Immunotherapy on the Horizon

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Image: NASA.gov

Disclaimer

By virtue of the fact this talk is about therapies on the horizon, I will discuss non-FDA approved therapies.

Research Funding:

Gilead, Halozyme, Immunomedics, Lilly, NewLink, Onconova, Seattle Genetics, Sirtex, Taiho, Xbiotech

Consulting:

Halozyme, Seattle Genetics

Outline

Checkpoint Blockade

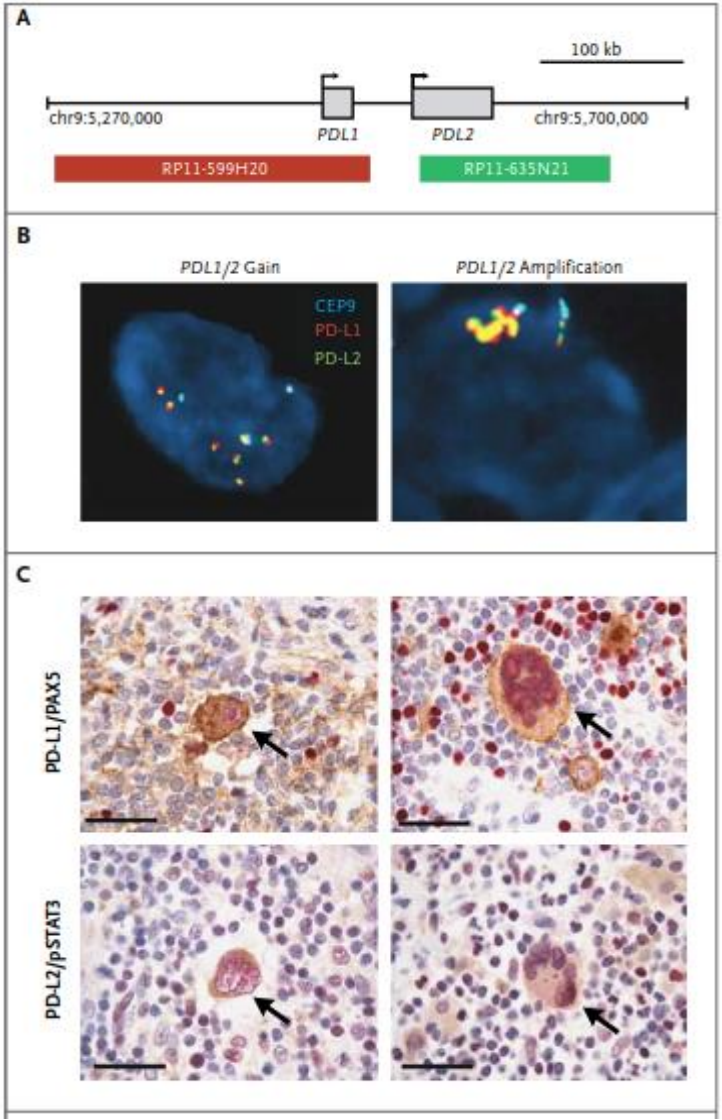
- Hodgkin Lymphoma
- Head and Neck Cancer
- Gastric Cancer
- Colon Cancer

CAR T Cells

- Leukemia
- Lymphoma

PD-1 Inhibitors
Hodgkin Lymphoma

Reed Sternberg cells uniformly overexpress PD-L1 and PD-L2



Ansell SM, NEJM 372:311

PD-1 Inhibitors Hodgkin Lymphoma

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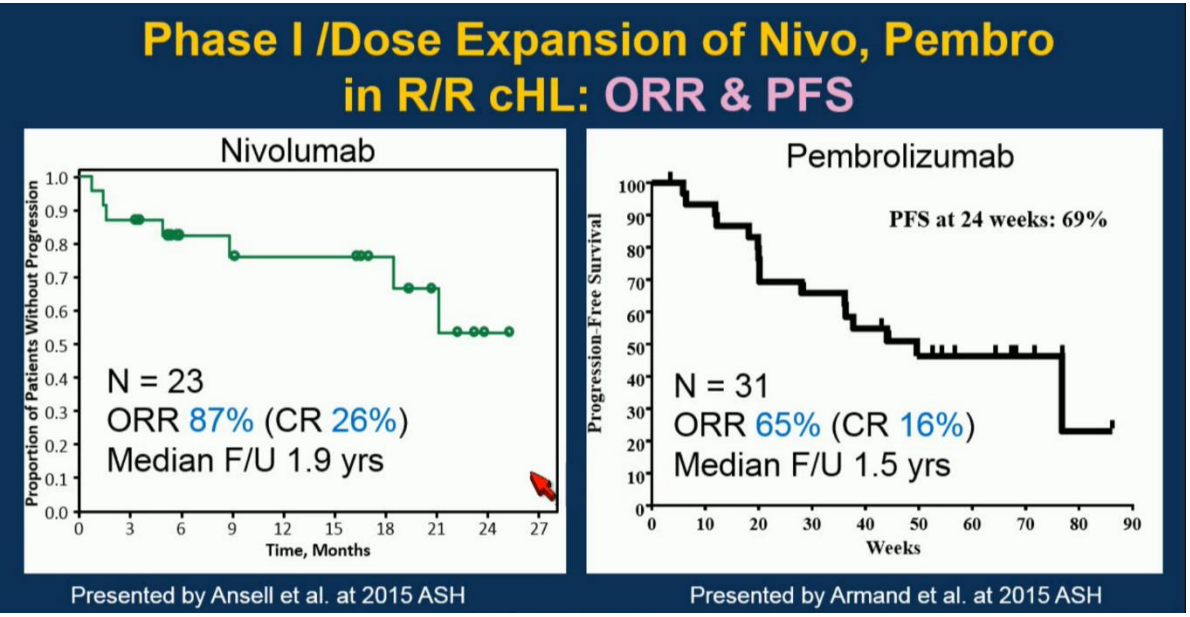

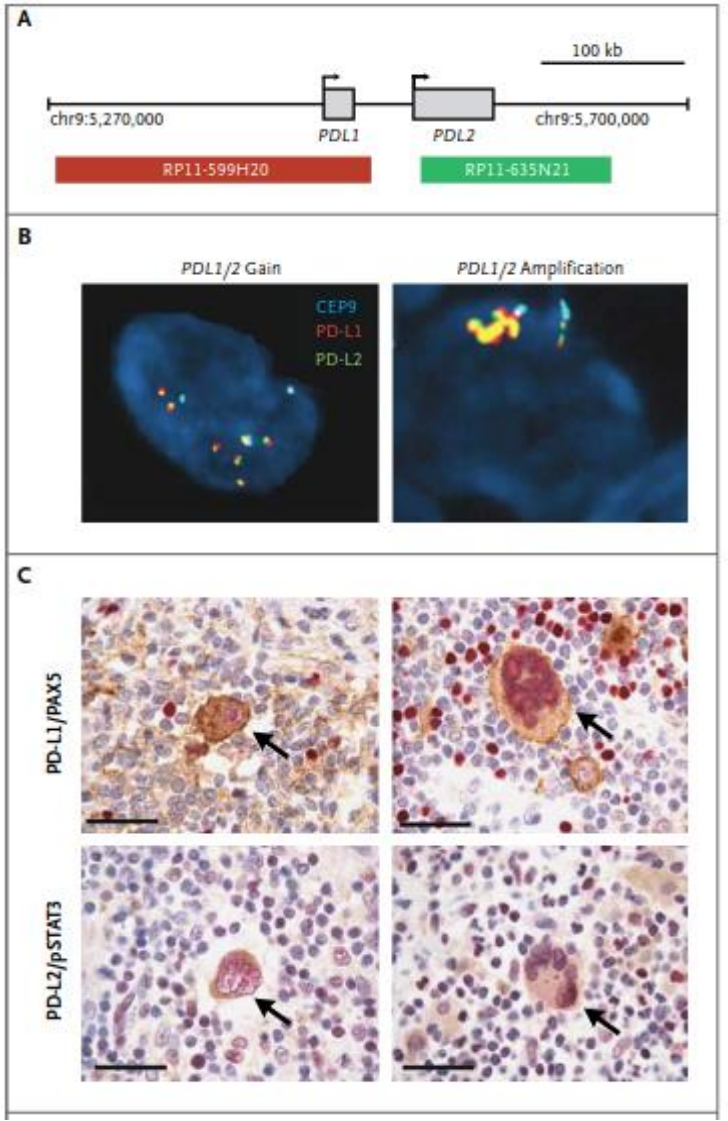

ASCO 2016, Nancy Bartlett
Ansell SM, NEJM 372:311 (Nivolumab)

