Immunotherapy for the treatment of other solid tumors

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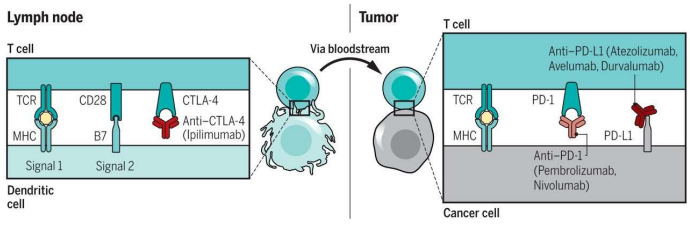
Disclosures

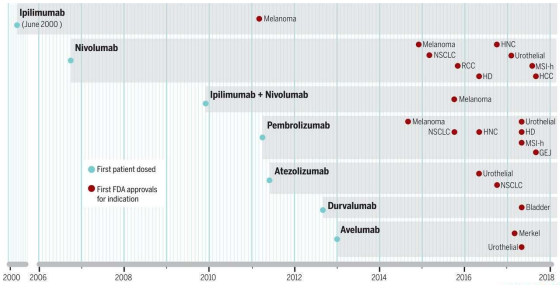
- Nektar Therapeutics – Advisory Board/Honorarium
- I will not be discussing non-FDA approved indications during my presentation.

Objectives

- Review novel indications of anti-PD1 therapy for gastric cancer and cervical cancer
  - Role of PD-L1 biomarker
- Understand how anti-PD1 therapy induces responses in tumors with microsatellite-instability and/or mismatch repair defects
  - Colorectal cancer
  - Non-colorectal cancers
  - Role of biomarkers (gene expression profile, PD-L1 expression and tumor mutational burden)
- Discover how anti-PDL1 therapy is the first checkpoint inhibitor to be approved for triple negative breast cancer
  - Role of PD-L1 biomarker
- Review the role of anti-VEGFR for Hepatocellular carcinoma

Checkpoint inhibitors have been developed to block CTLA-4 or PD-1 on T cells, or PD-L1 on the tumor





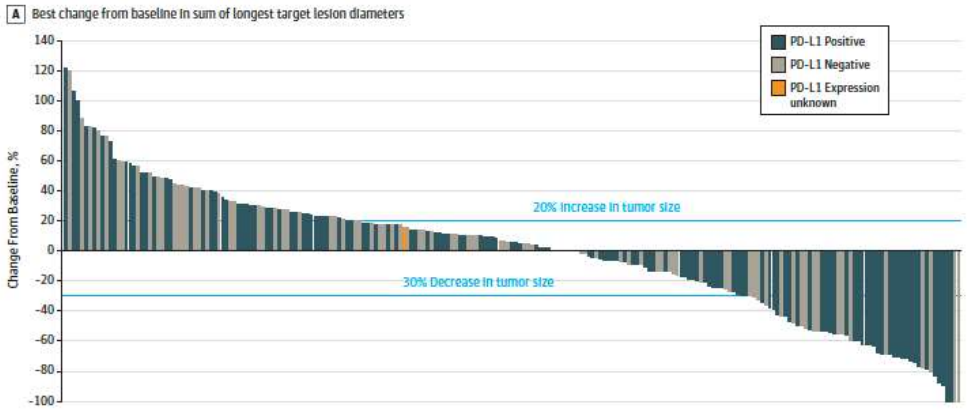
Ribas and Wolchok 2018 Science

Gastric cancer – anti-PD1

- KEYNOTE-059 was a nonrandomized, phase II study that evaluated pembrolizumab +/- chemotherapy (cisplatin + 5-FU or capecitabine) in advanced gastric/gastroesophageal cancer
- ORR 11.6%
  - 15.5% PD-L1+ for 16.3 months
  - 6.4% PD-L1- for 6.9 months
- Grade 3-5 AEs
  - 17.8% with 2 deaths

Fuchs et al. 2018 JAMA Oncol

KEYNOTE-059



(Pembrolizumab was approved along with PD-L1 IHC 22C3 companion diagnostic)

