Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Immunotherapy Resistance

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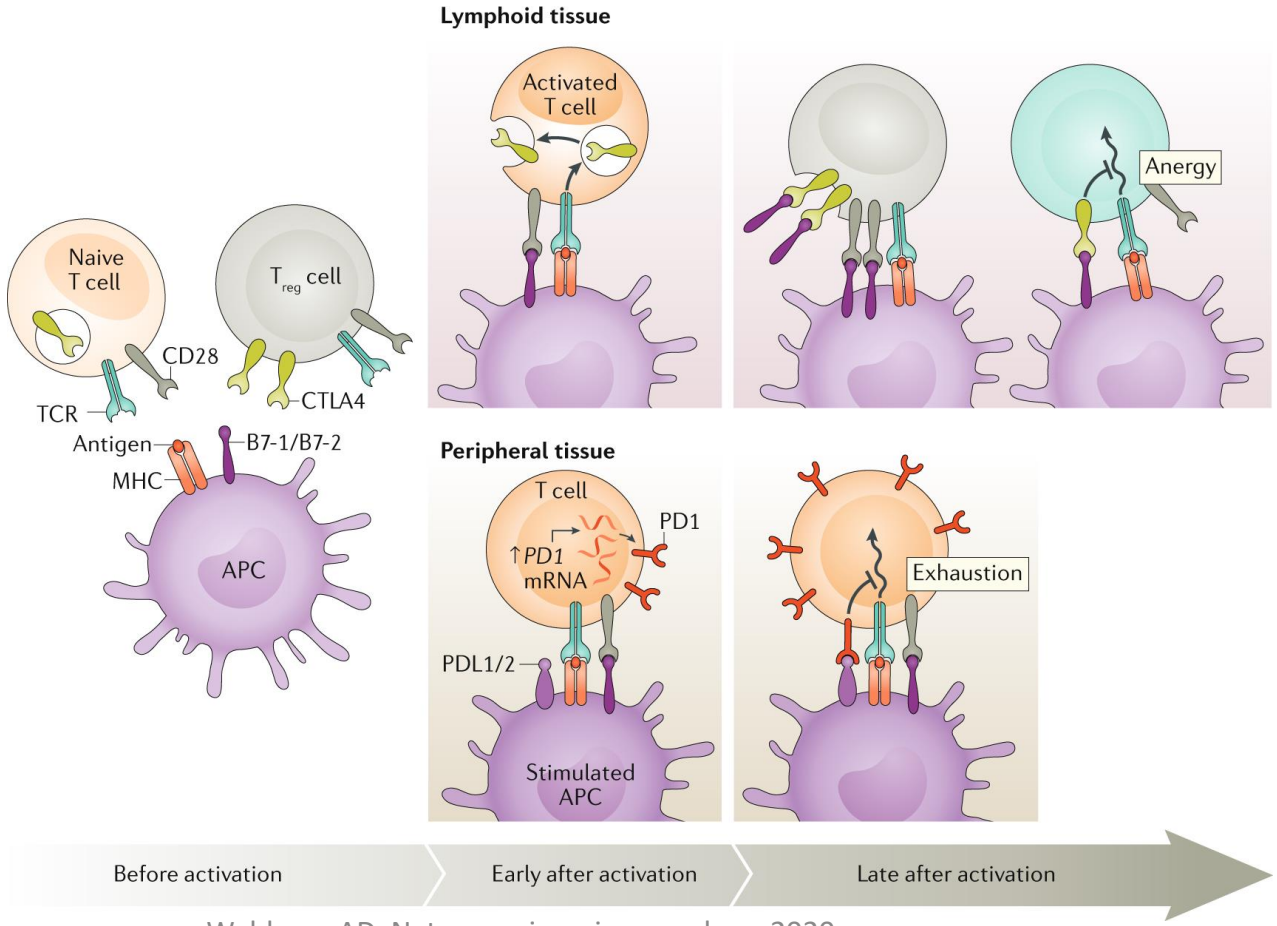
#LearnACI

Disclosures

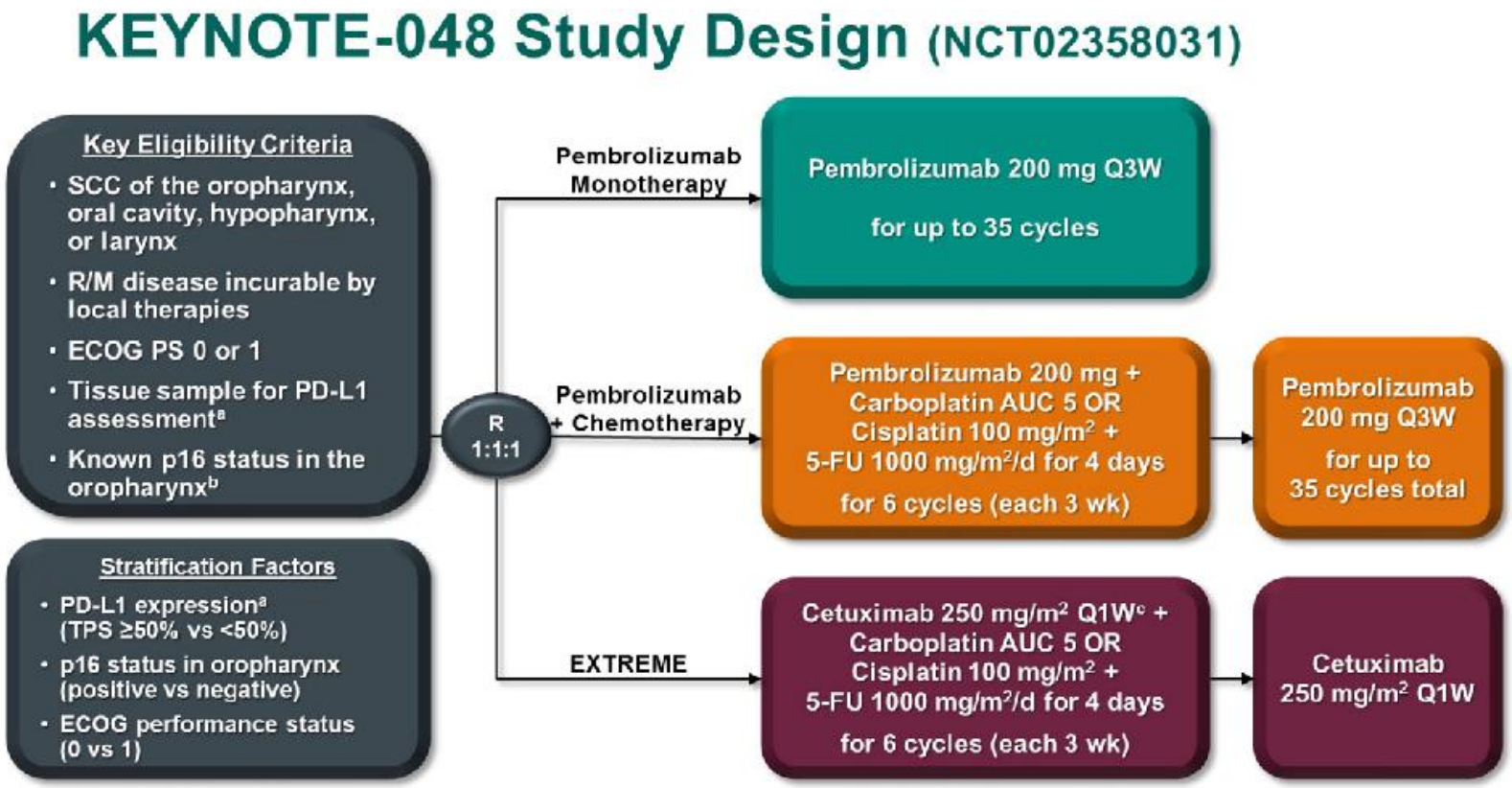
- Research funding: Boehringer-Ingelheim, Genentech
- Advisory Board: Merck, Regeneron Pharma, Sanofi/Genzyme
- I will be discussing non-FDA approved indications during my presentation.

Immune Regulation



Waldman AD. Nature reviews immunology, 2020.