PD-1 Inhibitors Hodgkin Lymphoma

Reed Sternberg cells uniformly overexpress PD-L1 and PD-L2

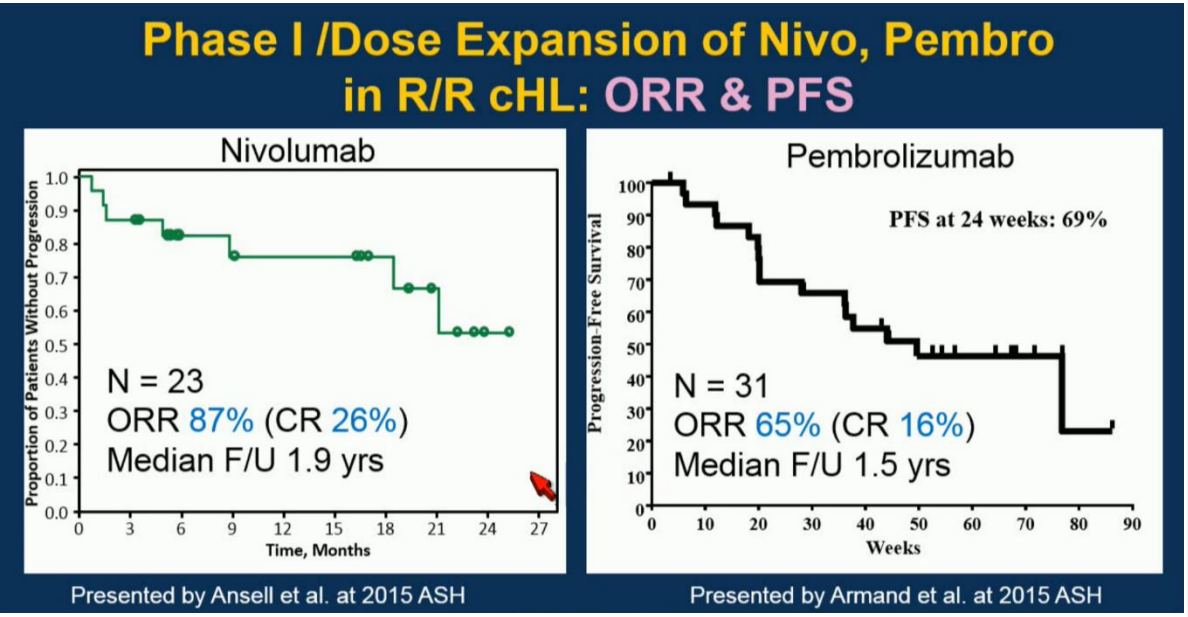

Table 2. Drug-Related Adverse Events in the 23 Patients.*

Event	Any Grade	Grade 3
	no. of patients (%)	
Any adverse event	18 (78)	5 (22)
Drug-related adverse events reported in ≥5% of patients		
Rash	5 (22)	0
Decreased platelet count	4 (17)	0
Fatigue	3 (13)	0
Pyrexia	3 (13)	0
Diarrhea	3 (13)	0
Nausea	3 (13)	0
Pruritus	3 (13)	0
Cough	2 (9)	0
Hypothyroidism	2 (9)	0
Decreased lymphocyte count	2 (9)	1 (4)
Hypophosphatemia	2 (9)	0
Hypercalcemia	2 (9)	0
Increased lipase level	2 (9)	1 (4)
Stomatitis	2 (9)	1 (4)
Drug-related serious adverse events		
Myelodysplastic syndrome	1 (4)	1 (4)
Lymph-node pain	1 (4)	0
Pancreatitis	1 (4)	1 (4)

ASCO 2016, Nancy Bartlett
Ansell SM, NEJM 372:311

PD-1 Inhibitors in HL

Checkmate 205: Nivolumab in HL after ASCT and brentuximab vedotin (cohort B). (Younes et al)

- Nivolumab 3mg/kg IV q2 weeks

Keynote-087: Pembrolizumab for relapsed/refractory HL (Chen et al)

- Pembrolizumab 200mg IV q3 weeks.

PD-1 Inhibitors in HL

	Nivolumab	Pembrolizumab		
Cohort	B	1	2	3
N =	80	30	30	30
Prior ASCT	Yes	Yes	No	Yes
Prior BV	Yes	Yes	Yes	No
ORR				
CR				

Nivolumab:

Pembrolizumab:

PD-1 Inhibitors in HL

	Nivolumab	Pembrolizumab		
Cohort	B	1	2	3
N =	80	30	30	30
Prior ASCT	Yes	Yes	No	Yes
Prior BV	Yes	Yes	Yes	No
ORR	66%	73%	83%	73%
CR	9%	27%	30%	30%