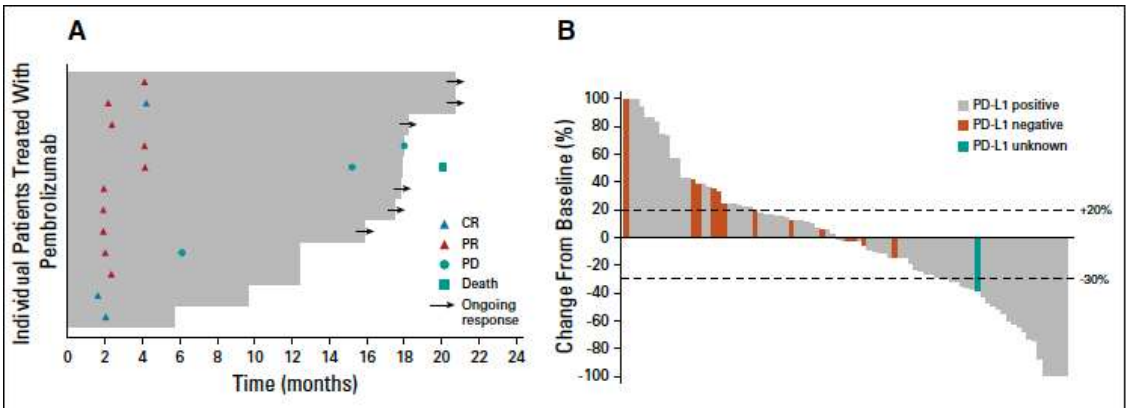
Fuchs et al. 2018 JAMA Oncol
Fashoyin-Aje et al. 2019 Oncologist

Cervical cancer – anti-PD1

- KEYNOTE-158 was a phase II basket trial that included safety and efficacy data of pembrolizumab on advanced cervical cancer.
- ORR: 14.6%
  - Median DOR was not reached
- Grade 3/4 AEs: 12.2%

Chung et al. 2019 J Clin Oncol

KEYNOTE-158



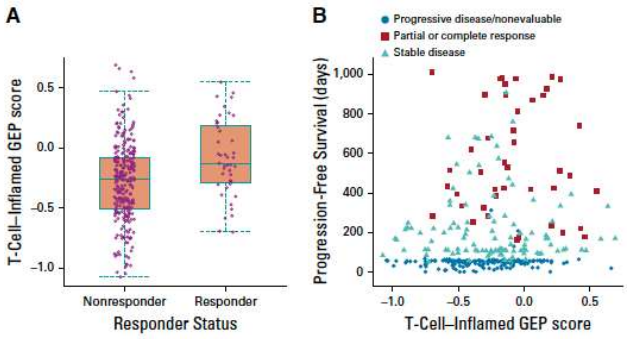
Chung et al. 2019 J Clin Oncol

Biomarkers that predict efficacy of anti-PD1 therapy in solid tumors

- KEYNOTE-028 was a nonrandomized, phase 1b trial of patients with PD-L1+ solid tumors treated with pembrolizumab
- Higher response rates and longer PFS were seen in tumors with
  - T cell enflamed gene expression profiles (GEP)
  - PD-L1 expression
  - Tumor mutational burden (TMB)

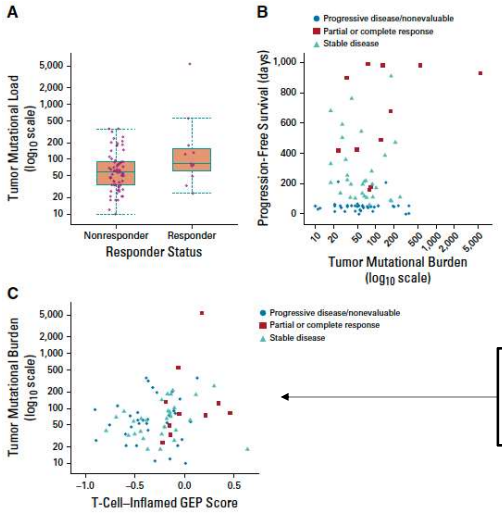
Ott et al. 2018 J Clin Oncol

T cell inflamed GEP scores were higher in patients who achieved ORR and had longer PFS