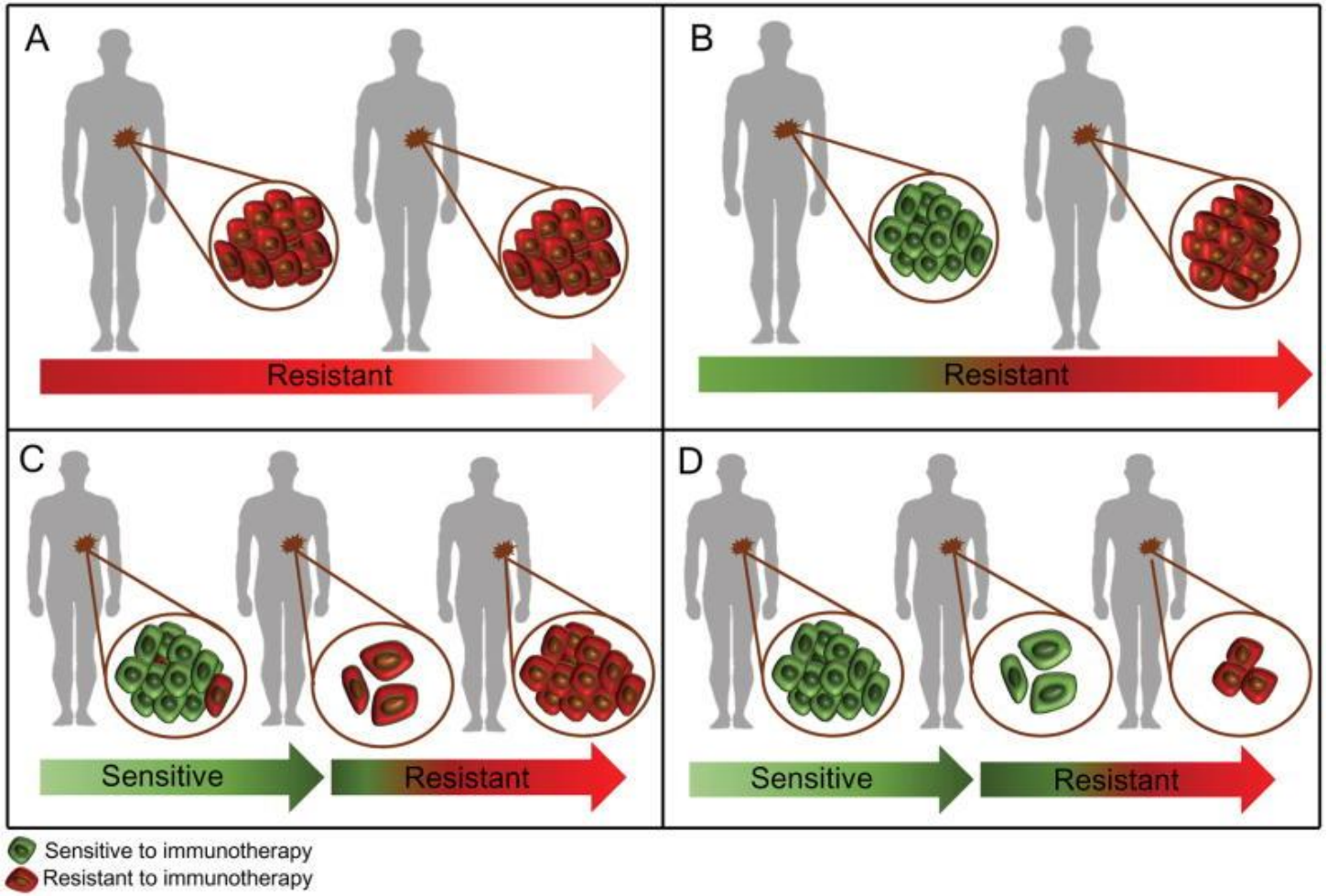
Anti-PD-1 as First-line treatment



Burtness BA. Lancet 2019.

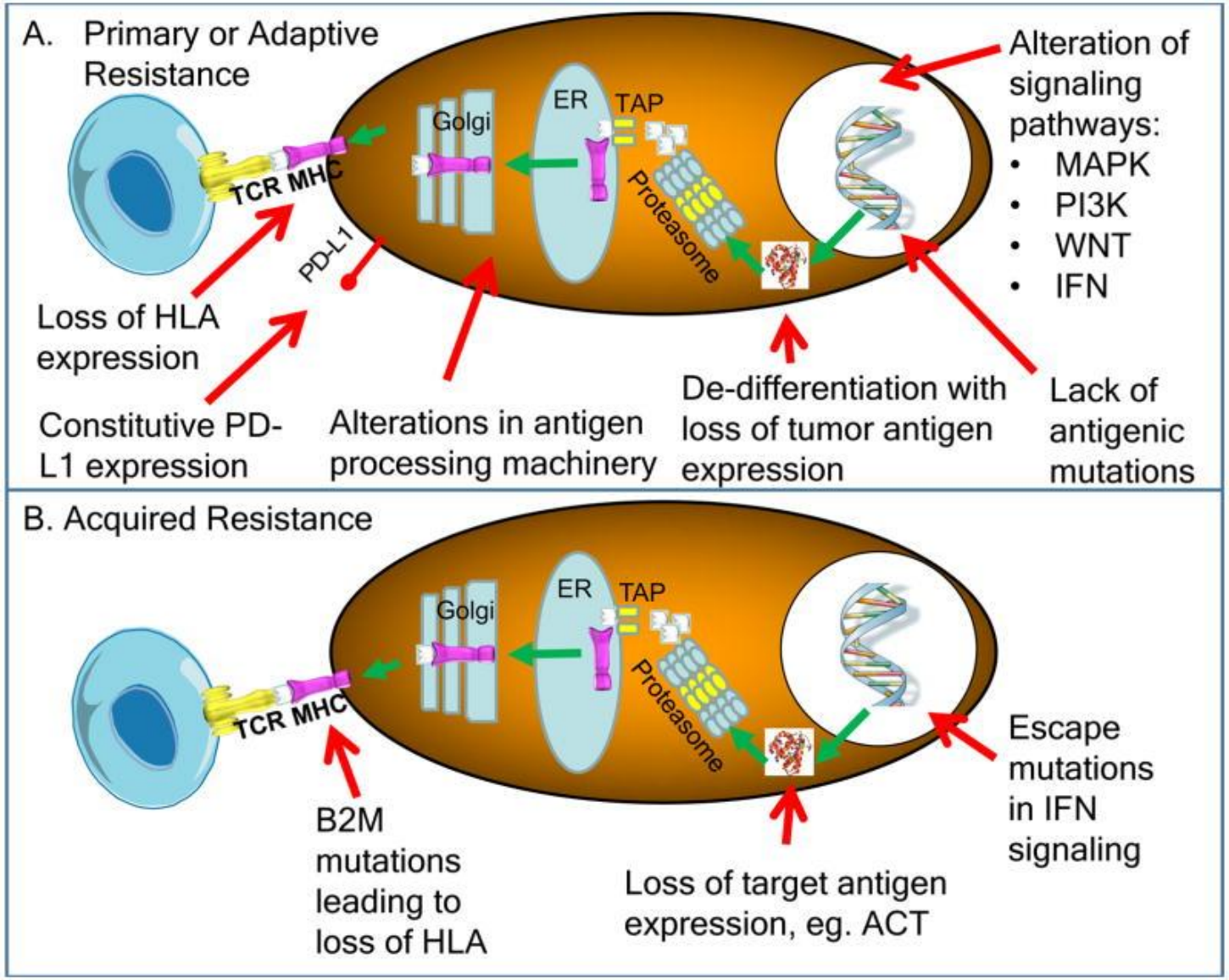
Mechanisms of Resistance

Primary, Adaptive and Acquired resistance



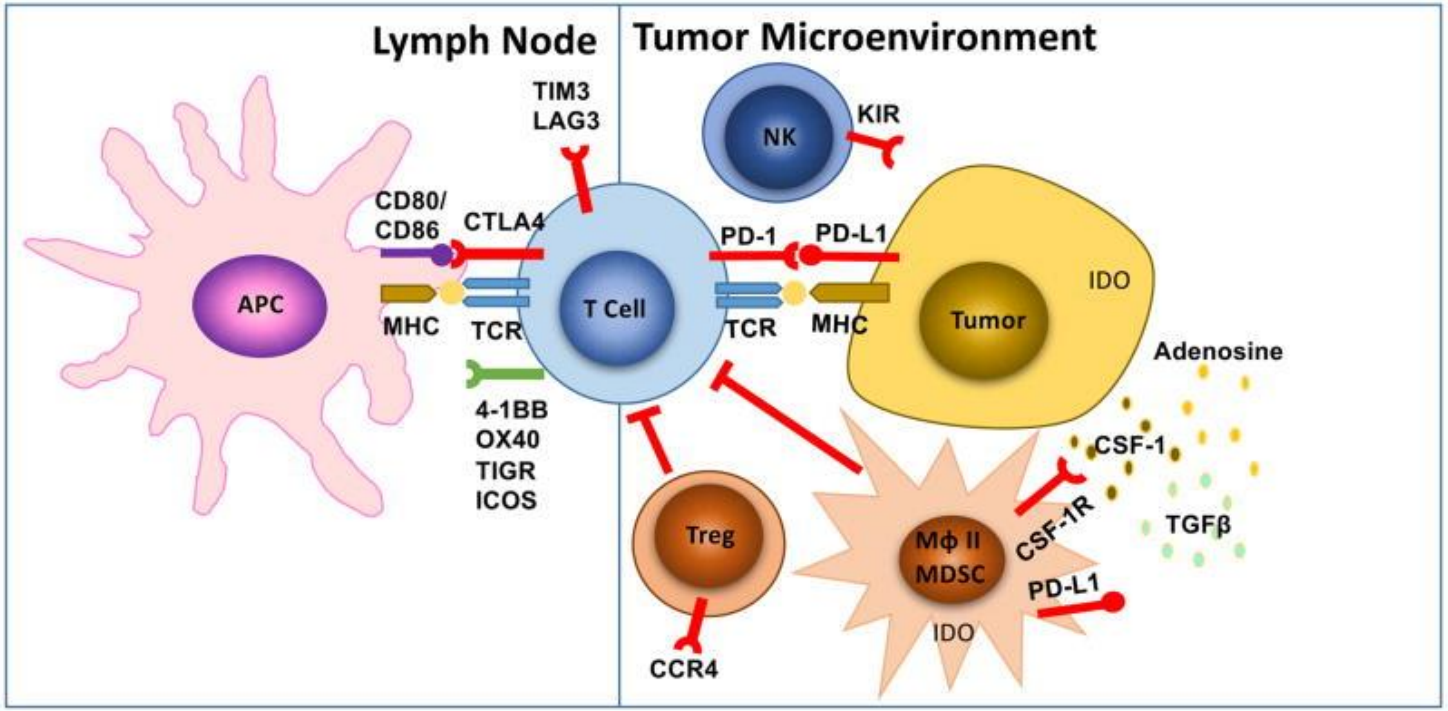
Sharma P. Cell 2017.

Intrinsic Mechanisms of Resistance



Sharma P. Cell 2017.