APPROVED

Nivolumab: mTTR = 2.1m, mPFS = 10m

Pembrolizumab: Most at 12 weeks, No PFS Data

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CAR T Cells

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- Lymphoma

Pembrolizumab in Head and Neck Cancer

APPROVED

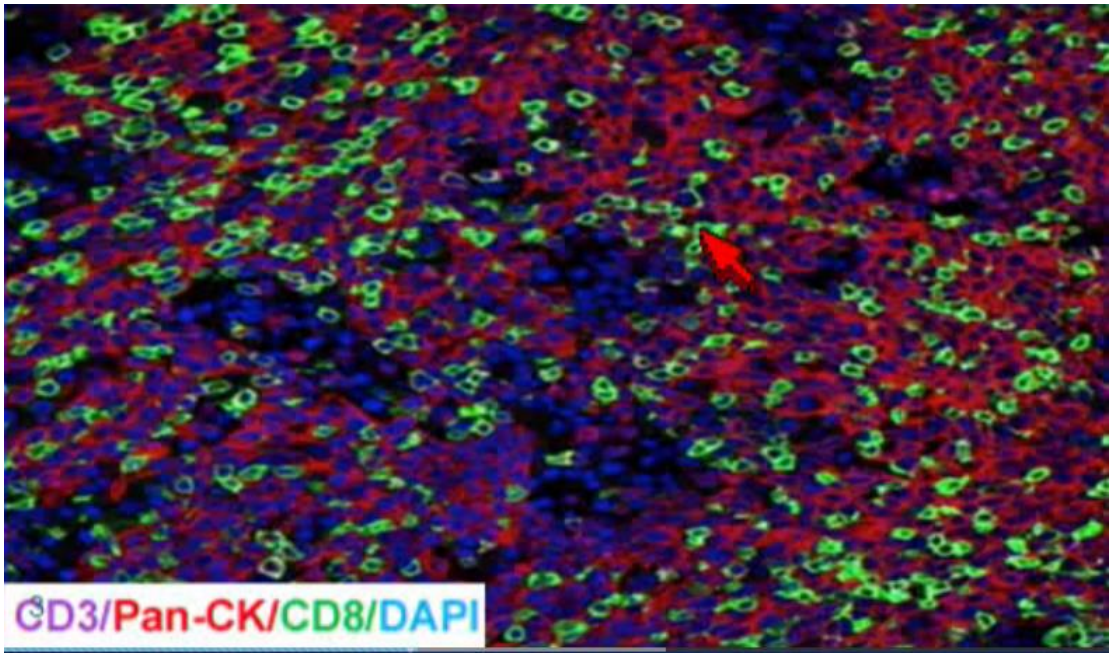
5th most common cancer worldwide

Recurrent / Metastatic HNSCC mOS 10months

- Previously treated mOS is 6 months

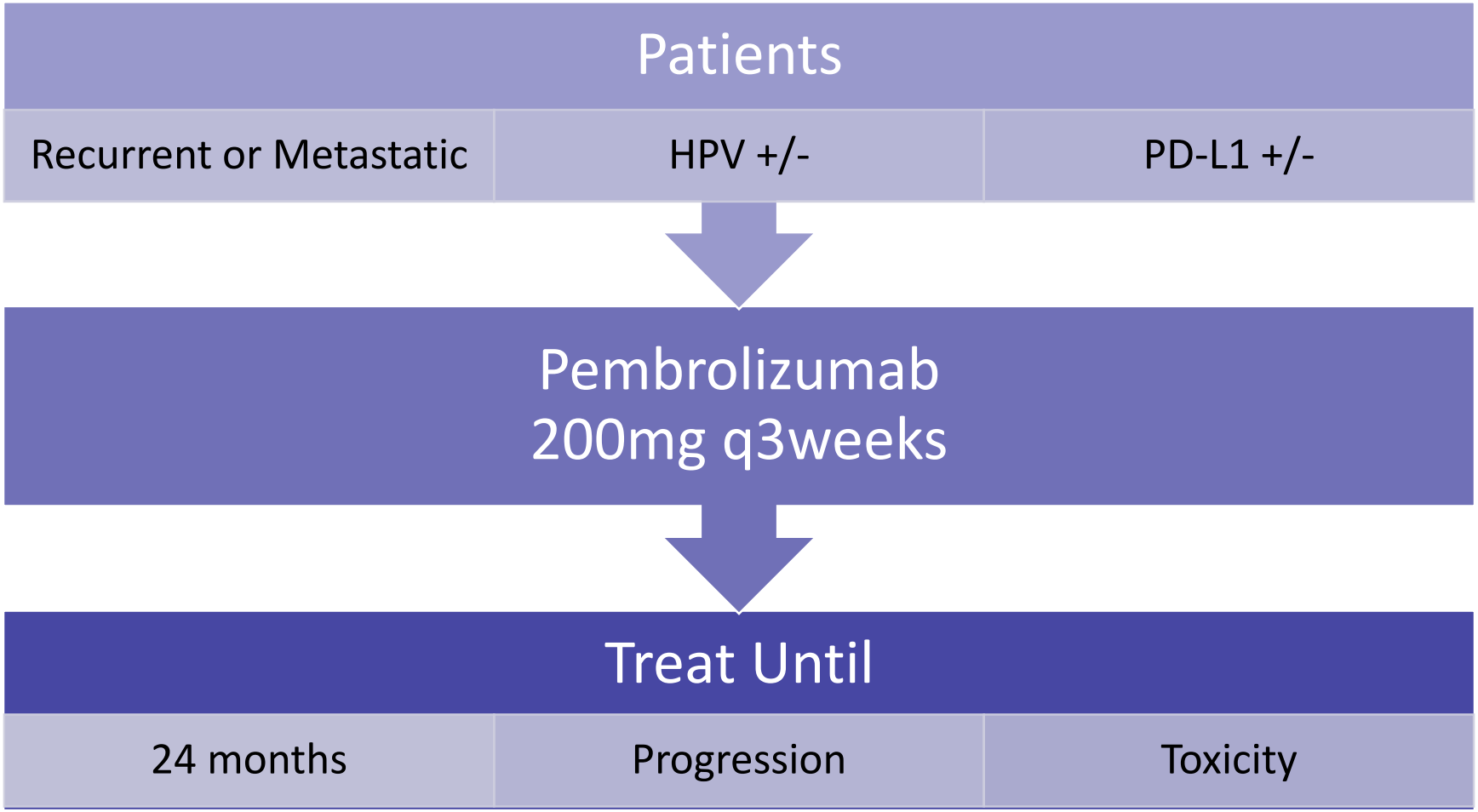
Immune Escape

- TILs + PD+L1
- HPV +/-



ASCO 2015, Seiwert et al.
KEYNOTE-012

HNSCC expansion cohort Pembrolizumab



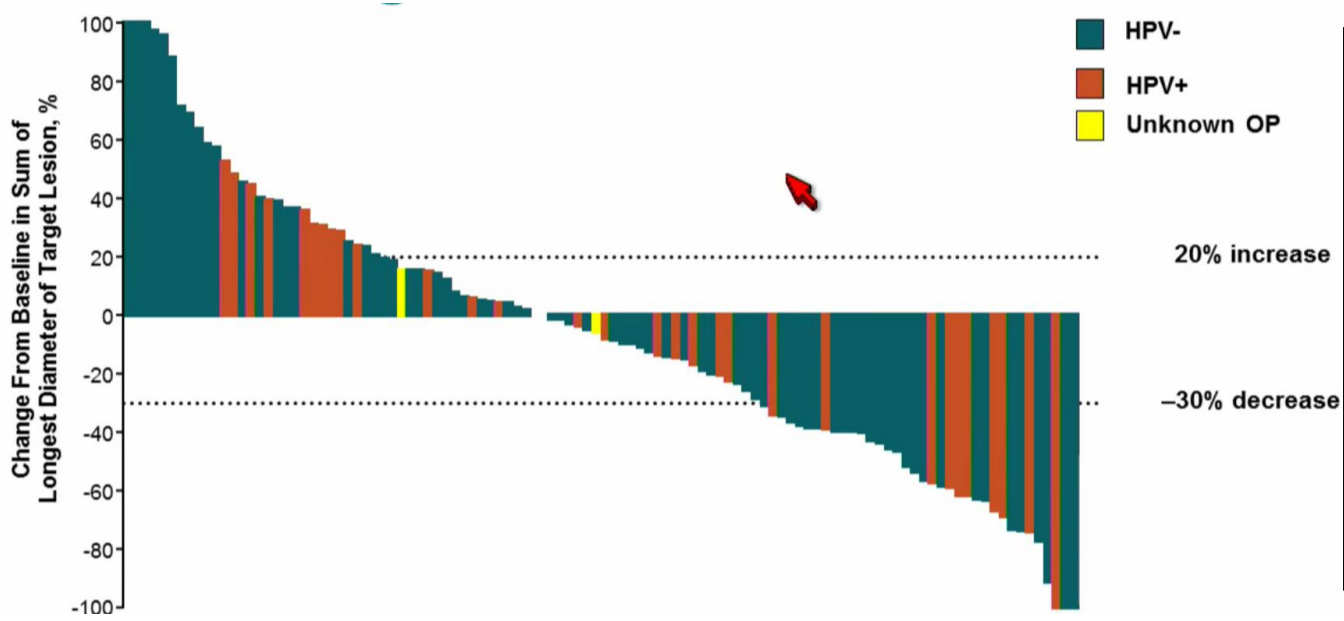
Adverse Events Pembrolizumab in HNSCC

Event, (n) %	Grade 1-2		Grade 3		Grade 4
Hypothyroidism	(14)	11%			
Pneumonitis	(2)	1.5%	(2)	1.5%	
Thyroiditis	(3)	2.3%			
Colitis			(1)	0.8%	
Interstitial Lung Dz	(1)	0.8%			

ASCO 2015, Seiwert et al.
KEYNOTE-012

Pembro in HNSCC, Response

	Total N=117	HPV+ n=34	HPV- n=81
ORR	25%	21%	27%
CR	1%	3%	0%
PR	24%	18%	27%
SD	25%	27%	24%
PD	41%	38%	42%



Median Time to Response:
9 weeks

Median Duration of Response:
Not Reached

ASCO 2015, Seiwert et al., KEYNOTE-012

Pembro FDA Results

173 evaluable patients (of 192 safety evaluable)

ORR	CR	2
	PR	39 (24%)
PFS	at 6m	28%
	at 12m	18%
	mPFS	2.2m
OS	at 6m	60%
	at 12m	47%
	mOS	9.6m (historically 6 months)

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- Leukemia
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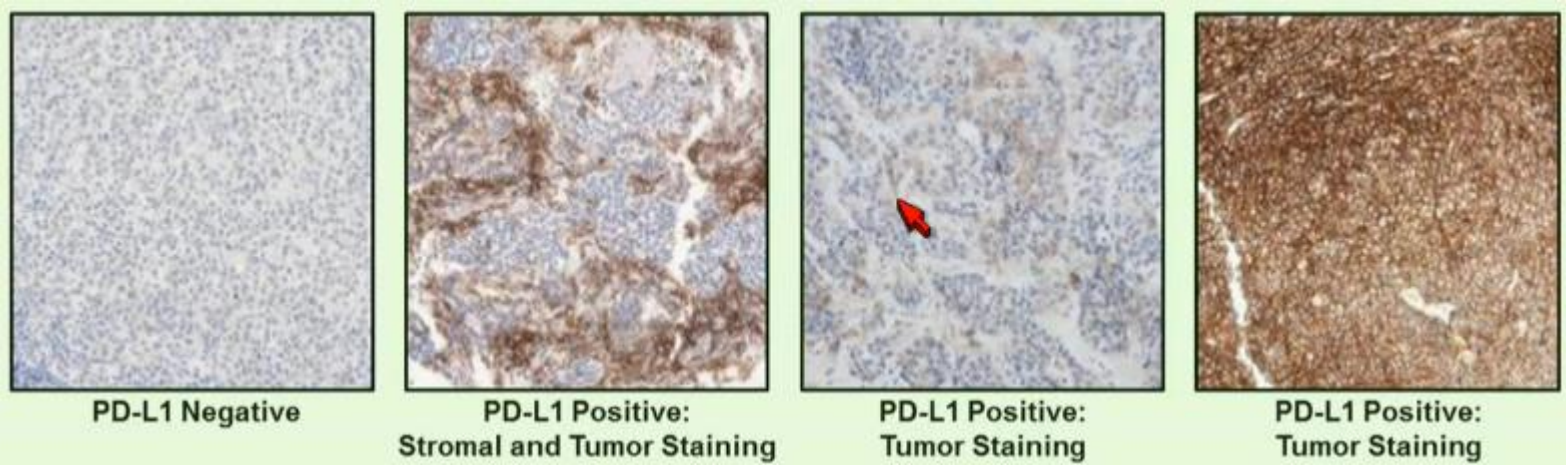
Gastric Cancer and Pembrolizumab

