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Advances in immunotherapy for gastrointestinal (GI) malignacies

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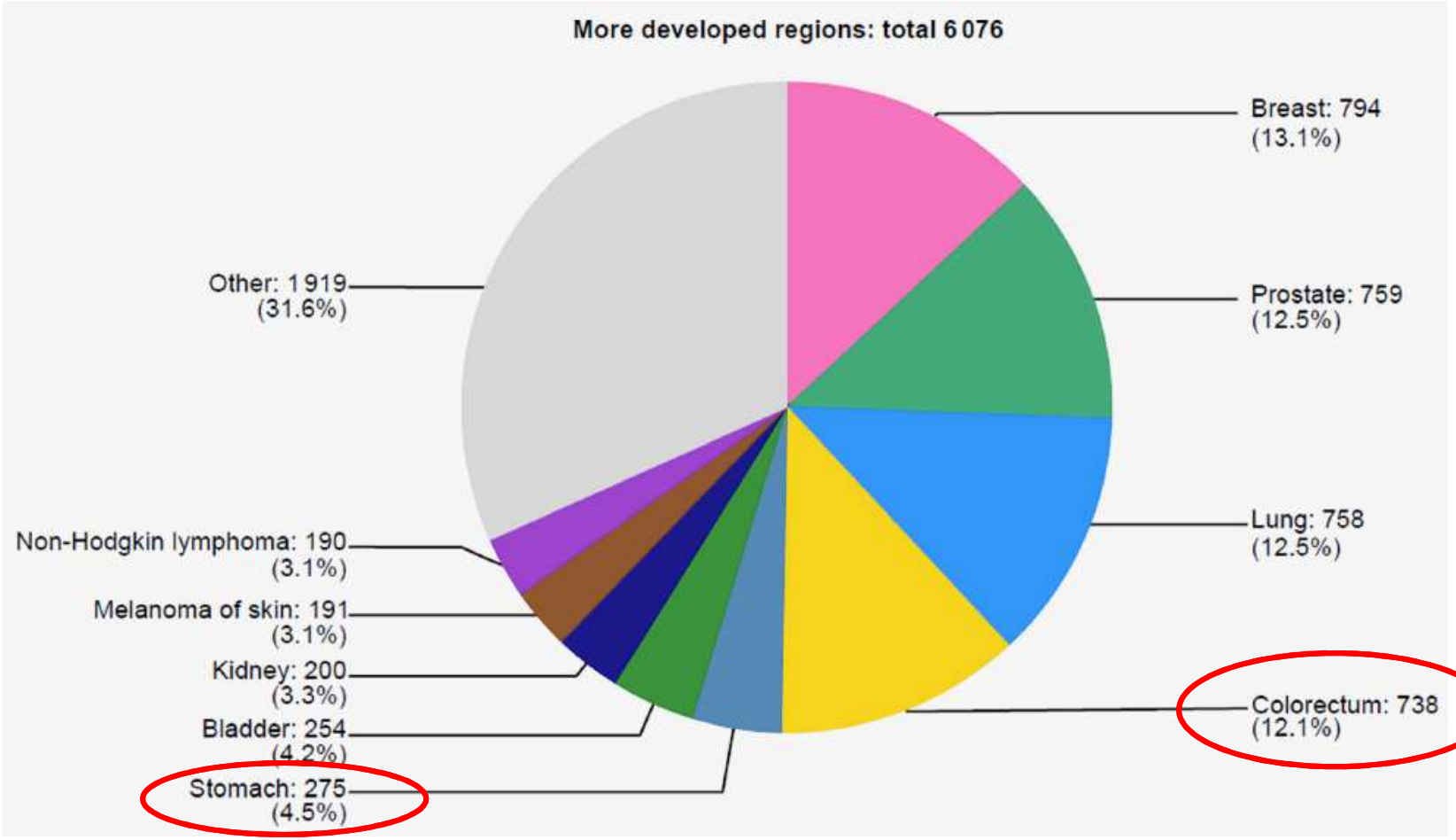
Disclosures

- Potential conflicts of interest: consulting for Taiho Oncology and EMD Serono
- I will discuss therapeutic uses that are off-label (clinical trials)