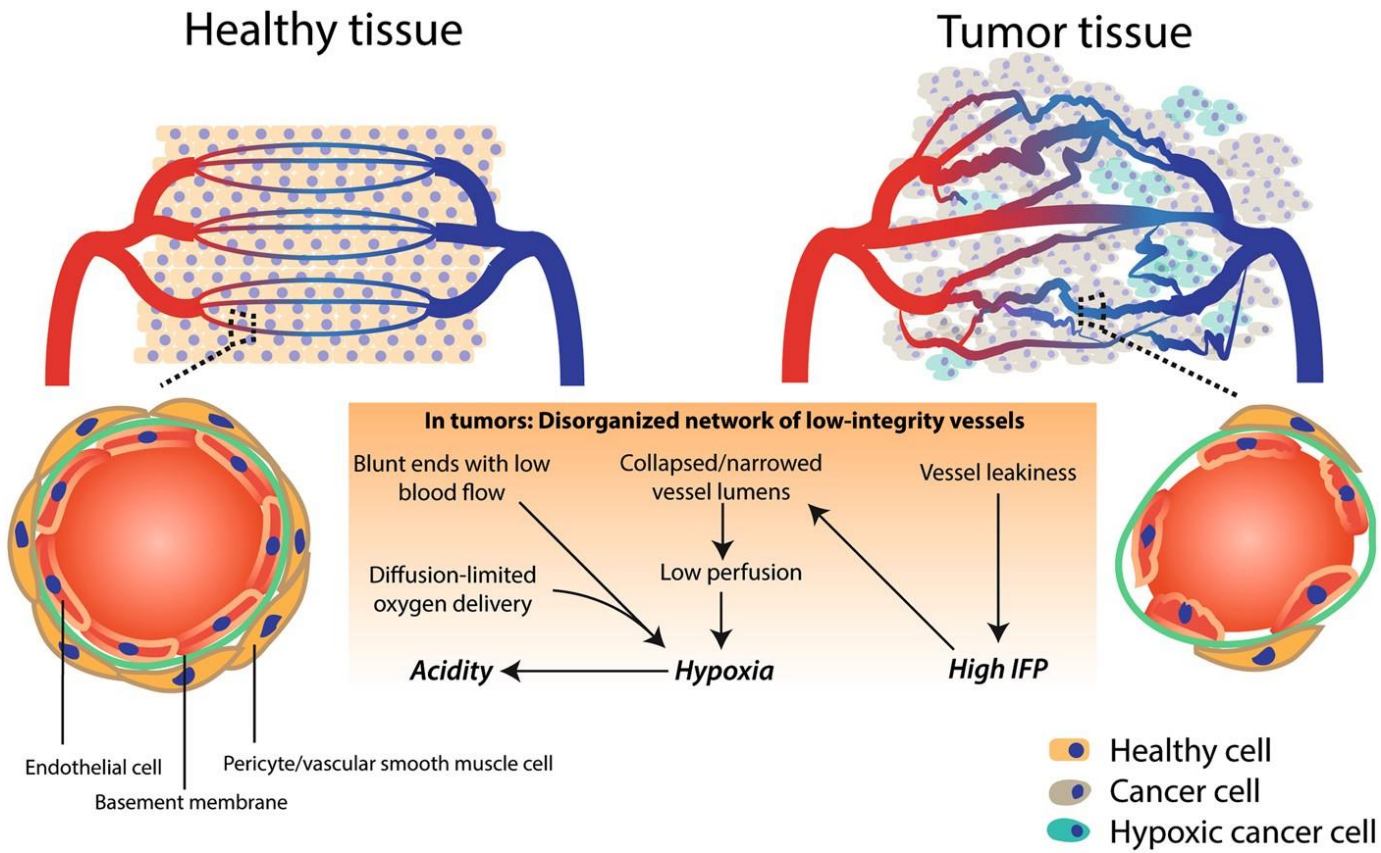
Extrinsic Mechanisms of Resistance



Sharma P. Cell 2017.

