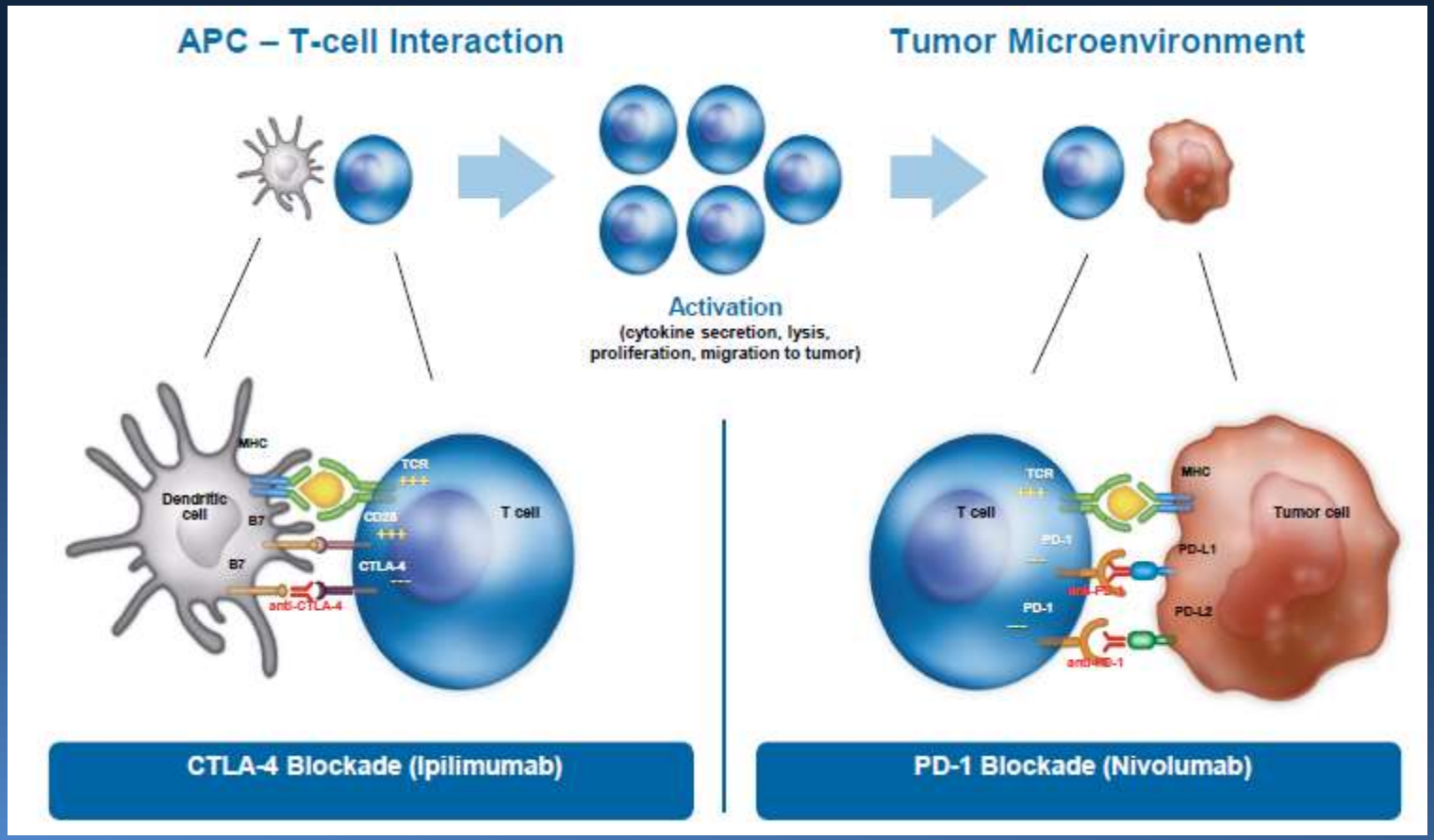
Stratification factor: PD-L1, HPV, and smoking status

- Durvalumab + Tremelimumab
- Durvalumab
- Active Comparator (Cetuximab, 5FU, Cisplatin/ Carboplatin)

APF12, alive & progression-free at 12 months; DoR, duration of response; OS24, overall survival at 24 months; PFS2, second progression-free survival; PK, pharmacokinetics; Pt, platinum

1. National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT02551159. Accessed: April 10, 2017. 2. Mellman I, et al. *Nature.* 2011;480(7378):480-489.