Learning objectives

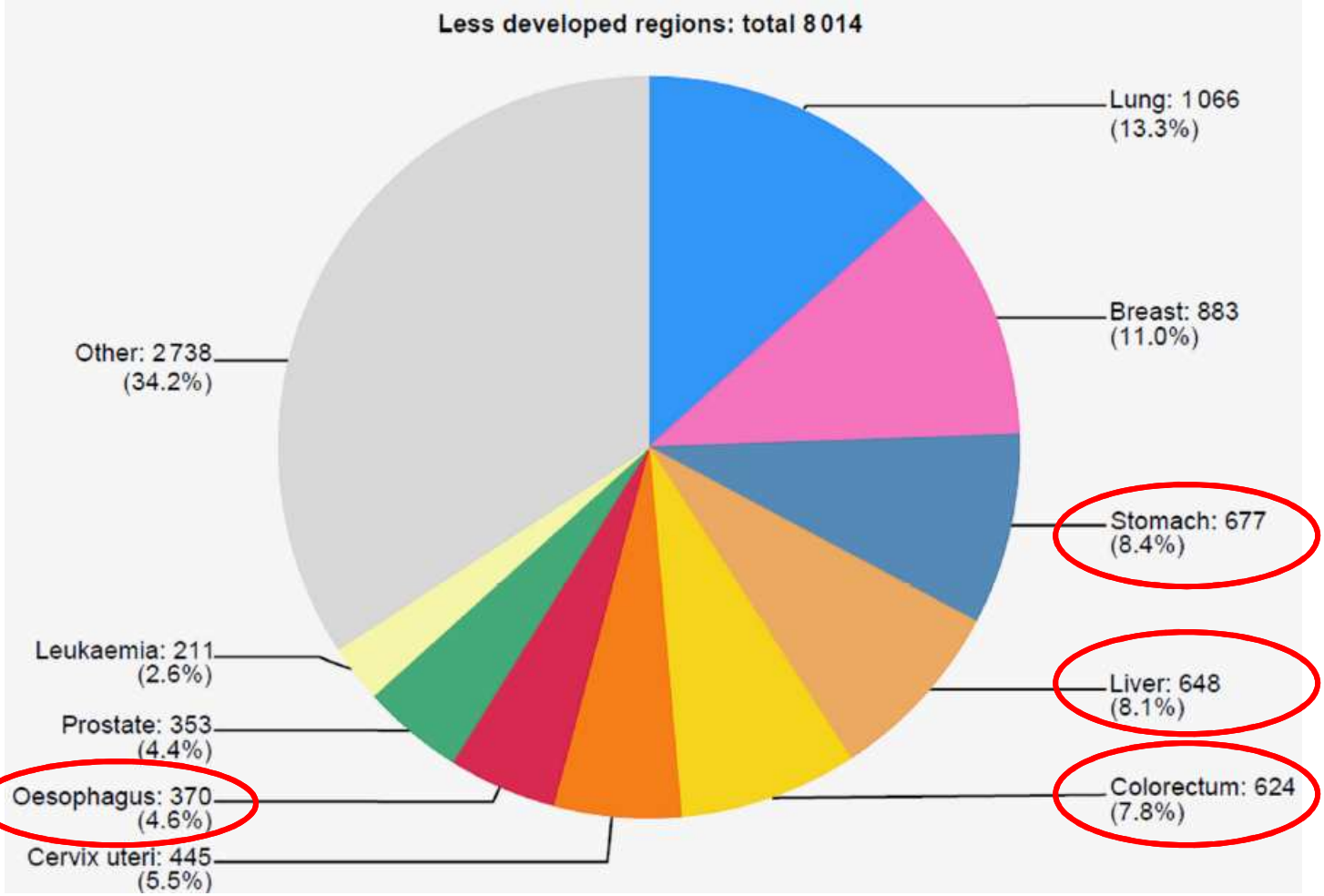
- To review preliminary data regarding immunotherapy for colorectal, gastric, hepatocellular and pancreatic cancer.
- To be aware of ongoing/upcoming immunotherapy trials for colorectal, gastric, hepatocellular and pancreatic cancer.

Global cancer incidence



Ferlay J, *et al*. *Int J Cancer* 136: E359-386, 2015.

Global cancer incidence



Ferlay J, *et al*. *Int J Cancer* 136: E359-386, 2015.

Global cancer mortality

- 8.2 million people die annually
- 2.7 million people (33%) die of GI malignancies
- By site
  - Lung (1.6 million)
  - Liver (745,000)
  - Stomach (723,000)
  - Colorectal (694,000)

Ferlay J, *et al*. *Int J Cancer* 136: E359-386, 2015.

Immunotherapy for colorectal cancer (CRC)

- Monotherapy with antibodies that target immune checkpoints has been unsuccessful in unselected patients
- Current strategies
  - Combination therapy including antibodies that target immune checkpoints
  - Monotherapy with antibodies that target immune checkpoints in selected populations with mismatch repair deficiency (~5% of patients with metastatic disease)

Targeting CD137 enhances the efficacy of cetuximab

CD137 (4BB1) is a costimulatory receptor of the TNF superfamily that positively regulates T and NK cell activation