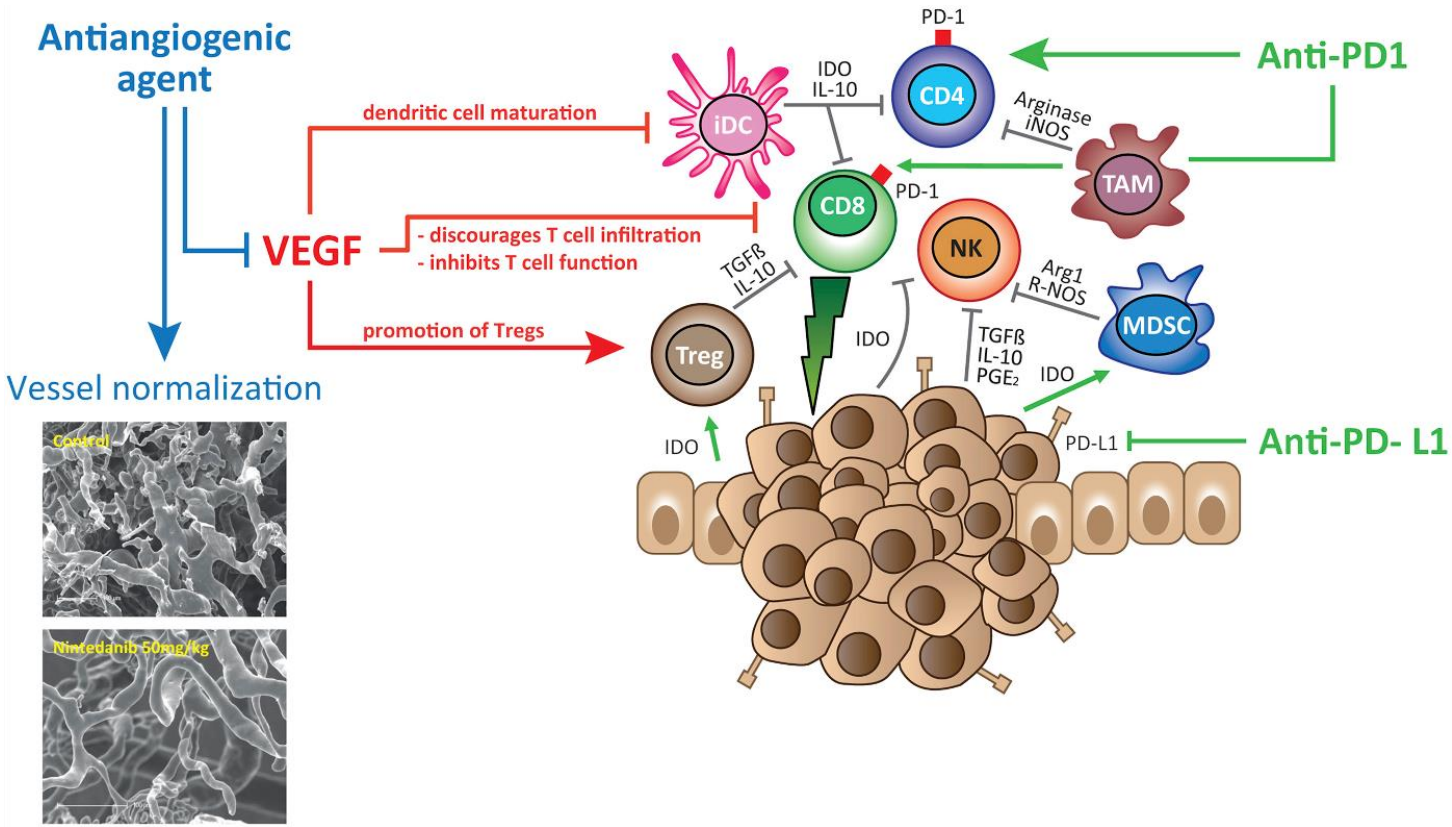
The TME

- Neo-vascularization leads to hypoxia in the TME



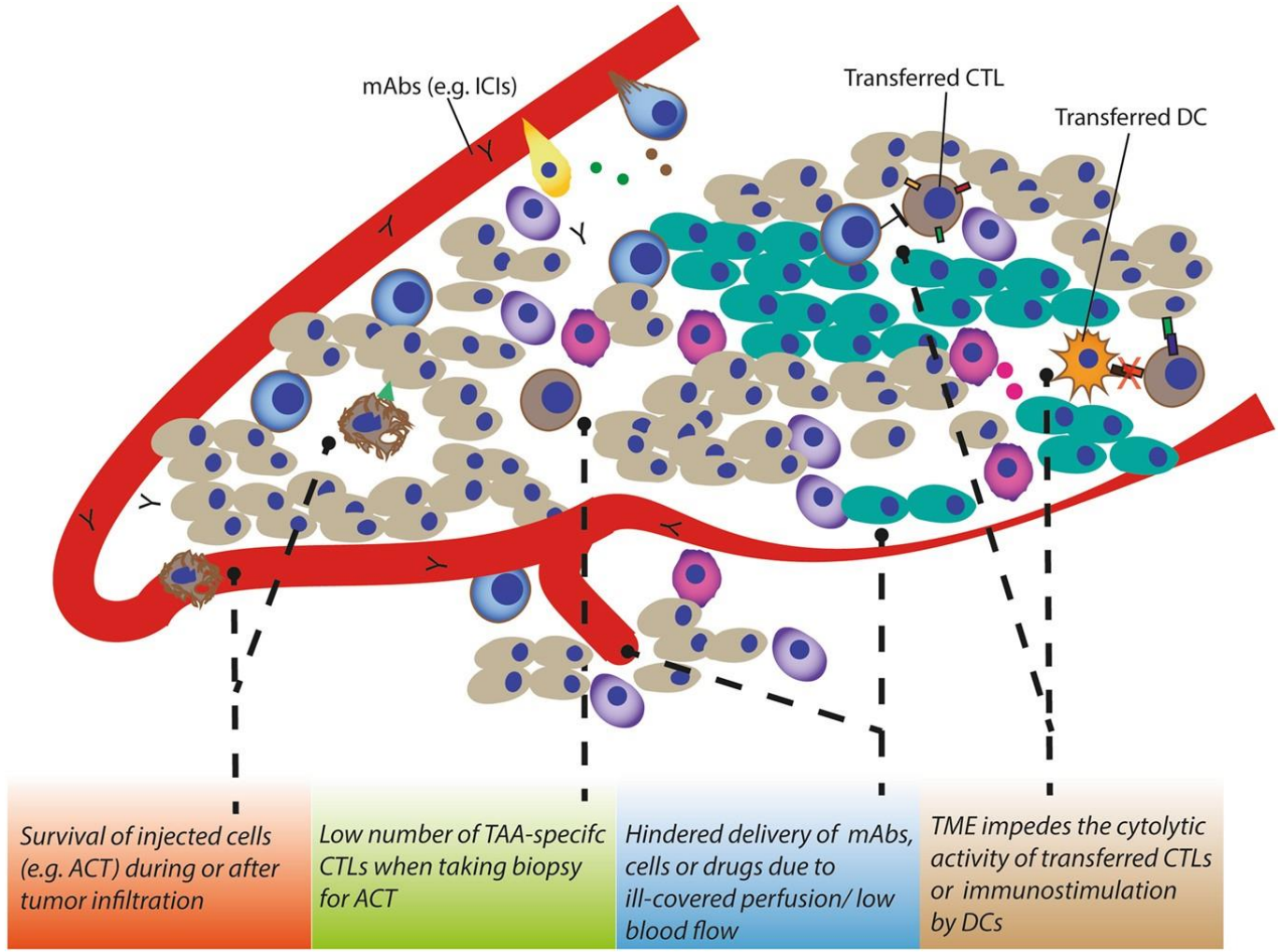
Schaaf MB. Cell death and disease, 2018

Immunosuppressive effects in the TME



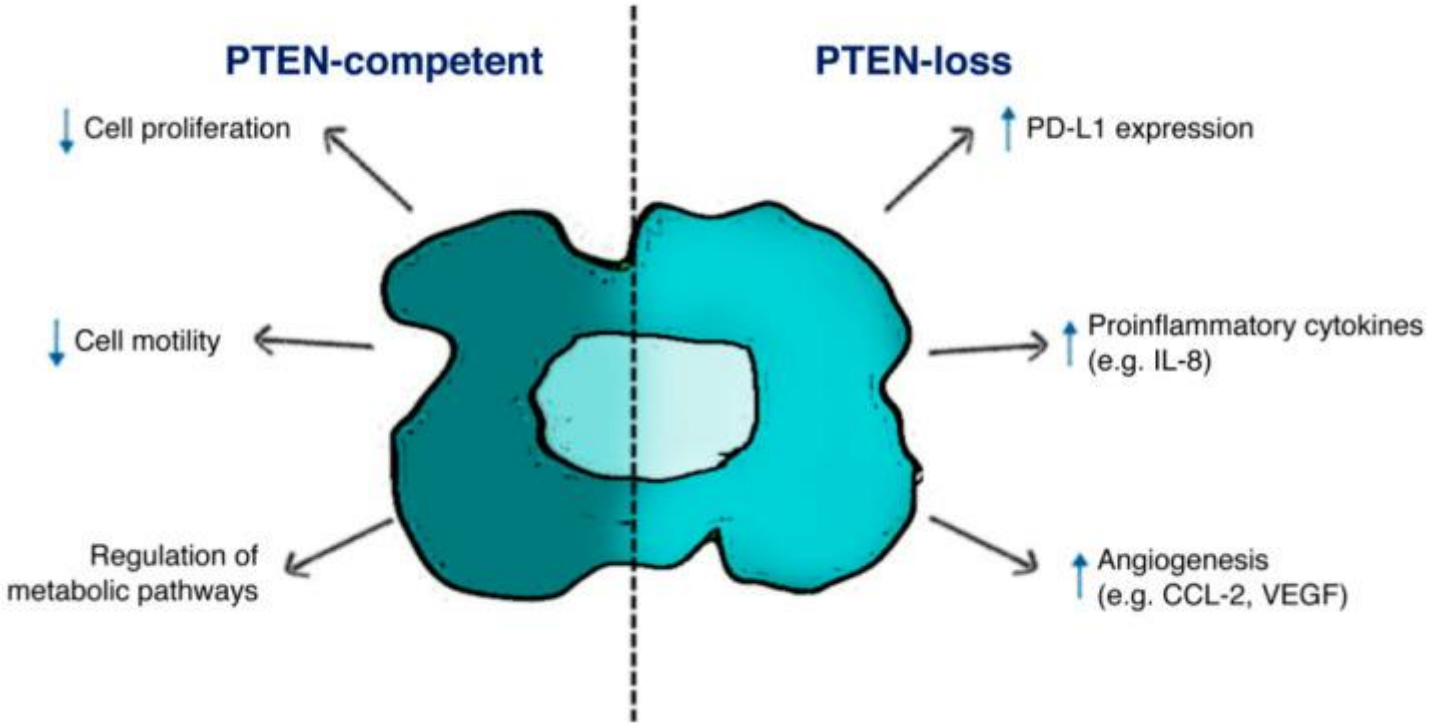
Manegold C. Journal of Thoracic Oncology, 2017.

Impaired Immunotherapy Efficacy



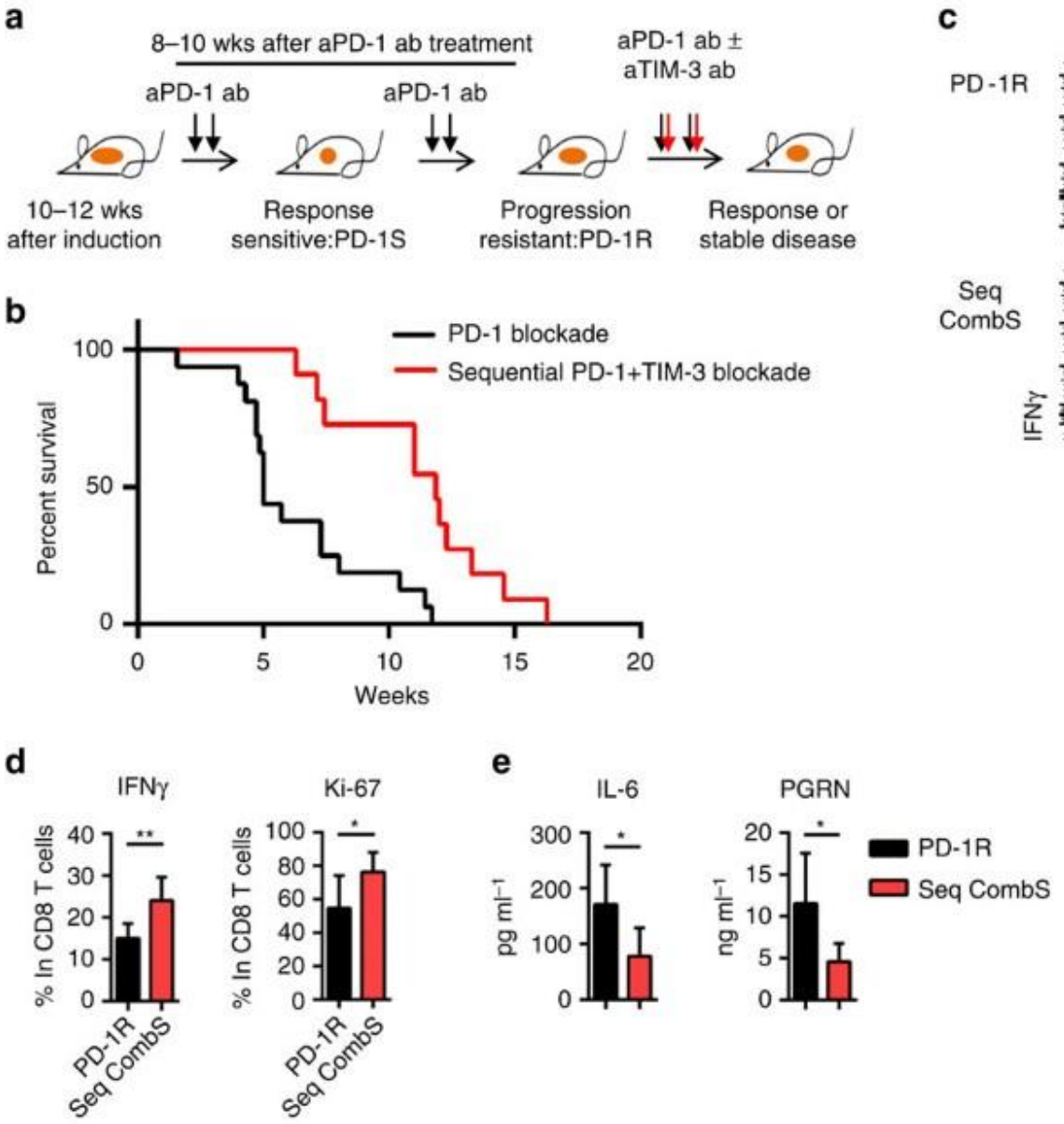
Schaaf MB. Cell death and disease, 2018

PTEN Loss



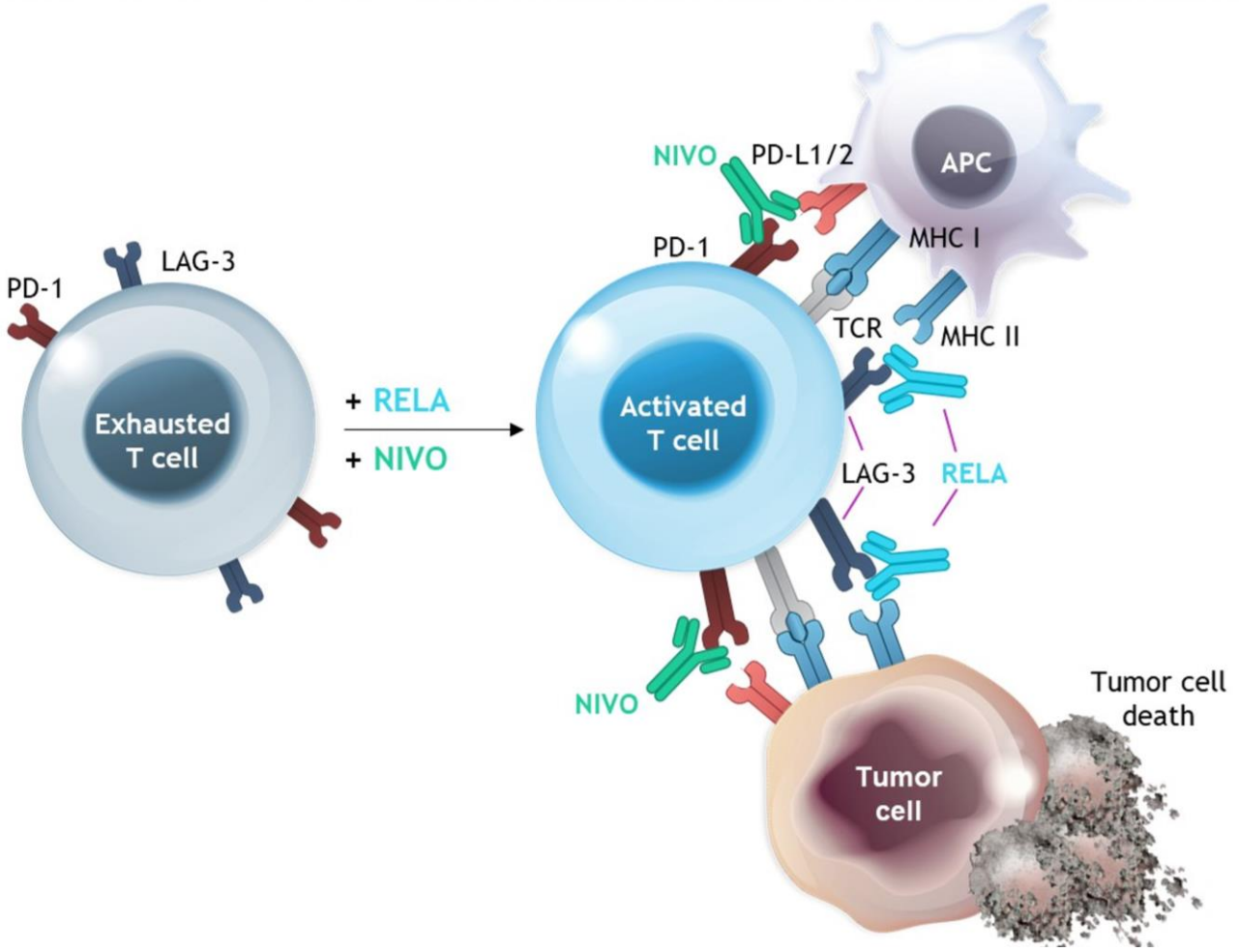
Conciatori F. Int J Mol sci 2020.