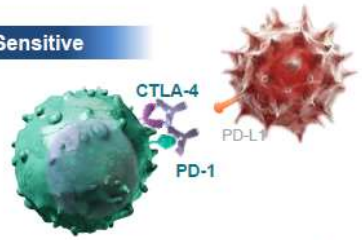
Ipilimumab and Nivolumab: Complementary Mechanism of Action



CheckMate 651: Study Design

Phase III randomized, open-label of nivolumab + ipilimumab compared to the EXTREME regimen as first-line treatment in patients with R/M HNSCC[1]

Platinum Sensitive



Adapted from Mellman I, et al 2011.[2]

Start Date: August 2016

Primary Endpoints: OS, PFS
Other Endpoints: ORR, time to deterioration, PD-L1 expression as biomarker

Key Eligibility Criteria
- No prior systemic therapy for R/M disease except if chemotherapy was part of multimodal treatment ≤6 months prior to enrollment
- Tumor tissue required for HPV p16 (for OPC) and PD-L1 testing prior to randomization

Randomized

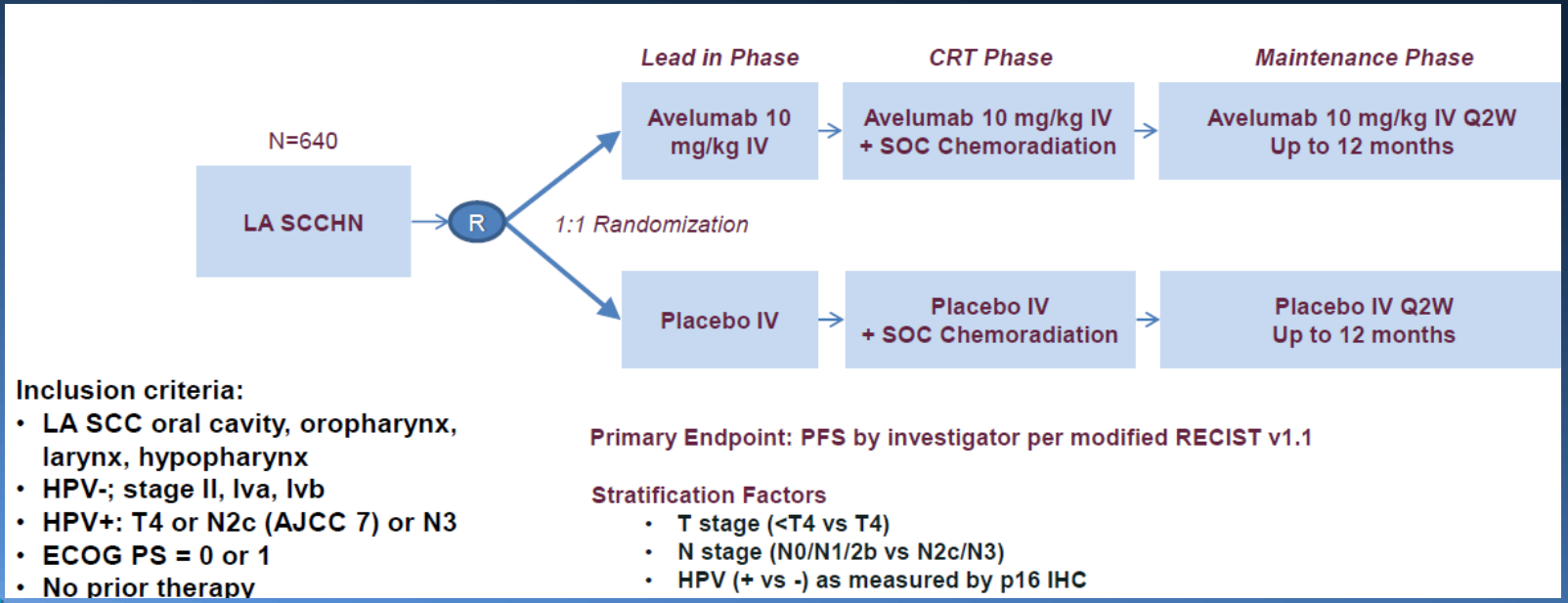
Nivolumab + Ipilimumab	EXTREME Cetuximab + Cisplatin/Carboplatin + 5FU