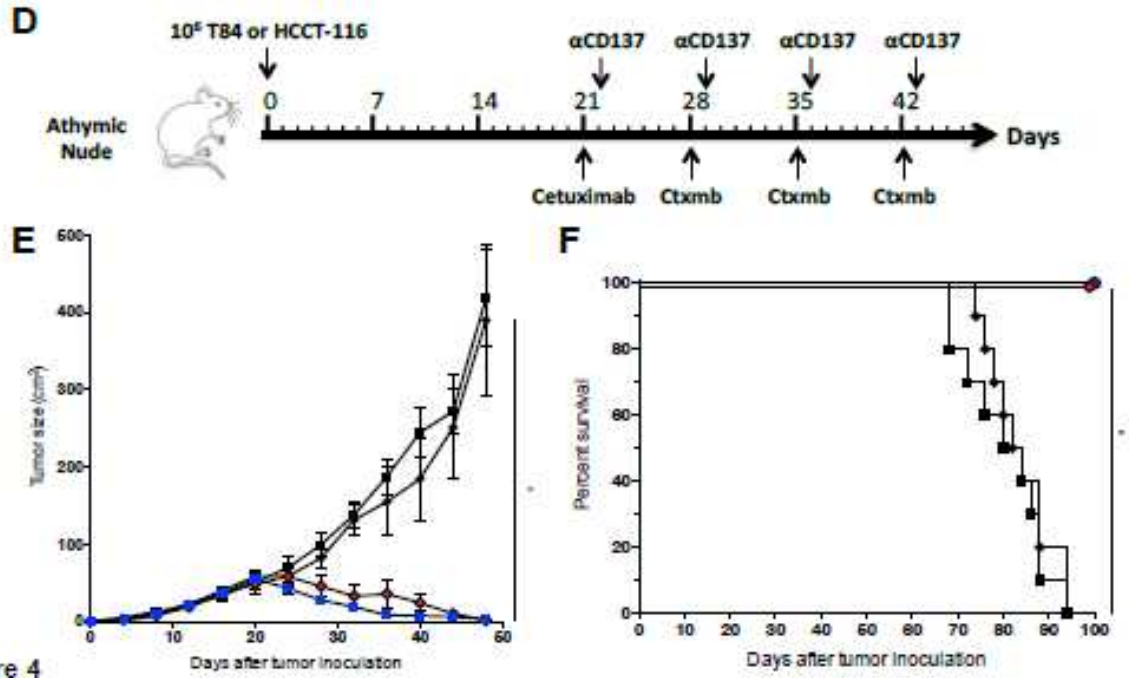


Figure 4

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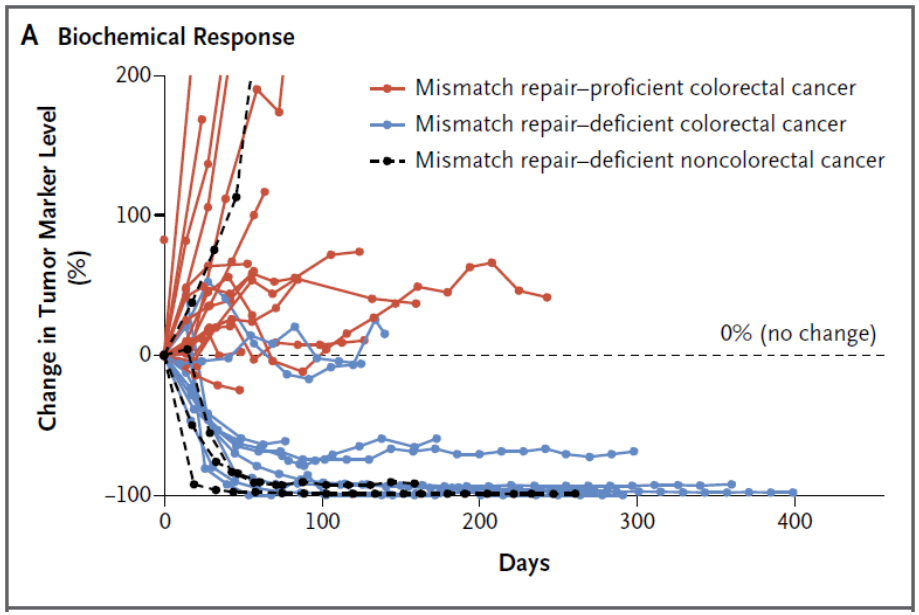
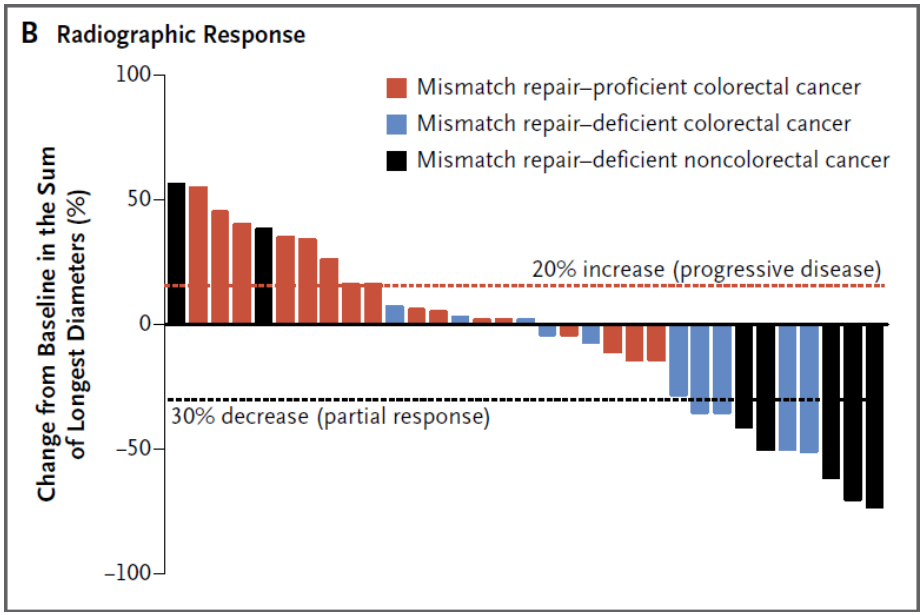
Kohrt HE, *et al*. *J Clin Invest.* 124: 2668-82, 2014.