5th most common cancer worldwide*

Recurrent / Metastatic mOS 16 months

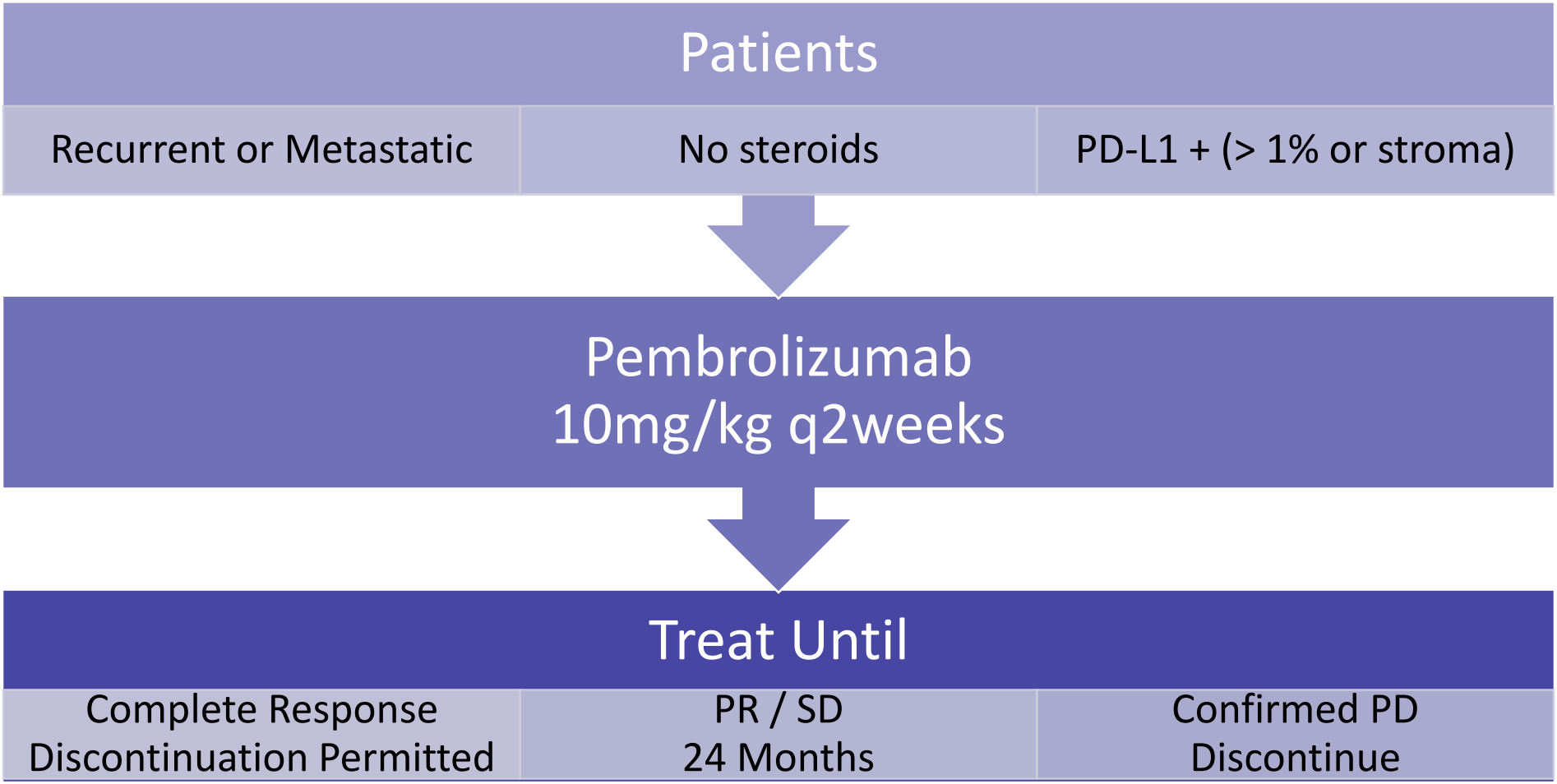
KEYNOTE-012 Patient Characteristics (n=39)

- Previous Therapy: 24% ≤1 line , 66% ≥ 2
- 40% PD-L1+ (of screened for KEYNOTE-012)



Muro et al. Lancet Oncol 2016; 17(6)717-726.
KEYNOTE-012, ASCO GI 2015

GEJ/Gastric expansion cohort Pembrolizumab



Adverse Events Pembrolizumab in Gastric Cancer

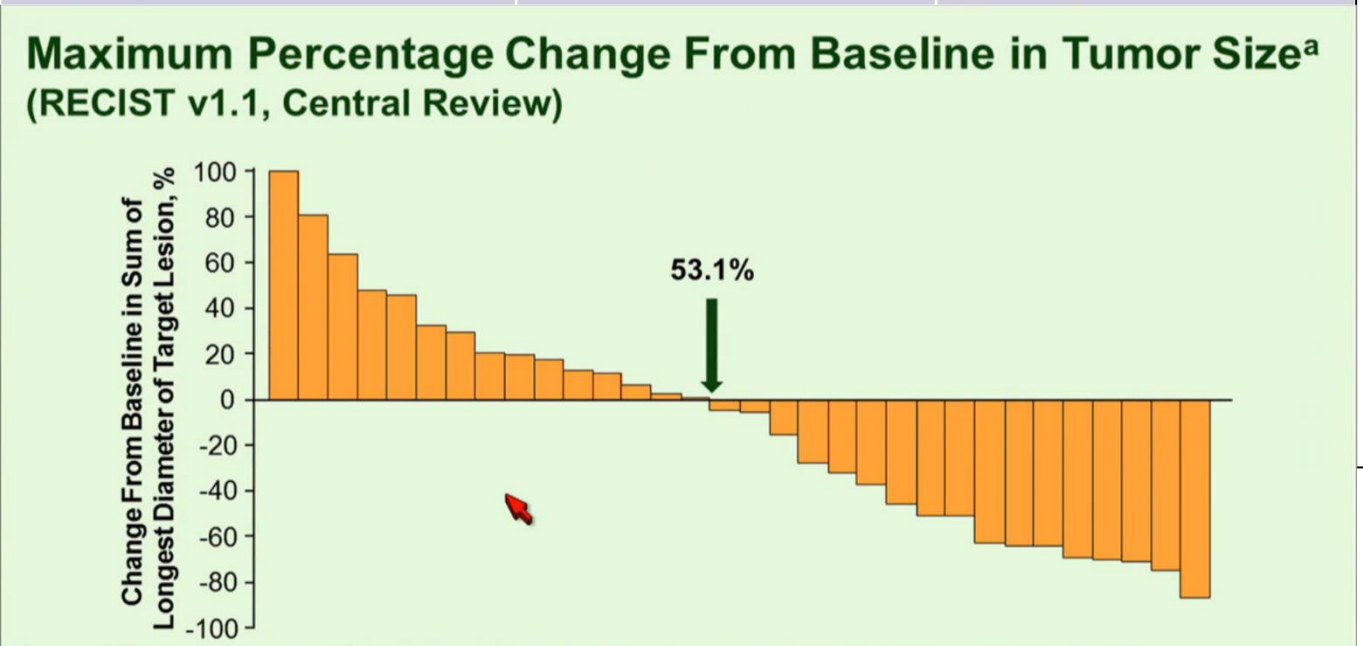
Event, (n) %	> 6%	Related
Any	(26)	67%
Fatigue	(7)	18%
Anorexia	(5)	13%
Hypothyroidism	(5)	13%
Arthralgia	(4)	10%
Hyperthyroidism	(3)	8%
Nausea	(3)	8%
Pruritus	(3)	8%

Event, (n) %	Grade 3-5	
Patients with event	(4)	10%
Anorexia	(1)	2.5%
Fatigue	(1)	2.5%
Neuropathy	(1)	2.5%
Pneumonitis	(1)	2.5%

Muro et al. Lancet Oncol 2016; 17(6)717-726.
KEYNOTE-012, ASCO GI 2015

Pembro in Gastric Ca, Response

	Total N=36	
ORR	22%	
CR	0%	
PR	22%	
SD	14%	
PD	53%	



Median Time to Response:
8 weeks

Median Duration of Response:
24 weeks

6 of 8 responses ongoing at analysis.

Muro et al. Lancet Oncol 2016; 17(6)717-726.
KEYNOTE-012, ASCO GI 2015

Pembro Gastric Trials

KEYNOTE-059 — Closed

- Pembro for ≥2 lines
- Pembro + Cis/5FU (First Line)
- Pembro (First Line)

KEYNOTE-061 (Second Line) — Closed

- Pembro vs Paclitaxel

KEYNOTE-062 (First Line) — Open

- Pembro
- Pembro + Cis/5FU
- Placebo + Cis/5FU

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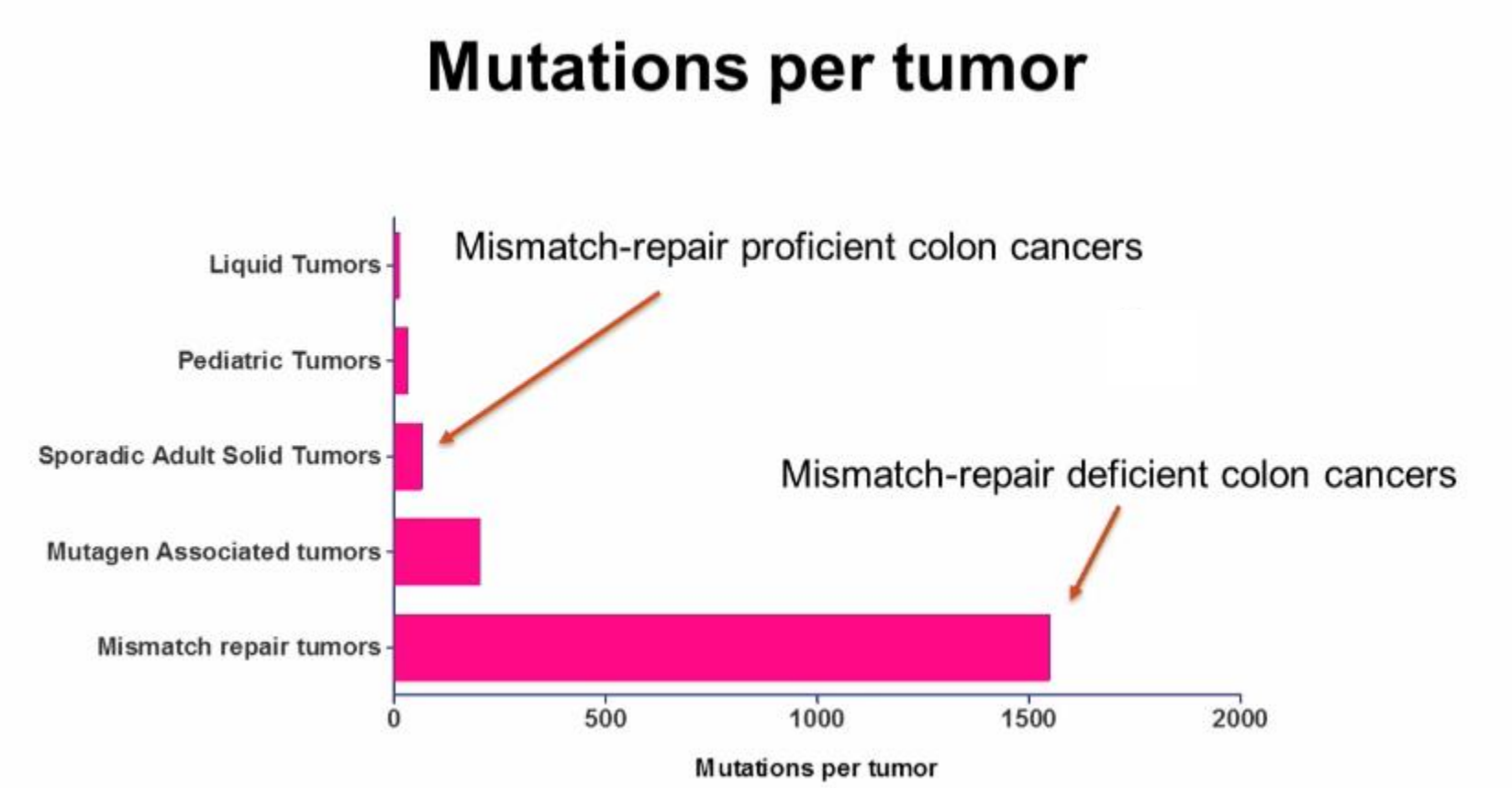
Mismatch Repair Deficiency