CTLA-4, cytotoxic T-lymphocyte-associated protein 4

1. National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT02741570. Accessed: April 10, 2017. 2. Mellman I et al. *Nature.* 2011;480(7378):480-489.

JAVELIN Head and Neck 100: Study Design

A randomized double-blind phase III study of avelumab in combination with standard of care (SOC) chemoradiotherapy (cisplatin plus definitive radiation therapy) versus SOC chemoradiotherapy in the front-line treatment of patients with locally advanced (LA) HNSCC



Inclusion criteria:

- LA SCC oral cavity, oropharynx, larynx, hypopharynx
- HPV-; stage II, IVa, IVb
- HPV+: T4 or N2c (AJCC 7) or N3
- ECOG PS = 0 or 1
- No prior therapy

Primary Endpoint: PFS by investigator per modified RECIST v1.1

Stratification Factors

- T stage (<T4 vs T4)
- N stage (N0/N1/2b vs N2c/N3)
- HPV (+ vs -) as measured by p16 IHC

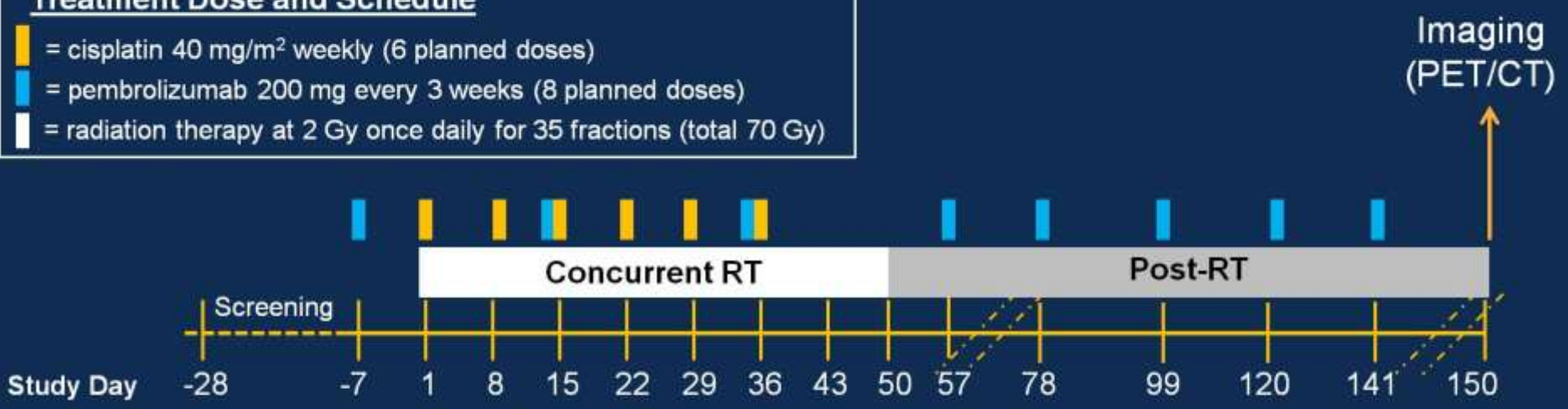
2017

Pembrolizumab with CRT

Study Design

Treatment Dose and Schedule

- = cisplatin 40 mg/m^2 weekly (6 planned doses)
- = pembrolizumab 200 mg every 3 weeks (8 planned doses)
- = radiation therapy at 2 Gy once daily for 35 fractions (total 70 Gy)