Urelumab (anti-CD137) plus cetuximab in CRC

- A Phase 1b, Open-label, Multicenter Study of Urelumab (BMS-663513) in Combination With Cetuximab in Subjects With Advanced/Metastatic Colorectal Cancer or Advanced/Metastatic Squamous Cell Carcinoma of the Head and Neck
- NCT02110082 (clinicaltrials.gov)
- Estimated start/end dates: 4/2014 – 1/2017

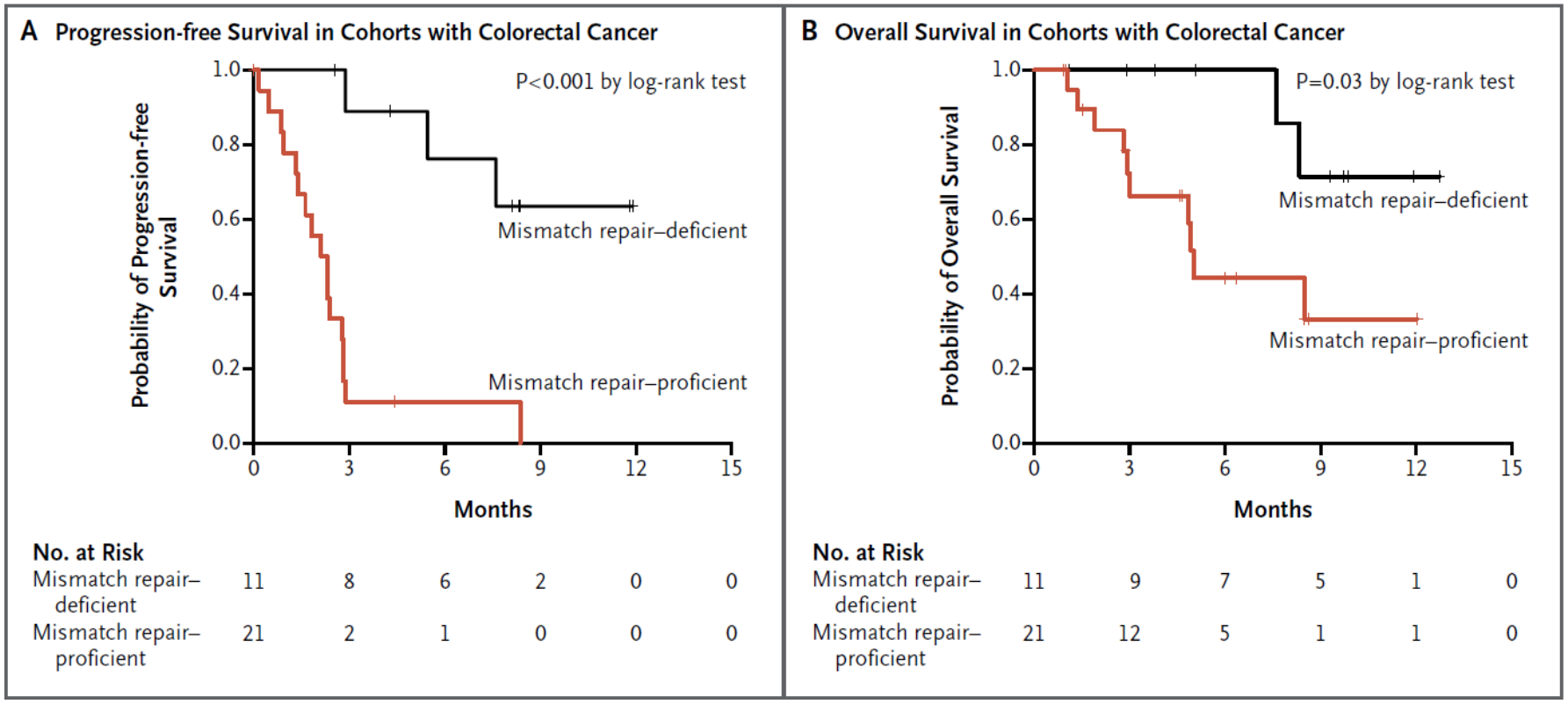
Pembrolizumab in MMR-deficient CRC





Le D, *et al*. *N Engl J Med.* 372: 2509-20, 2015.