Microsatellite instability

- Due to deficient DNA mismatch repair
  - Germline (Lynch)
  - Sporadic (MLH1, MSH2, MSH6, PMS2, EpCAM)
  - Epigenetic (MLH1 hyper-methylation)
- Tumors
  - 15% of Sporadic CRC (5% of Advanced)
  - Endometrial, Gastric, Small Bowel, Ampullary, Cholangiocarcinoma, Pancreatic, Sarcoma, Prostate, Gliomas and others

ASCO 2015, Le et al.
Le et al. NEJM 2015

Mismatch Repair Deficiency



ASCO 2015, Le et al.
Le et al. NEJM 2015

Pembro for dMMR Tumors

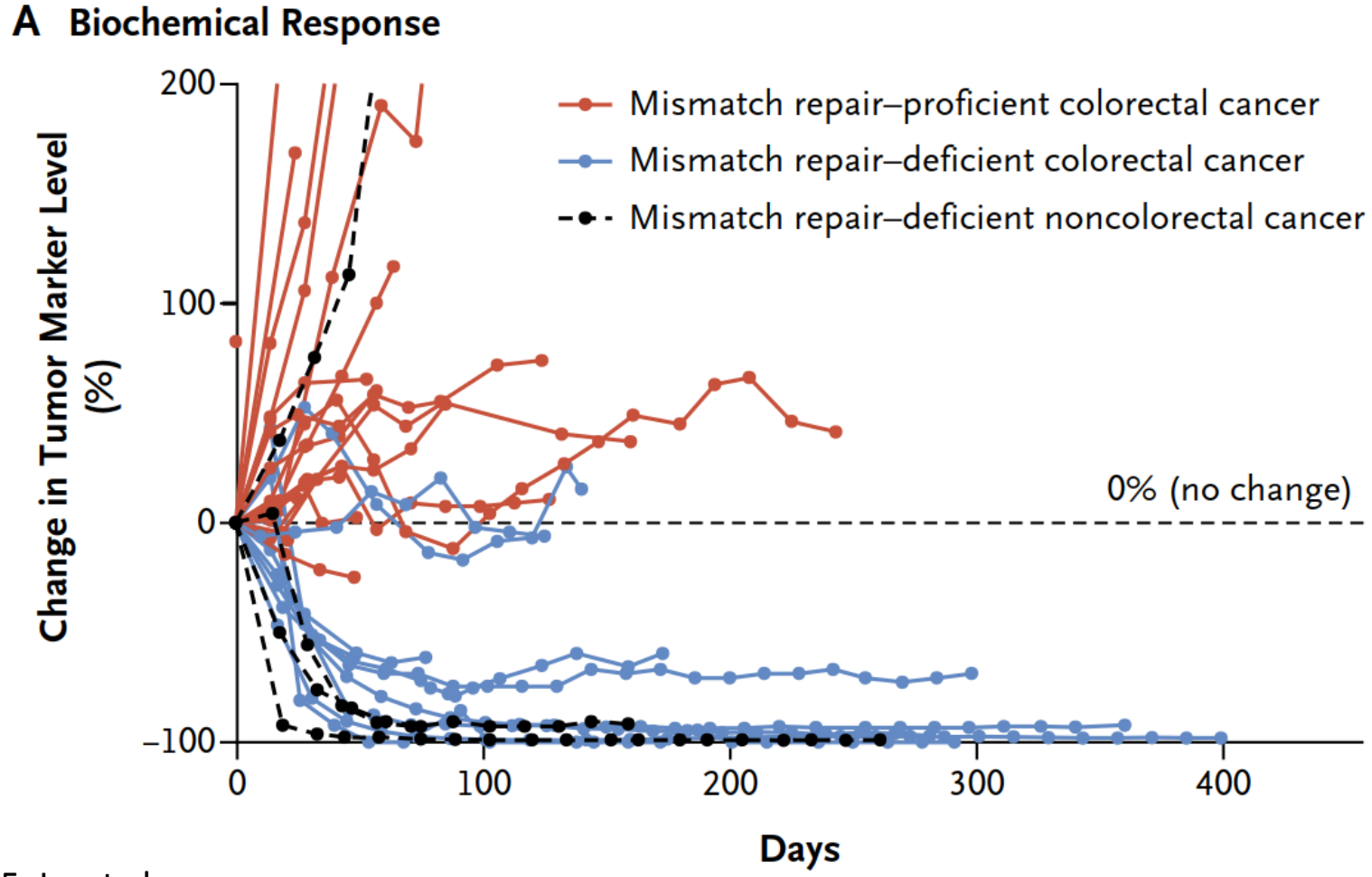
Pembro 10mg/kg q 2weeks
MMR testing by PCR for MSI

Colorectal		Non CRC
dMMR	pMMR	dMMR

Pembro for dMMR Tumors

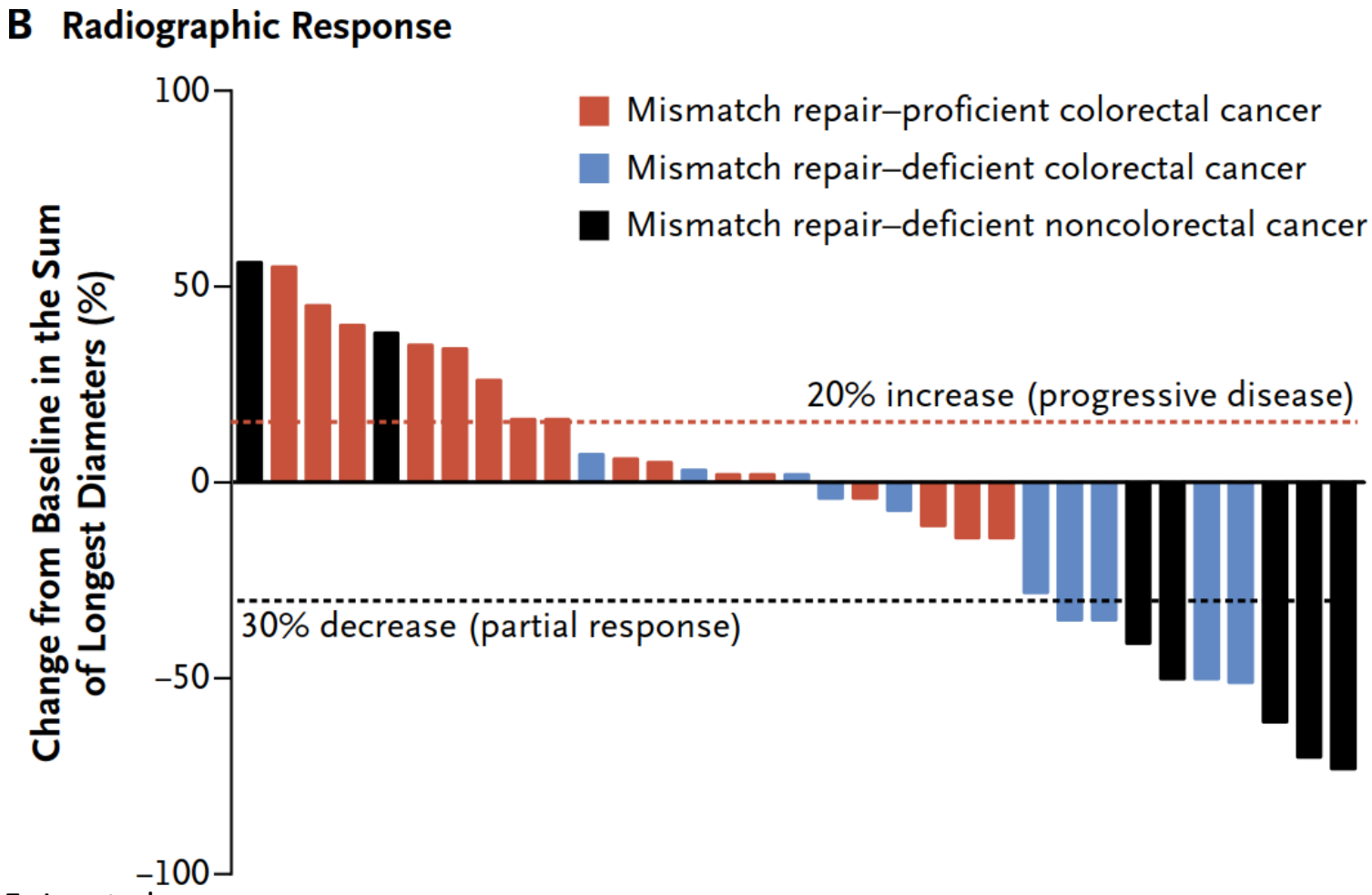
Colorectal		Non CRC
dMMR N=13	pMMR N=25	dMMR N=10
ORR: 62% DCR: 92%	ORR: 0% DCR: 16%	ORR: 60% DCR: 70%