Primary end points:

- Safety - dose-limiting adverse events (AEs) and immune-related AEs (irAEs)
- Efficacy - complete response (CR) rate on imaging or salvage surgery at day 150

Secondary end points: PFS, OS, locoregional control, distant metastasis rate, quality-of-life (FACT H&N)

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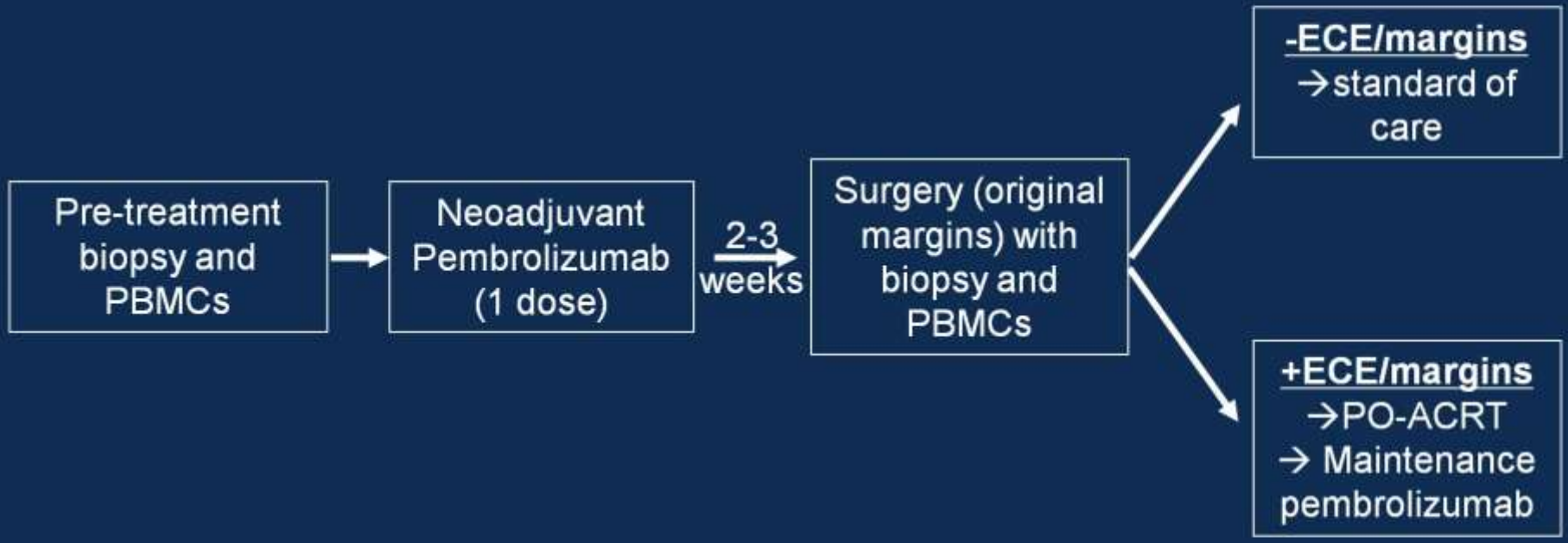
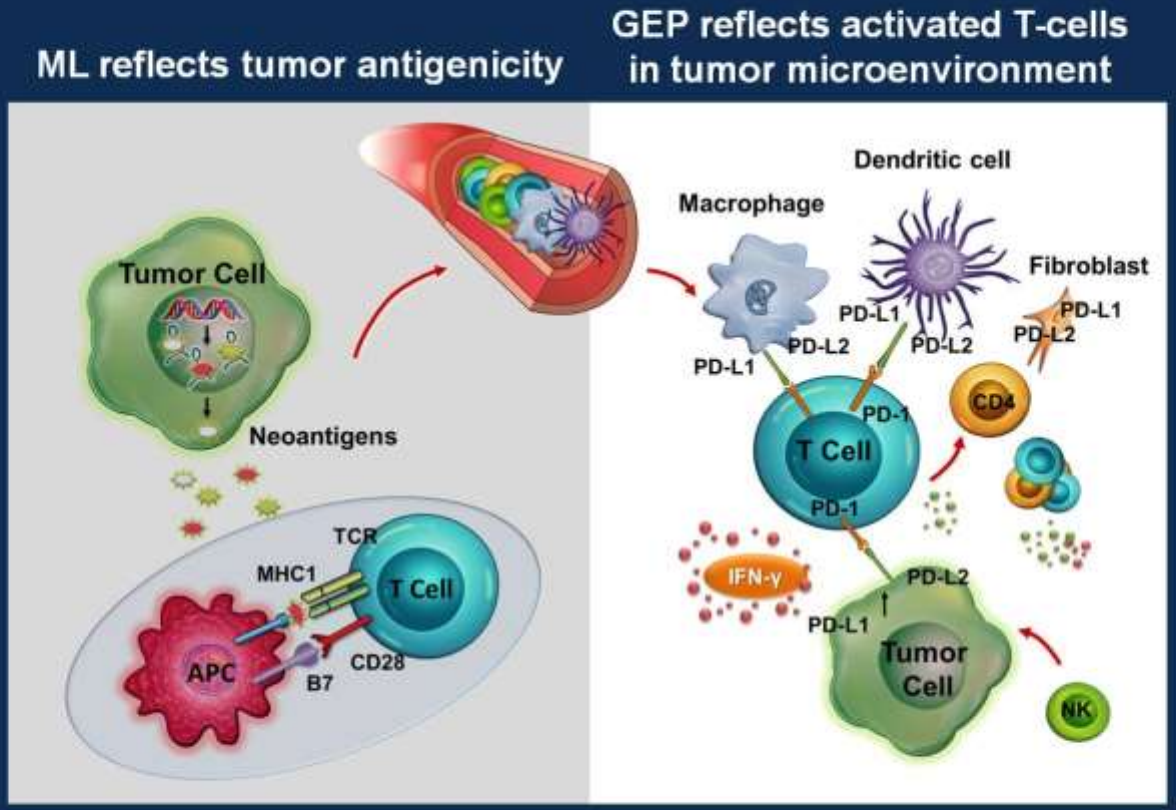
Presented By Steven Powell at 2017 ASCO Annual Meeting