Ott et al. 2018 J Clin Oncol

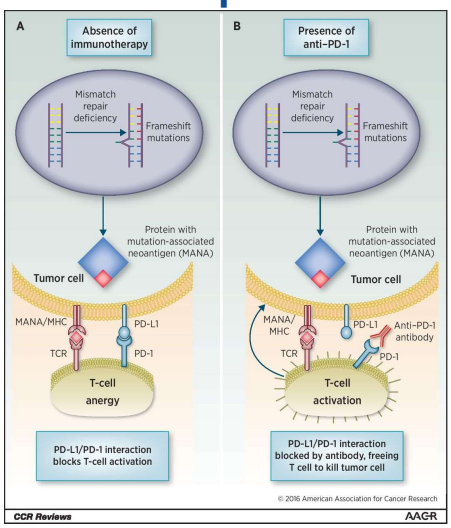
Higher TMB was significantly associated with patients who achieved ORR and had longer PFS



TMB and GEP had a low but significant association for both assays

Ott et al. 2018 J Clin Oncol

Proposed relationship between MSI status and immunologic response.

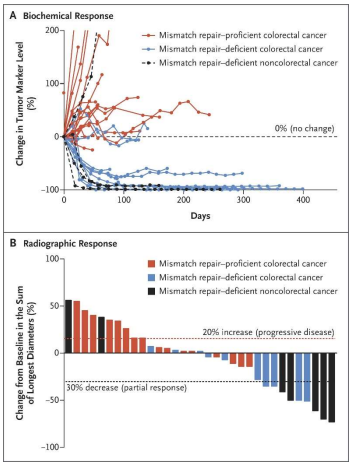


Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

Clinical Cancer Research

Anti-PD1 therapy induces reduction in biomarker levels and responses in MMR-d colorectal cancers and non-colorectal cancers

Mismatch repair defects



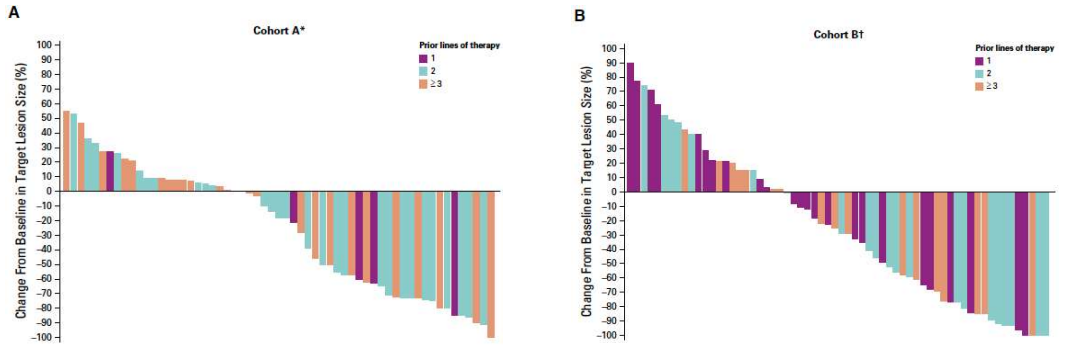
Le et al. 2015 New Engl J Med

MSI-H/MMR-D colorectal cancer and anti-PD1

- KEYNOTE-164 was a phase II open label study of pembrolizumab in refractory, MSI-H/MMR-D metastatic colorectal cancer.
  - 2 cohorts – (A) ≥ 2 or more prior lines of treatment; (B) ≥ 1 or more prior line of treatment
- ORR 33% for both cohorts
  - Median DOR not reached for both cohorts
  - PFS (A) 34% at 12 months and 31% at 24 months (B) 41% at 12 months and 37% at 24 months
  - OS (A) 72% at 12 months and 55% at 24 months (B) 76% at 12 months and 63% at 24 months
- Grade 3/4 AEs
  - (A) 16% and (B) 13%