Pembro for dMMR Tumors



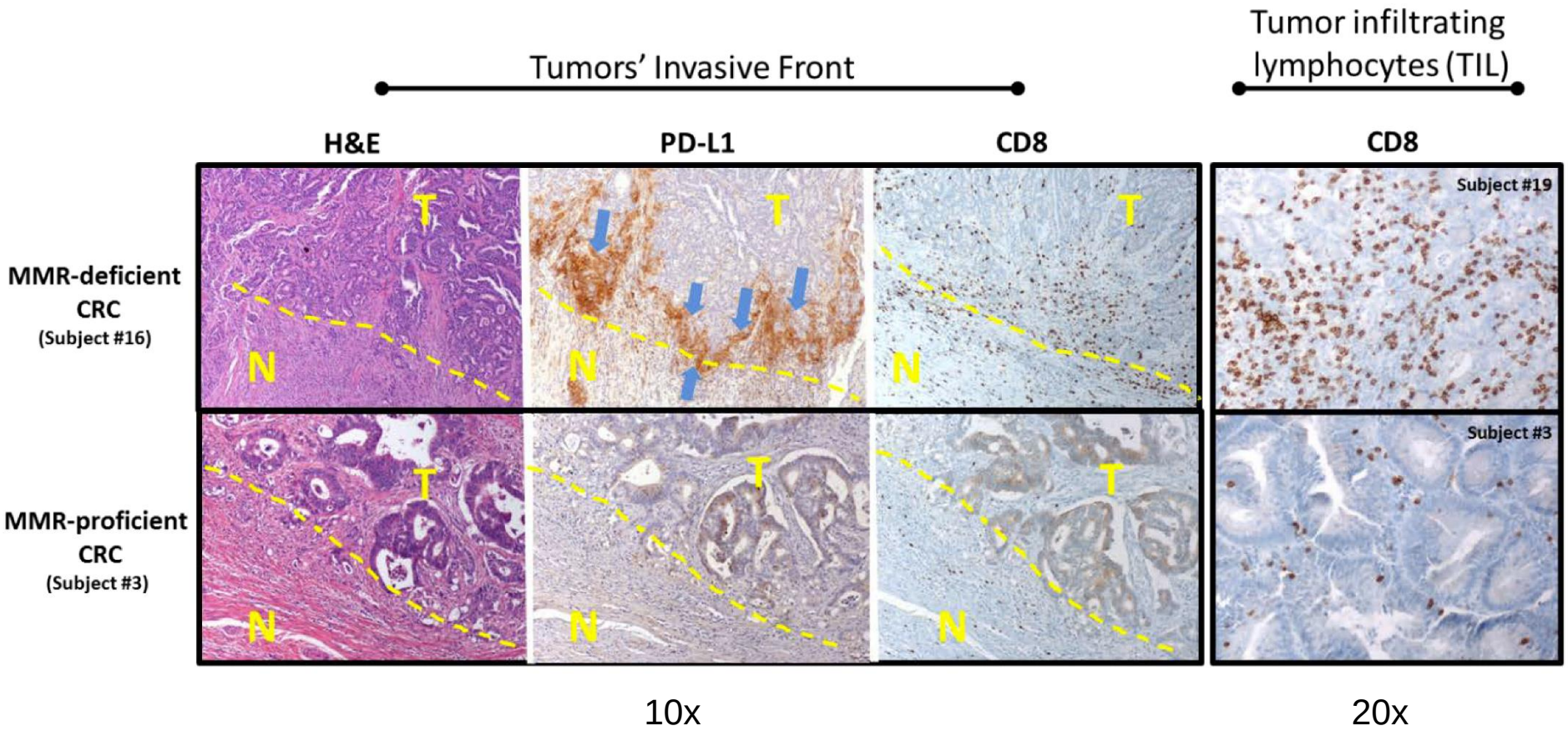
ASCO 2015, Le et al.
Le et al. NEJM 2015

Pembro for dMMR Tumors



ASCO 2015, Le et al.
Le et al. NEJM 2015

Pembro for dMMR Tumors



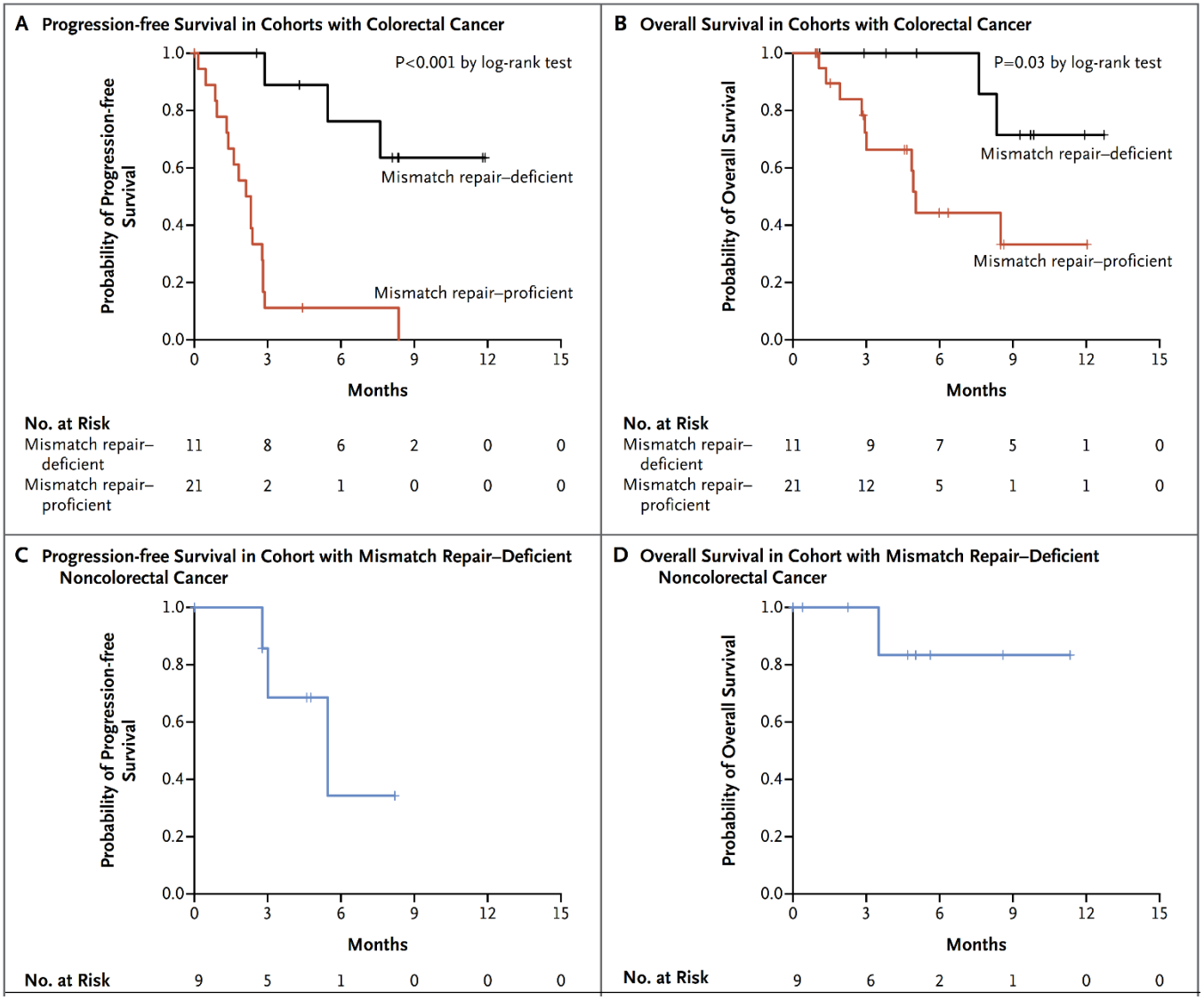
ASCO 2015, Le et al.
Le et al. NEJM 2015