Pembrolizumab in MMR-deficient CRC

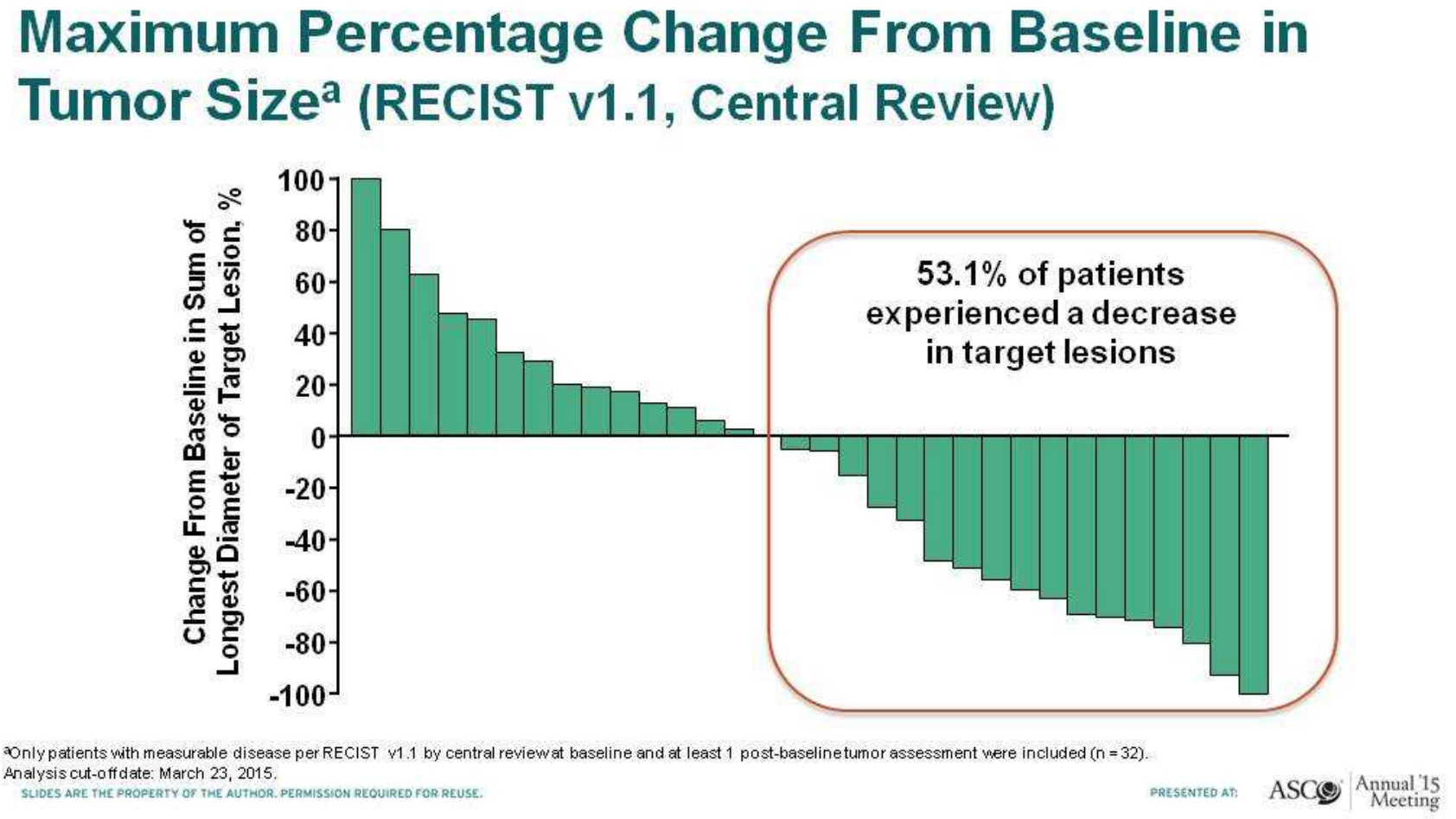


Le D, *et al*. *N Engl J Med.* 372: 2509-20, 2015.