TIM-3



Koyama S. Nature communications 2016.

LAG-3



Lipson EJ. 2021 ASCO Annual Meeting

Clinical Trials

Anti PD-1/L1 + Anti-CTLA4

- EAGLE and KESTREL

EAGLE: Phase 3 trial of D and D+T as 2L treatment of HNSCC

Key eligibility criteria

- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence within 6 months of multimodal therapy using platinum with curative intent
- ECOG PS 0 or 1
- Known HPV status (oropharynx)
- Tissue sample for PD-L1 assessment

Stratification factors

- PD-L1 status (TC ≥25% vs <25%)
- Tumor location/HPV status (OPC HPV– vs HPV+ vs non-OPC)
- Smoking history (<10 vs >10 pack/y)

R 1:1:1 N=736

n=247: **Durvalumab (D)** 20 mg/kg Q4W x 4, then 10 mg/kg Q2W until PD + **Tremelimumab (T)** 1 mg/kg Q4W x 4 doses

n=240: **D monotherapy** 10 mg/kg Q2W until PD

n=249: Methotrexate 40 mg/m² QW until PD or Docetaxel 40 mg/m² QW until PD or Cetuximab 250 mg/m² QW until PD or Paclitaxel 80 mg/m² QW until PD or 5-FU 2400 mg/m² over 46 hours Q2W or TS-1 80 mg/m² QD for 28 days (14-day rest) or Capecitabine 1000 mg/m² Q2D, 7 days (7-day rest)

Crossover not permitted

1° Endpoint:
- OS

2° Endpoints:
- PFS, ORR, DoR, DCR, OS12
- HRQoL
- Safety
- Biomarkers

2L, second-line; 5-FU, 5-fluorouracil; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; HRQoL, health-related quality of life; OPC, oropharyngeal cancer; ORR, objective response rate; OS, overall survival; OS12, overall survival at 12 months; PD, progressive disease; PFS, progression-free survival; QD, every day; QW, every week; Q2W, every two weeks; Q4W, every four weeks R, randomized; SCC, squamous cell carcinoma; TC, tumor cell; TS-1, tegafur/gimeracil/oteracil; y, year.

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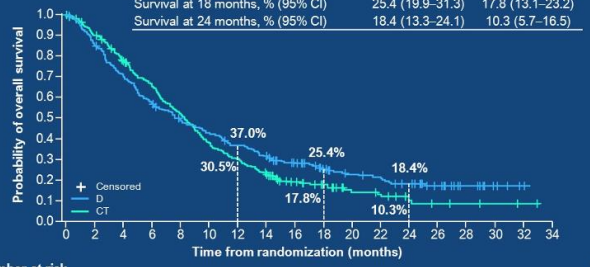
EAGLE: overall survival endpoint was not met

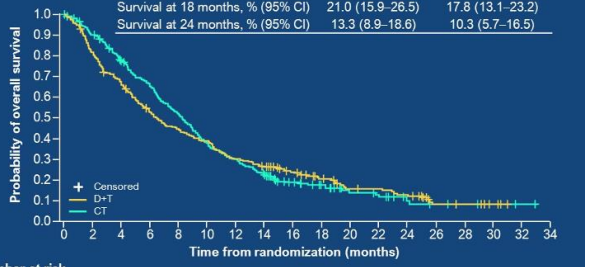
D versus CT

	D (n=240)	CT (n=249)
Median OS, months (95% CI)	7.6 (6.1–9.8)	8.3 (7.3–9.2)
HR (95% CI) (compared with CT)	0.88 (0.72–1.08)	
P value	*P*=0.20	
Survival at 12 months, % (95% CI)	37.0 (30.9–43.1)	30.5 (24.7–36.4)
Survival at 18 months, % (95% CI)	25.4 (19.9–31.3)	17.8 (13.1–23.2)
Survival at 24 months, % (95% CI)	18.4 (13.3–24.1)	10.3 (5.7–16.5)



D+T versus CT

	D+T (n=247)	CT (n=249)
Median OS, months (95% CI)	6.5 (5.5–8.2)	8.3 (7.3–9.2)
HR (95% CI) (compared with CT)	1.04 (0.85–1.26)	
P value	*P*=0.76	
Survival at 12 months, % (95% CI)	30.4 (24.7–36.3)	30.5 (24.7–36.4)
Survival at 18 months, % (95% CI)	21.0 (15.9–26.5)	17.8 (13.1–23.2)
Survival at 24 months, % (95% CI)	13.3 (8.9–18.6)	10.3 (5.7–16.5)



Ferris RL, et al. *Ann Oncol.* 2020. Epub ahead of print

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Checkmate 651

CheckMate 651 study design

Key eligibility criteria
- R/M SCCHN (oral cavity, oropharynx, hypopharynx, or larynx)
- No prior treatment for R/M disease
- Prior chemotherapy for LAD permitted if progression-free ≥6 months post-treatment
- ECOG PS 0–1

Stratified by:
p16 expression (OPC p16+ vs p16−/non-OPC)
Tumor PD-L1[a] status (<1% vs ≥1%)
Prior chemotherapy (yes vs no)

N = 947 → R 1:1

- n = 472 → **NIVO** 3 mg/kg Q2W + **IPI** 1 mg/kg Q6W
- n = 475 → **EXTREME regimen**[b]: Cetuximab + cisplatin/carboplatin + 5-FU Q3W for 6 cycles followed by cetuximab[c] monotherapy Q1W

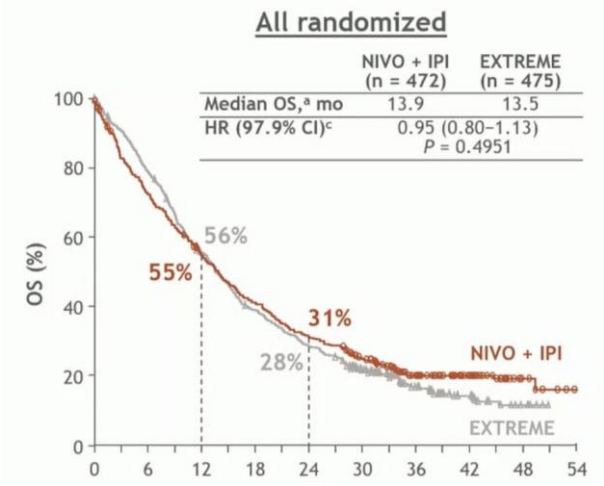
Until disease progression, unacceptable toxicity, *or* 2 years for NIVO + IPI

Primary endpoints (independently tested)
- OS in all randomized
- OS in PD-L1 CPS[a] ≥20

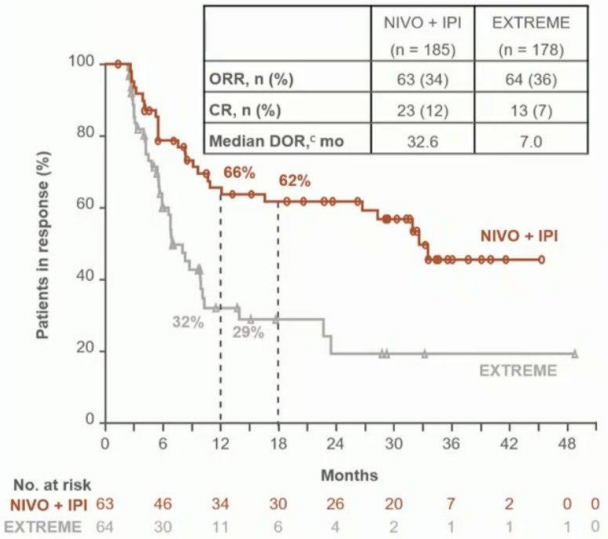
Secondary endpoints
- OS in PD-L1 CPS ≥1[d]
- PFS by BICR (all randomized, PD-L1 CPS ≥20)
- ORR/DOR by BICR (all randomized, PD-L1 CPS ≥20)

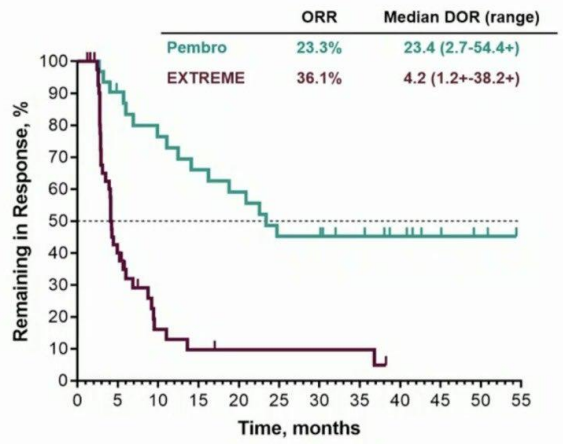
Exploratory endpoints
- PFS and ORR/DOR in PD-L1 CPS ≥1
- Patient-reported outcomes
- Safety