Mutation Burden and Not PDL1 Expression Predicted Response

PFS CRC
MMRd NR
MMRp 2.2m

OS CRC
MMRd NR
MMRp 5.0m

MMRd Non CRC
PFS 5.4m
OS NR



Le et al. NEJM 2015

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CAR T Cells

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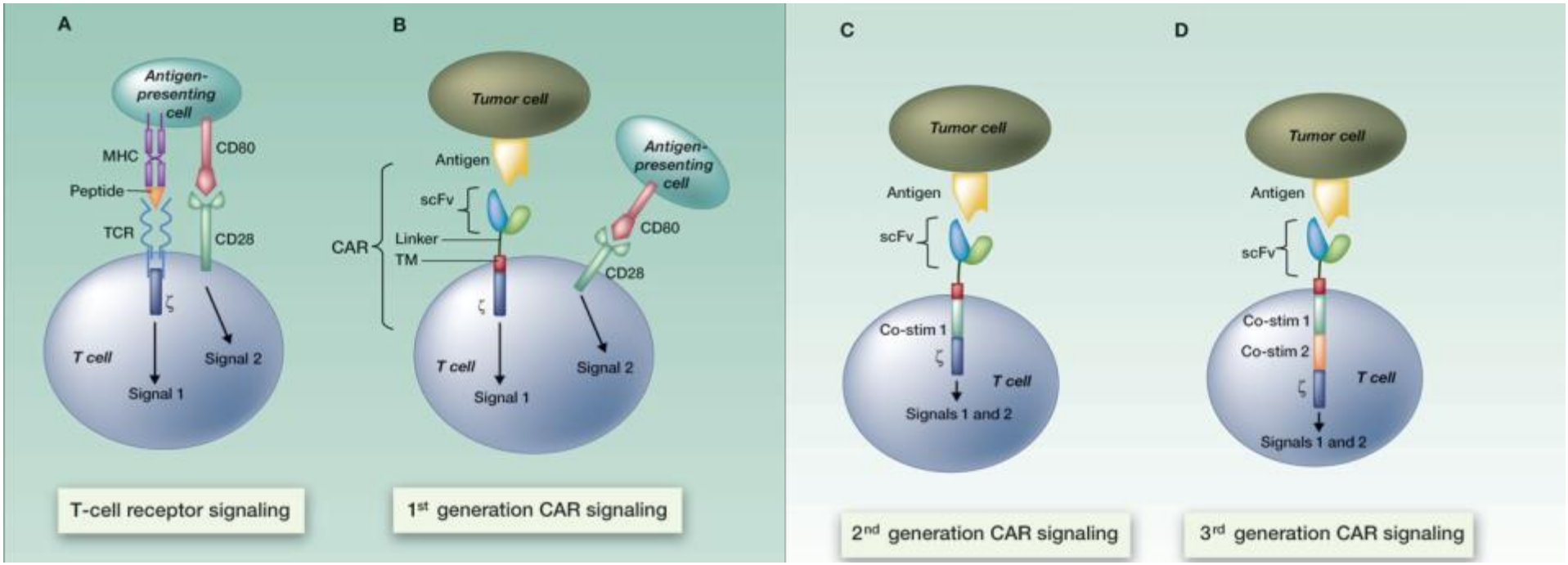
Chimeric Antigen Receptor T cells

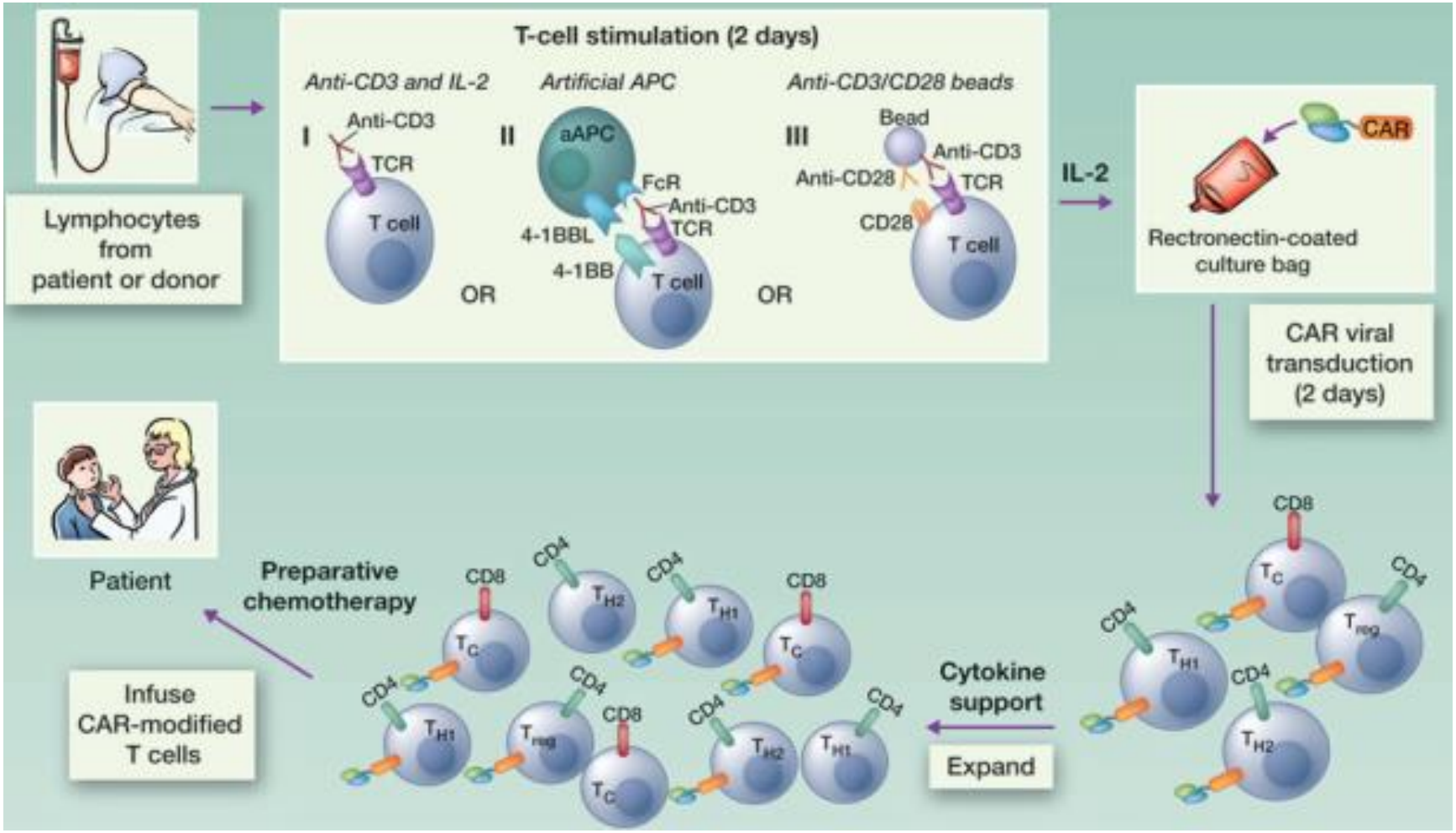
CARs were first generated in 1989!

Initially not very active, but they were optimized



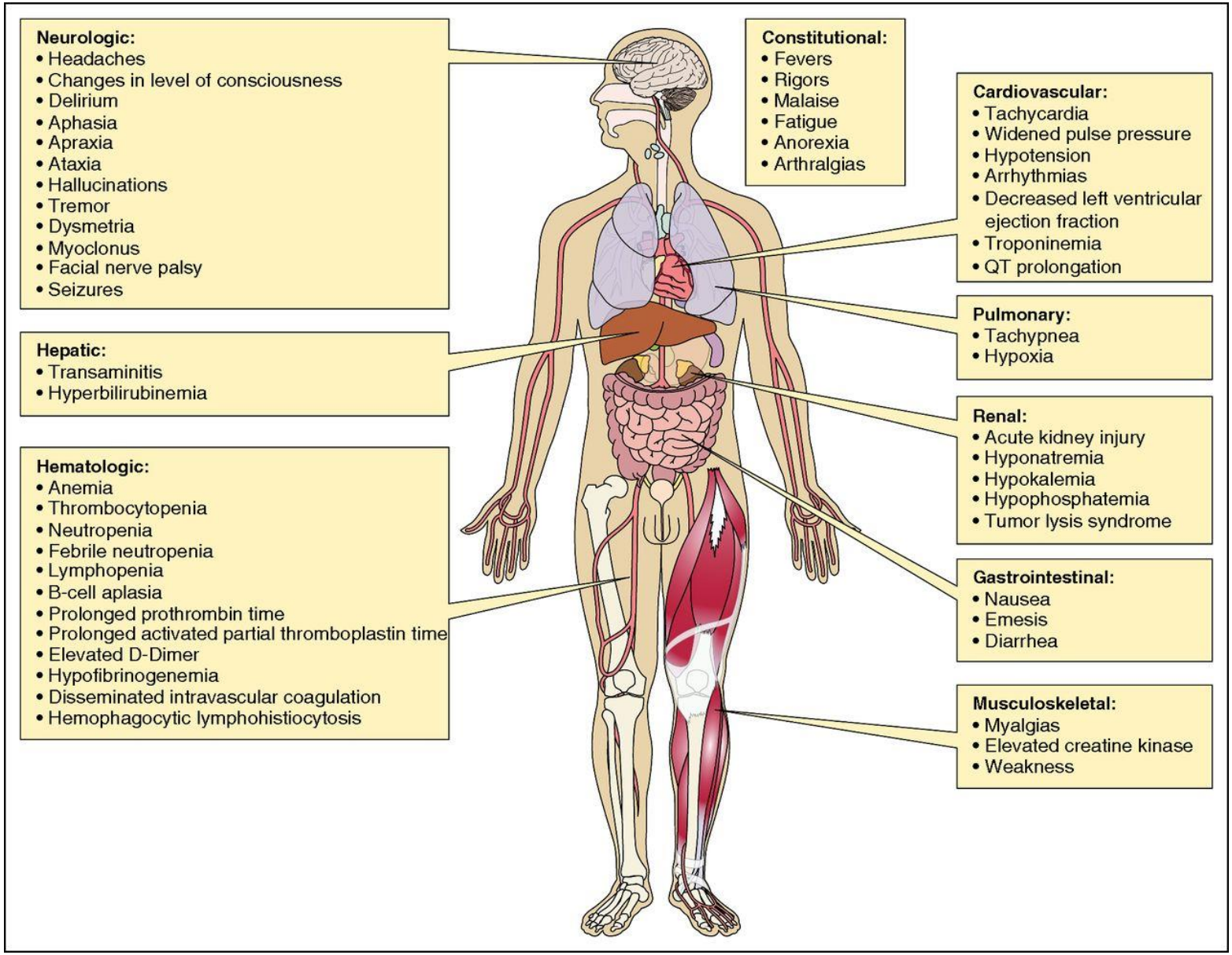
Clin Cancer Res; 2012;18(10); 2780–90.