Immunotherapy with pembrolizumab in HPV-negative locally advanced, surgically resectable HNSCC



NCT02296684

Immunobiology Related to ML and GEP



Adjuvant Studies in Locally Advanced HNSCC

Adjuvant (post-operative) studies also underway:

- University of Cincinnati: Pembrolizuamb + RT or CRT depending on pathologic risk factors
- University of Chicago: Pembrolizuamb vs placebo + CRT in high-risk patients
- UCSD: Pembrolizuamb in patients with recurrent/resectable disease

Conclusions: Present Role of PD-1 Inhibitors in HNSCC

- Immunotherapy is an option for patients with R/M SCCHN
- Nivolumab and pembrolizumab have demonstrated benefit +/- PD-L1 expression and p16 status, but greater in patients expressing PD- L1
- Safety profile is favorable

Conclusions

- Nivolumab and pembrolizumab are now standard of care options for patients with R/M HNSCC after platinum-based therapy

  -Pseudoprogression is unusual

- PD-L1 expression is an imperfect biomarker for the efficacy of immune checkpoint inhibitors; benefit in both HPV+ and HPV-; gene signatures are under evaluation
- Single agents and combination regimens are in late stage development in first-line treatment of R/M SCCHN
- Combination with radiotherapy and with other multimodality approaches are being investigated in potentially curable disease
- Preclinical studies suggests further improved efficacy with combinations of immunotherapeutic approaches that target tumor microenvironment