All randomized



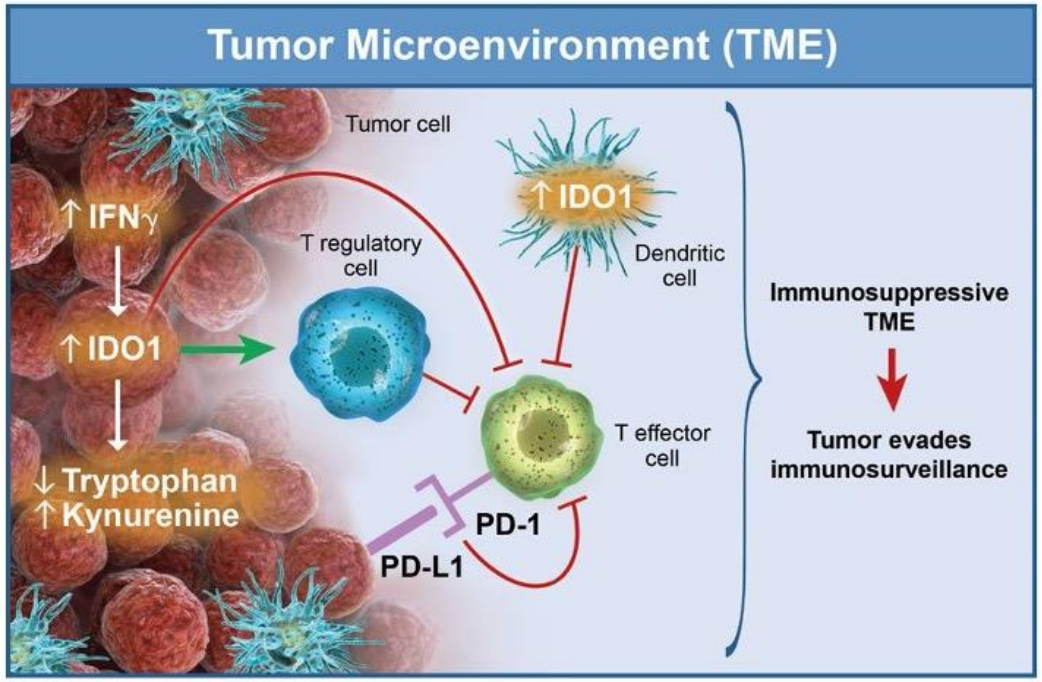
ORR and DOR in PD-L1 CPS ≥20 population: CM651 vs KN48



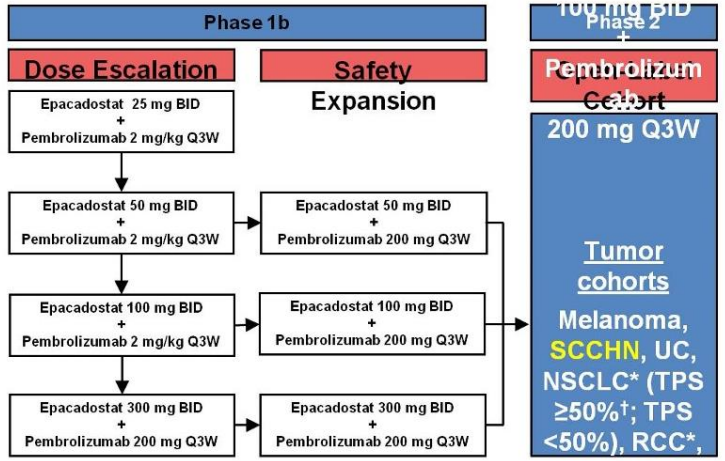


Argiris A. ESMO 2021

IDO Inhibitors

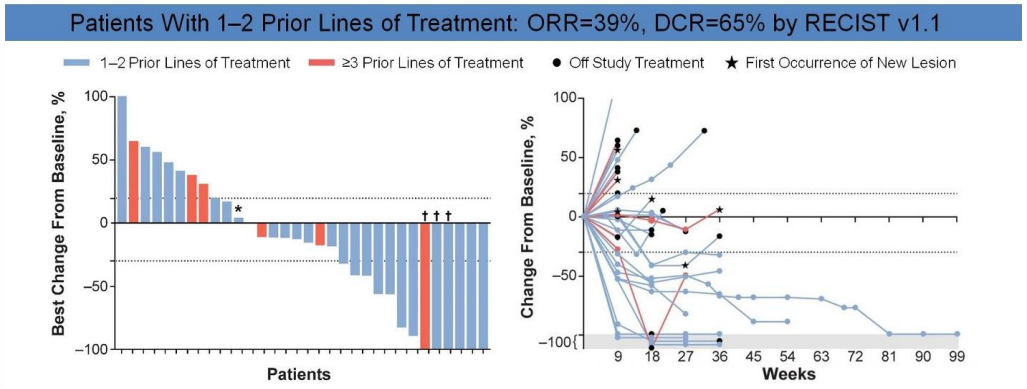


ECHO-202/KEYNOTE-037: Study Design



Percentage Change From Baseline in Target Lesions

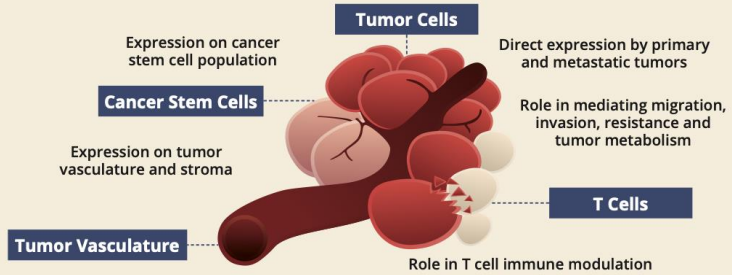
Epacadostat Plus Pembrolizumab
Phase 1/2 Metastatic or Recurrent SCCHN by Prior Lines of Treatment



Hamid O. ASCO Annual meeting 2017.

B7H3 Inhibitors

Rationale for Targeting B7-H3 in Cancer



- B7-H3 expression associated w/adverse clinical features/outcome in various solid tumors
- B7-H3 expression may inversely correlate w/responsiveness to anti-PD-1 therapy*

* Yonesaka, et al., CCR, 2018

Enoblituzumab + Pembrolizumab Study Design

Dose Escalation + Expansion

Dose Escalation
(Dosing completed, No MTD defined)

Cohorts 1–3
3, 10, 15 mg/kg enoblituzumab + 2 mg/kg pembrolizumab
B7-H3 Positive Tumors
3+3+3 Design

Dose Expansion

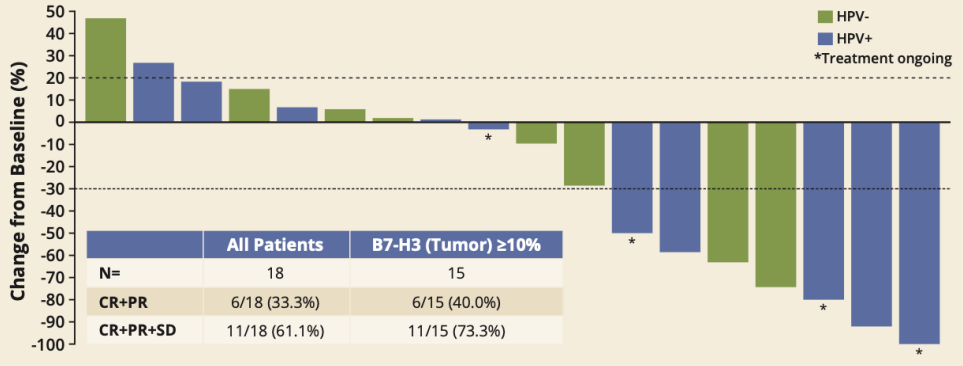
- NSCLC (anti-PD-1/PD-L1 Naïve, PD-L1<1%)
- NSCLC (Post anti-PD-1/PD-L1)
- SCCHN (anti-PD-1/PD-L1 Naïve)
- SCCHN (Post anti-PD-1/PD-L1)
- Melanoma (Post anti-PD-1/PD-L1)
- Urothelial (Post anti-PD-1/PD-L1)

Summary of Overall Best Response Status (RECIST)

	Anti-PD-1/PD-L1 Naïve		Prior Anti-PD-1/PD-L1			
Indication	SCCHN	NSCLC	SCCHN	NSCLC	Urothelial Cancer	Cutaneous Melanoma
Total Treated Patients	21	16	24	25	21	14
Age (years) Mean ± SD Median (Range)	62.8 ± 9.13 65.0 (44–74)	65.7 ± 7.75 65.0 (50–79)	62.7 ± 9.99 62.0 (34–76)	64.2 ± 8.73 63.0 (50–83)	67.1 ± 9.39 70.0 (40–79)	60.5 ±15.24 63.0 (25–79)
Gender Female Male	3 (14.3) 18 (85.7)	8 (50.0) 8 (50.0)	2 (8.3) 22 (91.7)	10 (40.0) 15 (60.0)	6 (28.6) 15 (71.4)	3 (21.4) 11 (78.6)
Response Evaluable	18	14	19	21	17	13
PR (confirmed)	6/18 (33.3%)	5/14 (35.7%)	0	1/21 (4.8%)	1/17 (5.9%)	1/13 (7.7%)
SD	5/18 (27.8%)	8/14 (57.1%)	9/19 (47.4%)	12/21 (57.1%)	8/17 (47.1%)	5/13 (38.5%)
PD	7/18 (38.9%)	1/14 (7.1%)	10/19 (52.6%)	7/21 (33.3%)	8/17 (47.1%)	6/13 (46.2%)
NE	0	0	0	1/21 (4.8%)	0	1/13 (7.7%)