Le et al. 2019 J Clin Oncol

KEYNOTE-164



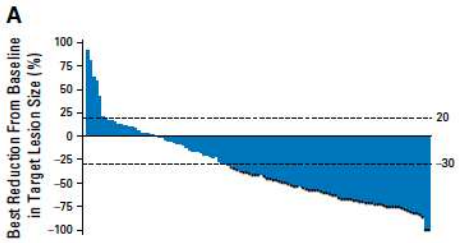
Le et al. 2019 J Clin Oncol

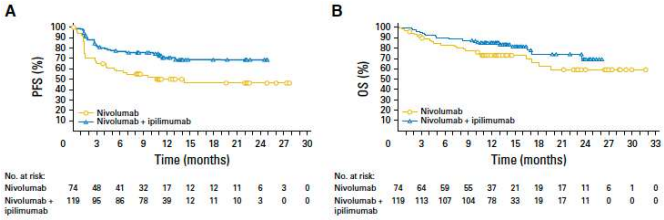
Colorectal cancer – anti-PD1 + anti-CTLA4

- CheckMate-042 is a multicenter, open-label, phase II trial that includes treatment with nivolumab and ipilimumab recurrent or metastatic colorectal cancer with dMMR or MSI-H.
- ORR was 55%
  - Median DOR was not reached
  - PFS 76% (9 months) and 71% (12 months)
  - OS 87% (9 months) and 85% (12 months)
- 13% discontinued treatment

Overman et al. 2019 J Clin Oncol

CheckMate-142





Overman et al. 2019 J Clin Oncol

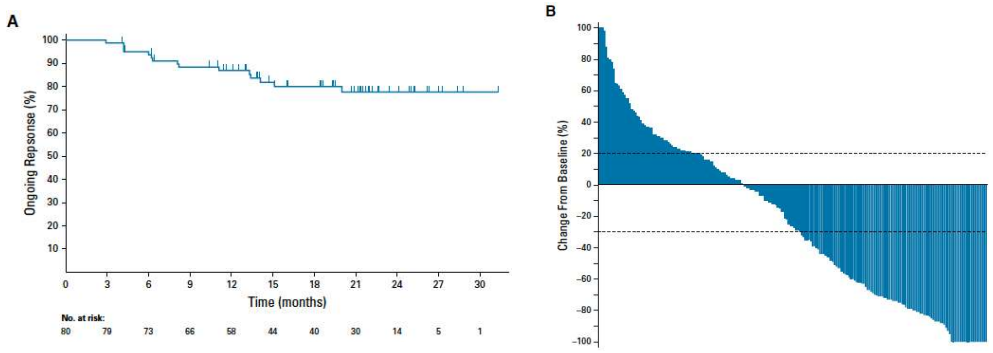
MSI-H/MMR-D Non-colorectal cancers and anti-PD1

- KEYNOTE-158 was a phase II of pembrolizumab in patients with previously treated, advanced noncolorectal cancer with MSI-H/MMR-D.
  - 27 different tumor types enrolled
- ORR 34.3%
- Grade 3/4 AEs 14.6% (1 death)

Cancer type of primary diagnosis	
Endometrial	49 (21.0)
Gastric	24 (10.3)
Cholangiocarcinoma	22 (9.4)
Pancreatic	22 (9.4)
Small intestine	19 (8.2)
Ovarian	15 (6.4)
Brain	13 (5.6)
Sarcoma	9 (3.9)
Neuroendocrine tumor	7 (3.0)
Cervical	6 (2.6)
Prostate	6 (2.6)
Adrenocortical	5 (2.1)
Breast	5 (2.1)
Thyroid	5 (2.1)
Urothelial	5 (2.1)
Mesothelioma	4 (1.7)
Small-cell lung cancer	4 (1.7)
Renal	3 (1.3)