Pembrolizumab in MMR-deficient CRC

- A Phase II Study of **Pembrolizumab** (**MK-3475**) as Monotherapy in Subjects With Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High **Colorectal** Carcinoma (KEYNOTE-164)
- NCT02460198 (clinicaltrials.gov)
- Estimated start/end dates: 8/2015-10/2017

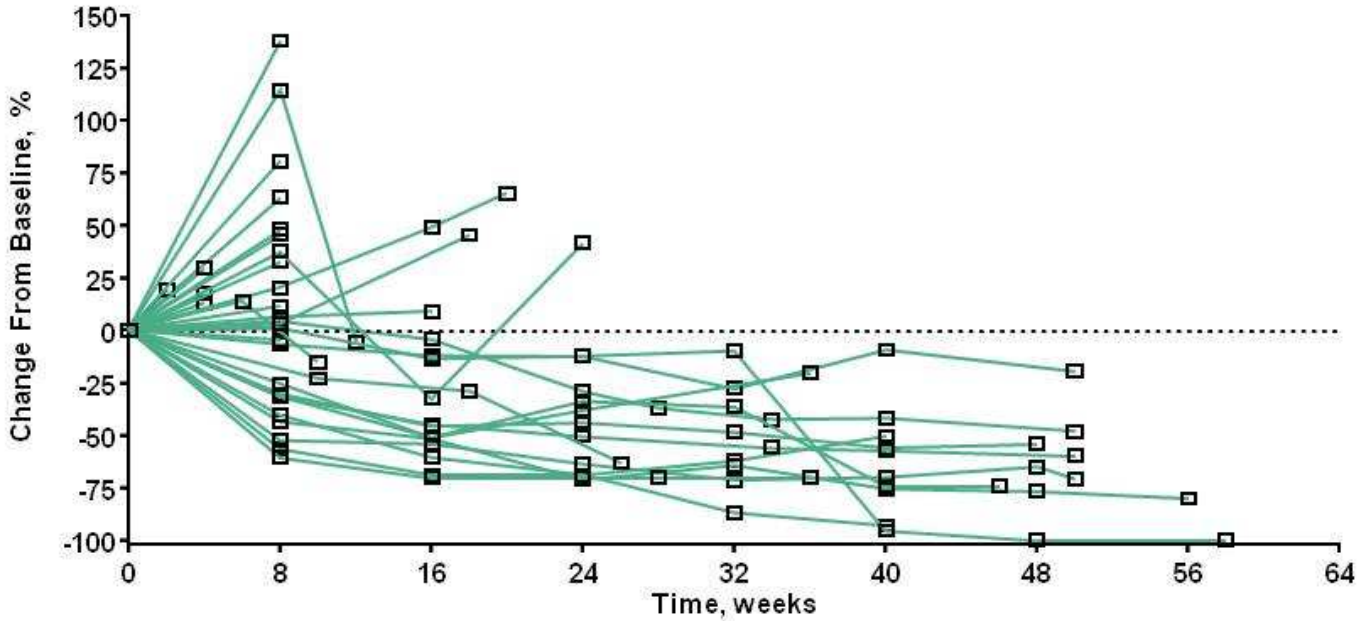
Pembrolizumab in gastric cancer



Bang Y-J, *et al*. ASCO 2015 Annual Meeting (abstract # 4001)

Pembrolizumab in gastric cancer

Longitudinal Change From Baseline in Tumor Size (RECIST v1.1, Central Review)



[a]Only patients with measurable disease per RECIST v1.1 by central review at baseline and at least 1 post-baseline tumor assessment were included (n = 32).
Analysis cut-off date: March 23, 2015.

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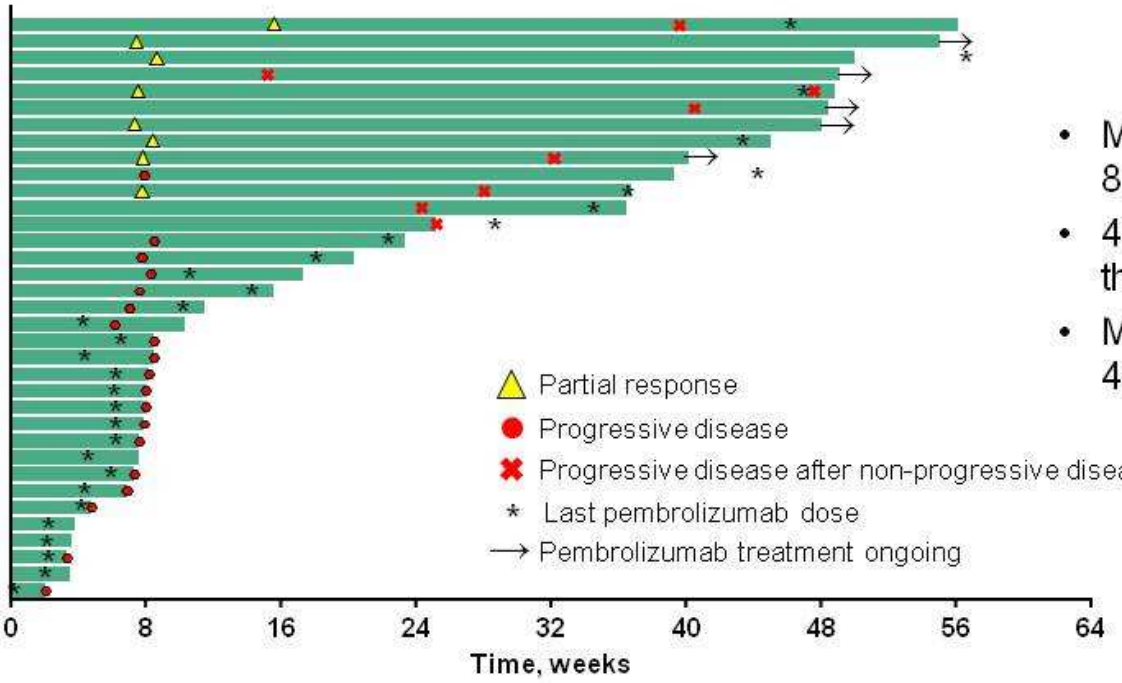
Pembrolizumab in gastric cancer