Chimeric Antigen Receptor T cells



Clin Cancer Res; 2012;18(10); 2780–90.

CAR T Cell Toxicities



Burton et al Blood 2016 127:3321-3330

Most Common: CRS
(Cytokine Release Syndrome)

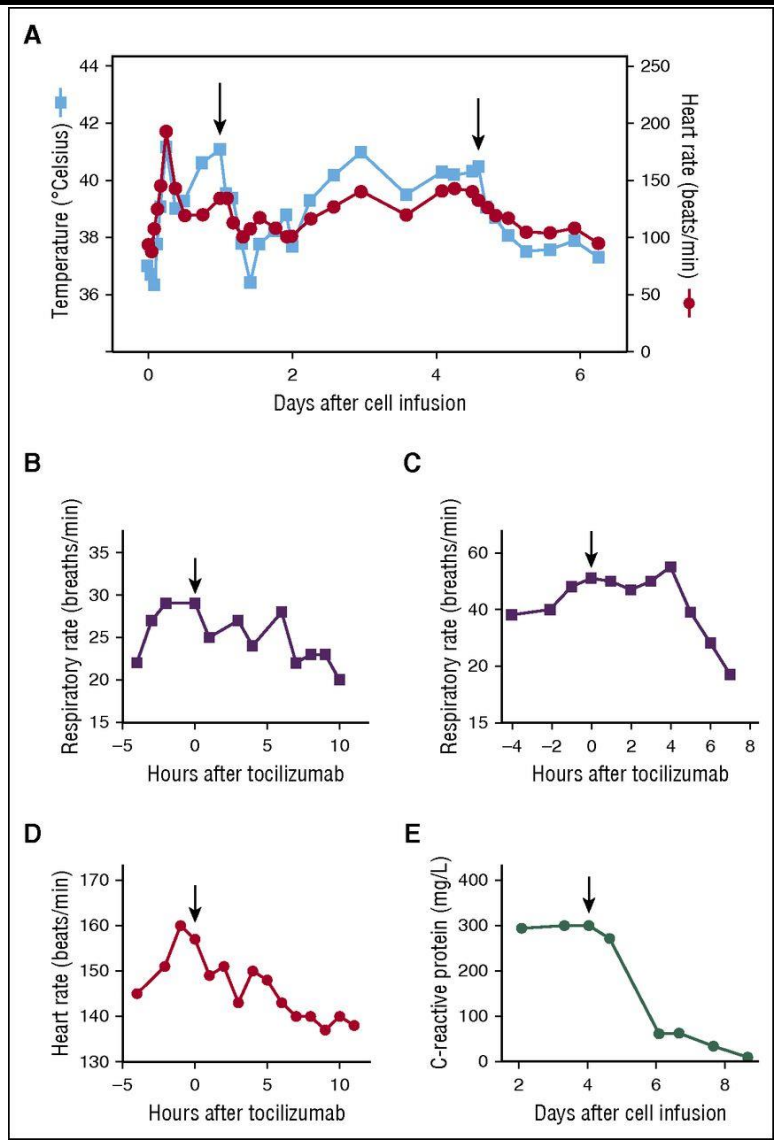
Cytokines

IL-6, 2, 8 and 10,

INF-gamma, TNF

Management

- APAP, Cooling Blankets
- Fluids
- Tocilizumab
  (IL-6 receptor antagonist)
- Steroids when needed



Burton et al Blood 2016 127:3321-3330

Summary of CD19-CAR Trials

Table 1. Summary of CD19-CAR constructs in clinical trials

Institution	Gene transfer method	ScFv*	Costimulatory domain	Patient populations	Lymphodepleting chemotherapy	Infused cell doses	Responses observed
CHOP[3,4]	Lentivirus	FMC63	4-1BB	Pediatric ALL; n = 53[4]	Investigator's choice	1.07×10^6 to 17.36×10^6 CAR^+ T cells/kg	CR: 50/53 (MRD− in 45/50) 12 mo RFS: 45% 12 mo OS: 78%
NCI[5]	γ-retrovirus	FMC63	CD28	Pediatric ALL; n = 20	Cy 900 mg/m^2 ×1 + Flu 25 mg/m^2 ×3 d	1×10^6 (N = 16) vs 3×10^6 (N = 4) CAR^+ T cells/kg	CR: 14/20 (MRD− in 12/14) LFS: 79% at 4.8 mo (MRD− CR patients) OS: 52% at 7.8 mo (all)
NCI[6]	γ-retrovirus	FMC63	CD28	Adult CLL and B-NHL; n = 8	Cy 60 mg/kg ×2 d + Flu 25 mg/m^2 ×5 d	0.3×10^7 to 3.0×10^7 CAR^+ T cells/kg	ORR: 6/8 (CLL, 3/4; FL, 2/3); CR, n = 1 (CLL) and PR, n = 5
NCI[7]	γ-retrovirus	FMC63	CD28	Adult B-NHL; n = 15	Cy 60 mg/kg ×1-2 d + Flu 25 mg/m^2 ×5 d	1×10^6 to 5×10^6 CAR^+ T cells/kg	CR: 4/7 (refractory DLBCL), 4/6 (indolent B-NHL)
MSKCC[8-10]	γ-retrovirus	SJ25C1	CD28	Adult ALL; n = 46[9]	Cy or Cy + Flu	1×10^6 vs 3×10^6 CAR^+ T cells/kg	CR: 37/45 (MRD− in 30/36) among evaluable patients 6 mo OS: 65% (all) and 80% (MRD− CR patients)
FHCRC[11]	Lentivirus	FMC63	4-1BB	Adult ALL; n = 29	Cy or Cy 60 mg/kg ×1 + Flu 25 mg/m^2 ×3 d	2×10^5, 2×10^6, and 2×10^7 CAR^+ T cells/kg; 1:1 $CD4^+$:$CD8^+$	CR: 10/12 (Cy only) and 14/14 (Cy + fludarabine); MRD status unspecified
FHCRC[12]	Lentivirus	FMC63	4-1BB	Adult B-NHL; n = 28 Adult CLL; n = 6	Cy 60 mg/kg ×1 ± etoposide or Cy 60 mg/kg ×1 + Flu 25 mg/m^2 ×3 d	2×10^5, 2×10^6, and 2×10^7 CAR^+ T cells/kg 1:1 $CD4^+$:$CD8^+$	ORR (B-NHL): 6/12 (CR, n = 1, PR, n = 5 in Cy cohort) and 8/12 (CR, n = 5, PR, n = 3 in Cy + Flu cohort) ORR (CLL): 5/6 (CR, n = 3, PR, n = 2)
UPenn[13]	Lentivirus	FMC63	4-1BB	Adult CLL; n = 14	Investigator's choice	0.14×10^8 to 11×10^8 CAR^+ T cells	ORR: 8/14 (MRD− CR, n = 4, PR, n = 4) Median PFS: 7 mo Median OS: 29 mo
UPenn[14]	Lentivirus	FMC63	4-1BB	Adult CLL; n = 26	Investigator's choice	5×10^7 vs 5×10^8 CAR^+ T cells	ORR: 9/23 (CR, n = 5, PR, n = 4)
UPenn[15]	Lentivirus	FMC63	4-1BB	Adult B-NHL; n = 24†	Investigator's choice	3.08×10^6 to 8.87×10^6 CAR^+ cells/kg	ORR: 15/22 (DLBCL, 7/13; FL, 7/7, MCL, 1/2) PFS: 62% at 11.7 mo
UPenn[14]	Lentivirus	FMC63	4-1BB	Adult ALL; n = 12	Investigator's choice	6.5×10^6 to 8.45×10^6 CAR^+ cells/kg	CR: 8/9 (all MRD− in all)

Park et al Blood 2016 127:3312-3320

CD19-CAR Trials: Responses

ALL	CR	50/53	12 mo RFS	45%	12 mo OS	78%
ALL	CR	14/20	5 mo LFS	79%	8 mo OS	52%
CLL, B-NHL	ORR	6/8 (1 CR)				
B-NHL	CR	4/7 DLBC 4/6 Indolent				
ALL	CR	37/45			6 mo OS	65% all 80% MRD
ALL (FHCRC)	CR	10/12 Cy 14/14 Cy+Flu				
B-NHL,CLL (FHCRC)	ORR, B-NHL ORR, CLL	6/12 8/12 5/6	(1 CR) Cy (5 CR) Cy Flu (3 CR)			

Thank You

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  (and other MSI tumors)

CAR T Cells

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- Lymphoma