Marabelle et al. 2019 J Clin Oncol

KEYNOTE-158



Marabelle et al. 2019 J Clin Oncol

KEYNOTE-158

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

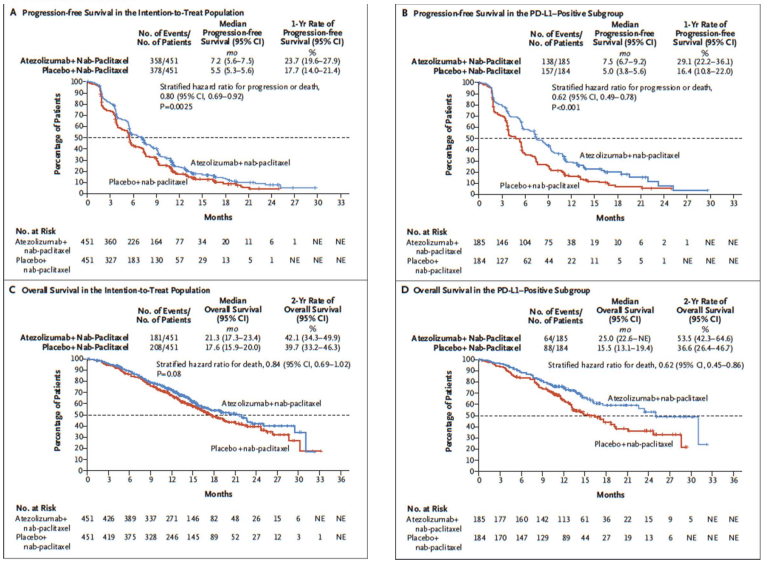
Marabelle et al. 2019 J Clin Oncol

Triple negative breast cancer – anti-PDL1

- IMpassion130 was a phase III randomized, placebo controlled, double blind trial comparing nab-paclitaxel and atezolizumab vs. nab-paclitaxel and placebo in advanced triple negative breast cancer.
- In an Intent-to-treat analysis,
  - Median PFS: 7.2 months vs. 5.5 months
  - Median OS: 21.3 months vs. 17.6 months
- AEs that led to treatment discontinuation
  - 15.9% (incl. 2 deaths) vs. 8.2% (incl. 1 death)

Schmid et al. 2019 New Engl J Med

Impassion 130



Atezolizumab is the first FDA approval for patients with locally advanced or metastatic TNBC, and the first checkpoint inhibitor approved for use in breast cancer.

Approved with the VENTANA PD-L1 (SP142) companion diagnostic assay

Schmid et al. 2019 New Engl J Med
Narayan et al. 2020 Clin Cancer Res

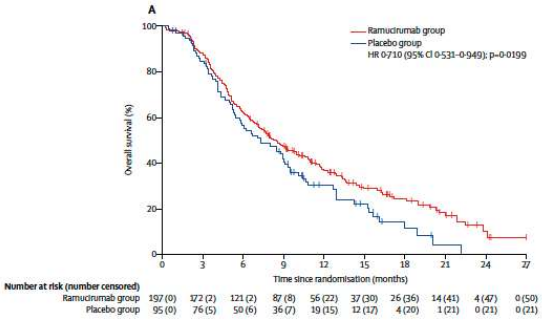
Hepatocellular carcinoma – anti-VEGFR2

- REACH-2 was a phase III, randomized, placebo controlled, double blind trial in sorafenib-treated advanced hepatocellular carcinoma patients comparing ramucirumab vs. placebo.
- Median OS: 8.5 months vs. 7.3 months
- Median PFS: 2.8 months vs. 1.6 months
- SAEs: 35% vs. 29%

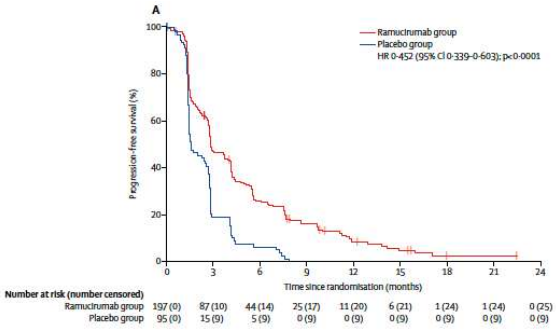
Zhu et al. 2019 Lancet Oncol

REACH-2

Overall Survival



Progression-free Survival



Zhu et al. 2019 Lancet Oncol

Conclusions

- An increasing number of solid tumors are showing responses to anti-PD1 or combination anti-PD-1 and CTLA-4 therapy
- Biomarkers like TMB +/- T cell inflamed GEP or PD-L1 expression predict efficacy of anti-PD1 across multiple solid tumor types
- Anti-PD1 therapy can induce responses in both colorectal and non-colorectal solid tumors with MSI-H and/or MMR-d
- Anti-PDL1 therapy is the first checkpoint inhibitor approved for triple negative breast cancer
- Anti-VEGFR therapy can provide an alternative immunotherapy target with patients with hepatocellular carcinoma