Treatment Exposure and Response Duration[a] (RECIST v1.1, Central Review)



- Median time to response: 8 weeks (range, 7-16)
- 4 of 8 responses ongoing at the time of data cutoff
- Median response duration: 40 weeks (range, 20+ to 48+)

[a]Patients with measurable disease per RECIST v1.1 by central review at baseline who had at least 1 postbaseline assessment (n = 35). The length of each bar is equivalent to the time to the last imaging assessment. Analysis cut-off date: March 23, 2015.

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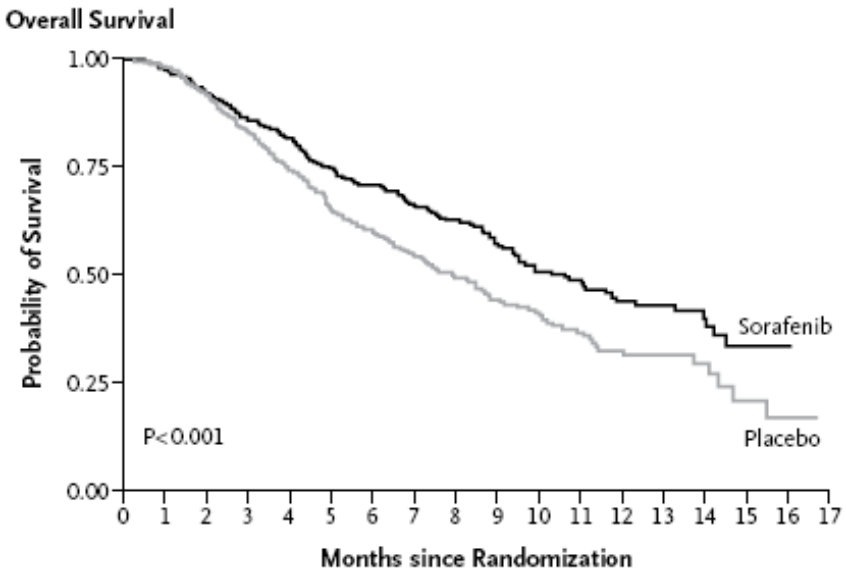
Pembrolizumab in gastric cancer

- A Randomized, Active-Controlled, Partially Blinded, Biomarker Selected, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination With Cisplatin+5-Fluorouracil Versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects With Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma
- NCT02494583(clinicaltrials.gov)
- Estimated start/end dates: 8/2015 – 10/2017

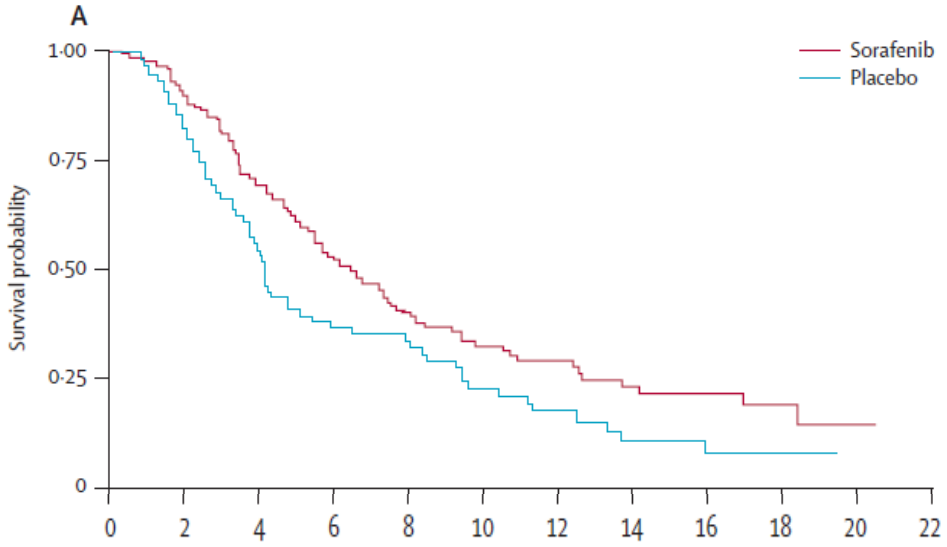
HCC: unmet need with sorafenib as the only approved therapy

Europe: Median OS 10.7 vs. 7.9 mos
(HR = 0.69, p < 0.001)



Llovet JM, *et al*. *N Engl J Med* 2008;359:378-90.