Antitumor Activity in SCCHN Patients, Anti-PD-1/PD-L1 Naïve

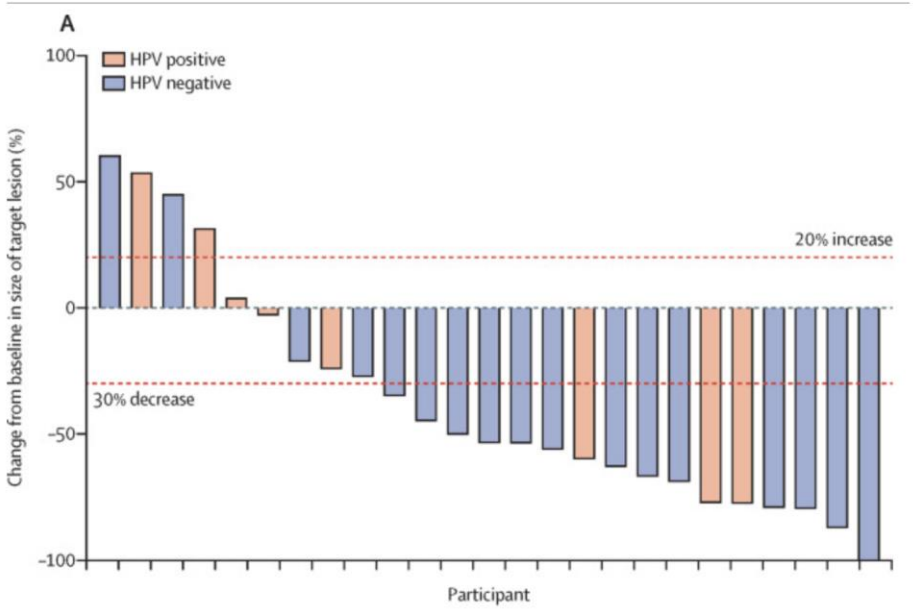
Tumor regression in patients with SCCHN, irrespective of HPV status



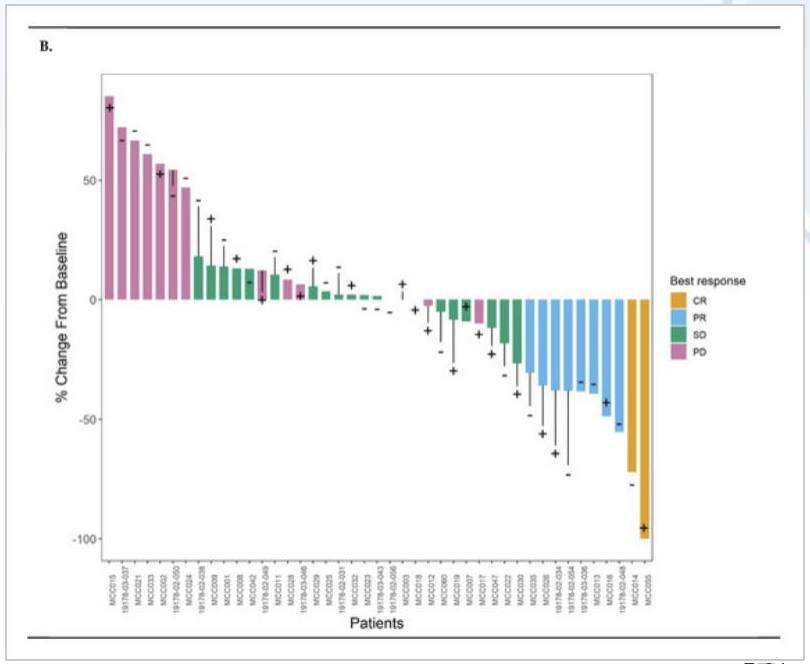
	All Patients	B7-H3 (Tumor) ≥10%
N=	18	15
CR+PR	6/18 (33.3%)	6/15 (40.0%)
CR+PR+SD	11/18 (61.1%)	11/15 (73.3%)

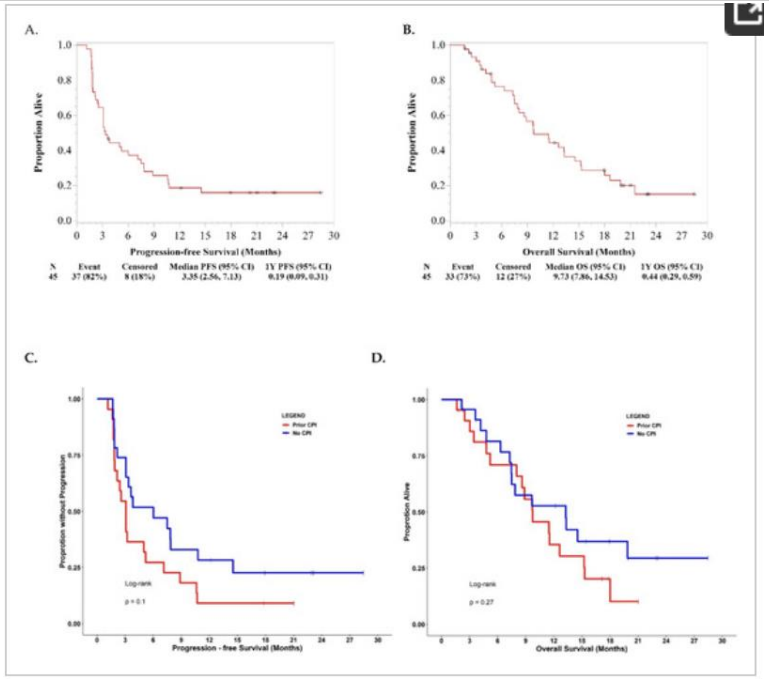
Agarwal C. SITC 2018.

EGFR Inhibitors



ORR 45% in anti-PD-1/EGFRi naïve patients





ORR 22%. 70% patients with prior anti-PD-1 or EGFRi treatment

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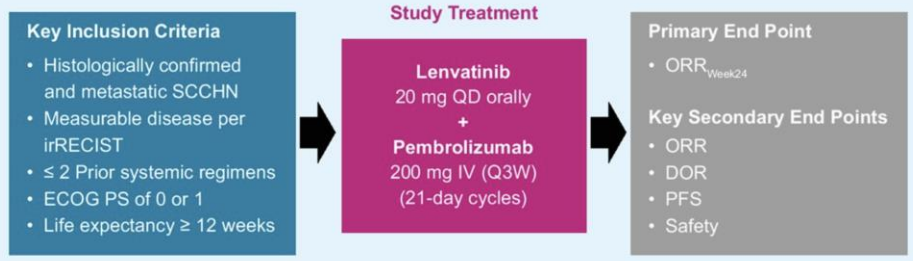
Sacco A. Lancet Onco 2021. Chung CH. Cancers 2021

VEGF Inhibitors

Figure 1. Summary of Phase 2 Study Design



DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; irRECIST, immune-related Response Evaluation Criteria In Solid Tumors; IV, intravenously; ORR, objective response rate; ORR_{Week24}, objective response rate at Week 24; PFS, progression-free survival; QD, once daily; Q3W, once every 3 weeks; SCCHN, squamous cell carcinoma of the head and neck.

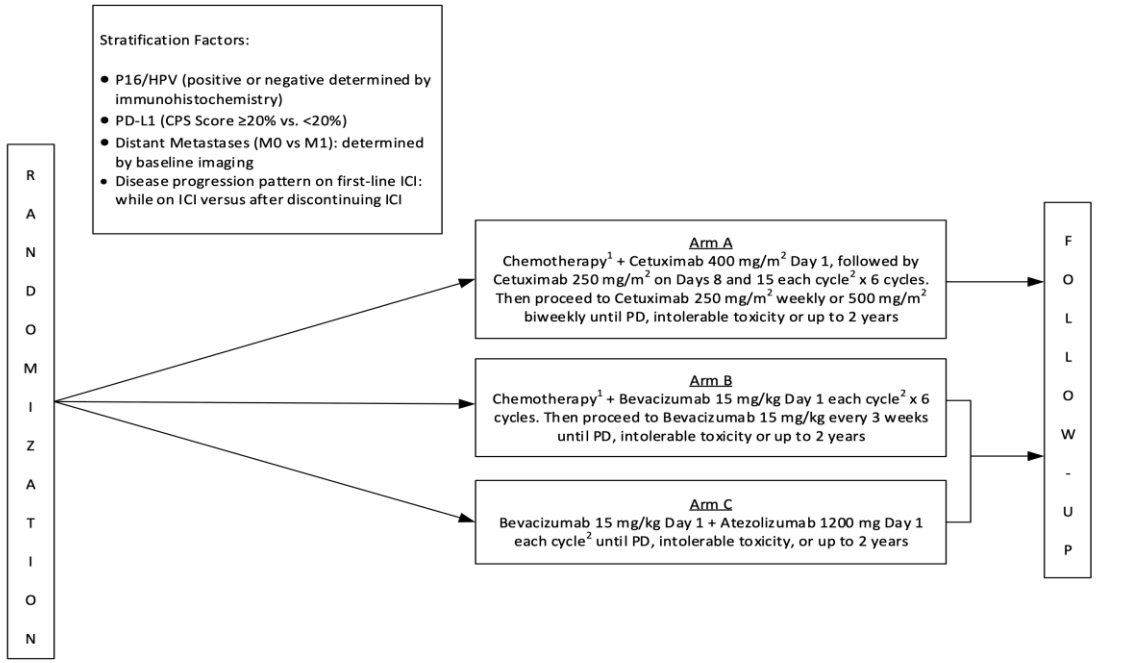
Table 2. Summary of Tumor Response

Outcome	Lenvatinib + Pembrolizumab (N = 22)
BOR, n (%)	
CR	1 (4.5)
PR	8 (36.4)
SD	11 (50.0)
PD	0 (0)
Unknown	2 (9.1)
ORR, n (%)	9 (40.9)
95% CI	20.7, 63.6
ORR_{Week24}, n (%)	8 (36.4)
95% CI	17.2, 59.3
Median DOR, months	13.3
95% CI	2.2, NE
Median PFS, months	8.2
95% CI	4.3, NE
12-Month PFS rate, %	41.9
95% CI	17.6, 64.7

Taylor MH. ASCO Annual Meeting 2018.

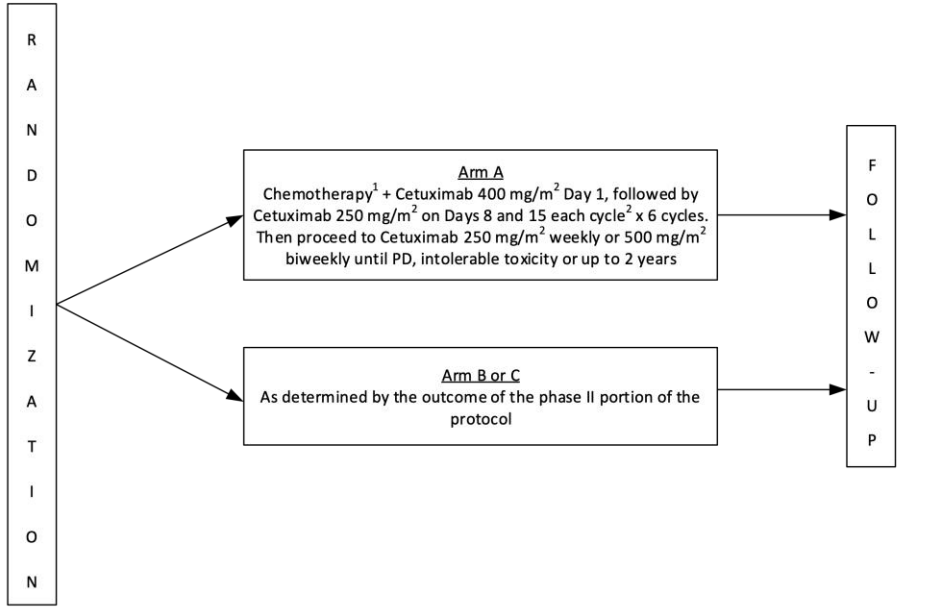
VEGF Inhibitors

Phase II



1. Arm A and B: Chemotherapy consists of Docetaxel 75mg/m² IV Day 1, Investigator Choice of Cisplatin 75mg/m² IV Day 1 or Carboplatin AUC 5 IV Day 1. Please refer to Section 5.1 for more details
2. One cycle = 21 days

Phase III

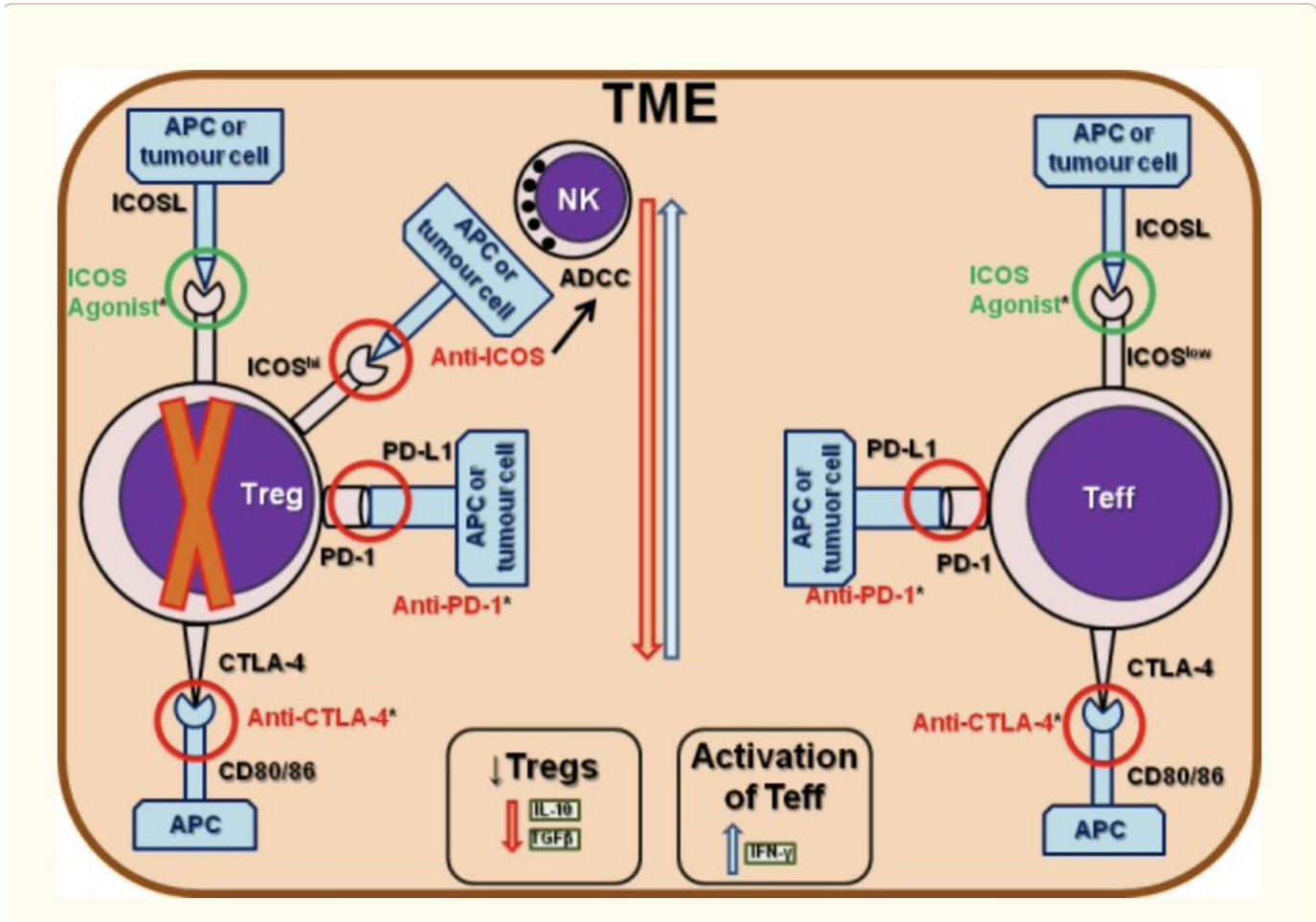


1. Arm A: Chemotherapy consists of Docetaxel 75mg/m² IV Day 1, Investigator Choice of Cisplatin 75mg/m² IV Day 1 or Carboplatin AUC 5 IV Day 1. Please refer to Section 5.1 for more details
2. One cycle = 21 days

Phase III sample size = 214

ICOS agonists

- Synergy observed in Phase 1 trials
- Randomized trials with pembrolizumab and pembrolizumab + chemo were launched then discontinued



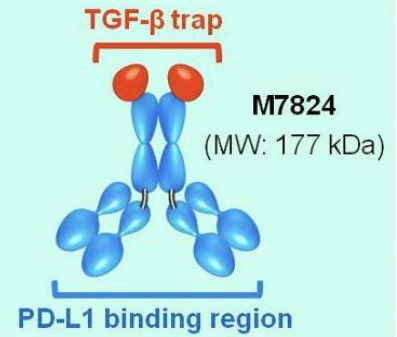
Solinas C. ESMO Open 2020. Hansen A, ESMO 2018.

Virally-mediated Head & Neck Ca

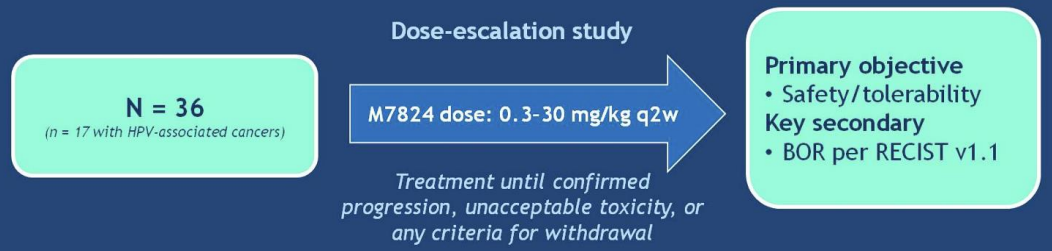
M7824

M7824

- Bifunctional targeting of the TGF-ß and PD-L1 pathways[7]
  - TGF-ß-neutralizing trap component: Extracellular domain of human TGF-ßR2, binds TGF-ß1, -ß2 and -ß3
  - Antibody component: Fully human IgG1 mAb against human PD-L1
- Ongoing phase 1 dose-escalation trial demonstrates range of clinical activity in heavily pre-treated solid tumors[8-11]



Study design



- Ongoing, phase 1, open-label trial of M7824 (NCT02517398)[1] in heavily pretreated patients with advanced solid tumors
- Here, we report on a retrospective subgroup analysis of the safety and efficacy of M7824 in patients with HPV-associated cancers (n = 17; including cervical, anal, and SCCHN)

BOR, n (%)	HPV-associated (n = 17)
CR	2 (11.8)[a]
PR	4 (23.5)[b]
SD	4 (23.5)
PD	7 (41.2)
ORR	6 (35.3)[b]
DCR	10 (58.8)[b]

Strauss J. ASCO Annual Meeting 2018.

HPV Vaccine Trials

- Target E6/E7 oncoproteins
- ISA101 + nivolumab (Ph 2): 33% ORR and mOS 17.5 months
- HPV DNA vaccine MEDI0457 + durvalumab (Ph 1b/2): 22% ORR
- Ongoing trials:
    1. M7824, the anti-PD-L1/TGF-b fusion protein, + HPV-16 cancer vaccine PDS0101 + immunocytokine NHS-IL12
    2. M7824 + PRGN-2009, a novel gorilla adenovirus GAd HPV vaccine with agonist epitopes of E6 and E7
    3. VERSATILE-002 (Ph 2): PDS0101 vaccine + pembrolizumab in R/M HPV+ HNC
    4. Adoptive cell therapy trials also underway

Massarelli E. JAMA oncology 2018. Aggarwal C. Annal Onc 2020.

EBV Targeting

- Latent antigens: EBNA1 (maintains viral genome in infected cells) and LMP2 (facilitates proliferation, survival and migration of infected cells)
- Early-phase trials using these antigens as part of vaccine drugs have shown immunogenecity
- LMP2 specific T cell therapy trial ongoing

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Thank you!!