Asia-Pacific: Median OS 6.5 vs. 4.2 mos
(HR = 0.68, p = 0.014)



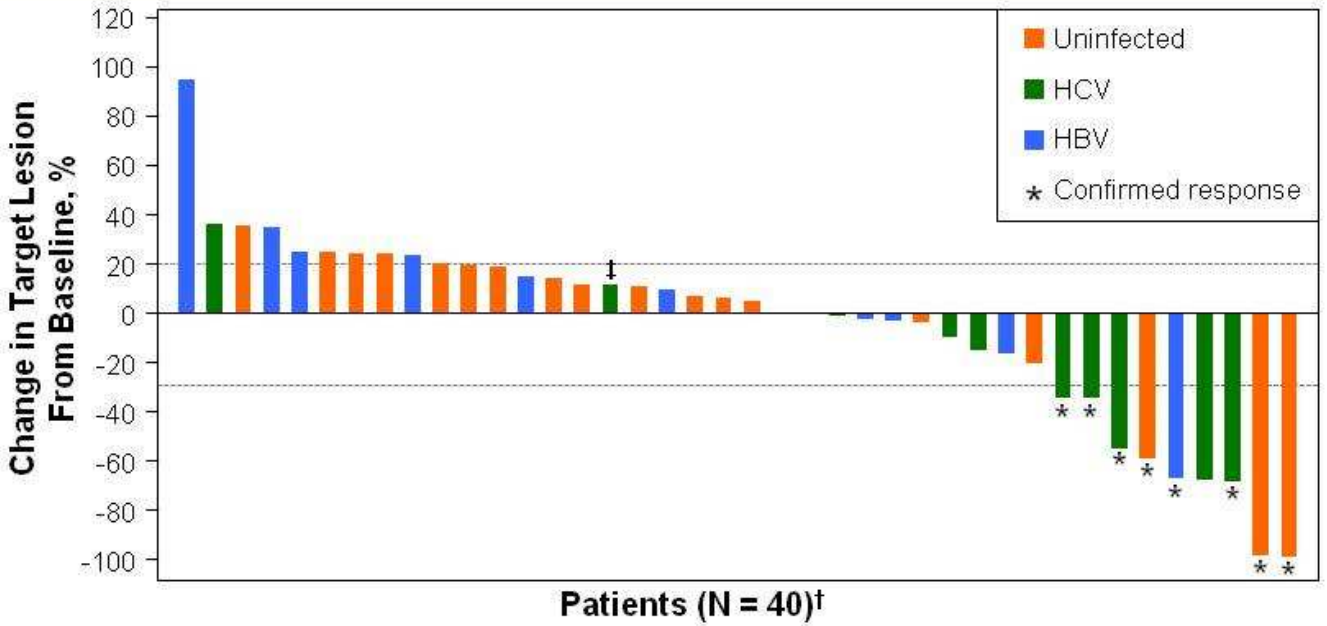
Cheng AL, *et al*. *Lancet Oncol* 2009;10:25-34.

Systemic therapies compared to sorafenib in phase III trials

Trial	Median survival (p-value)	Hazard ratio (95% CI)	Reference
brivanib vs. sorafenib	9.5 vs. 9.9 mos (NS)	1.06 (0.93 - 1.22)	Johnson PJ, *et al*. *J Clin Oncol* 2013;31:3517-24.
sunitinib vs. sorafenib	7.9 vs. 10.2 mos (p = 0.0014)	1.30 (1.13 – 1.50)	Cheng AL, *et al*. *J Clin Oncol* 2013;31:4067-75.
linifanib vs. sorafenib	9.1 vs. 9.8 mos (NS)	1.05 (0.90 - 1.22)	Cainap C, *et al*. *J Clin Oncol* 2015;33:172-9.
sorafenib + erlotinib vs. sorafenib	9.5 vs. 8.5 mos (NS)	0.93 (0.78 - 1.11)	Zhu AX, *et al*. *J Clin Oncol* 2015;33:559-66.

Nivolumab in HCC

Maximal Change in Target Lesions From Baseline



†2 uninfected patients not shown: 1 had disease progression before the first assessment; 1 had a maximal change of +23%
‡Patient with resolved HCV infection

15

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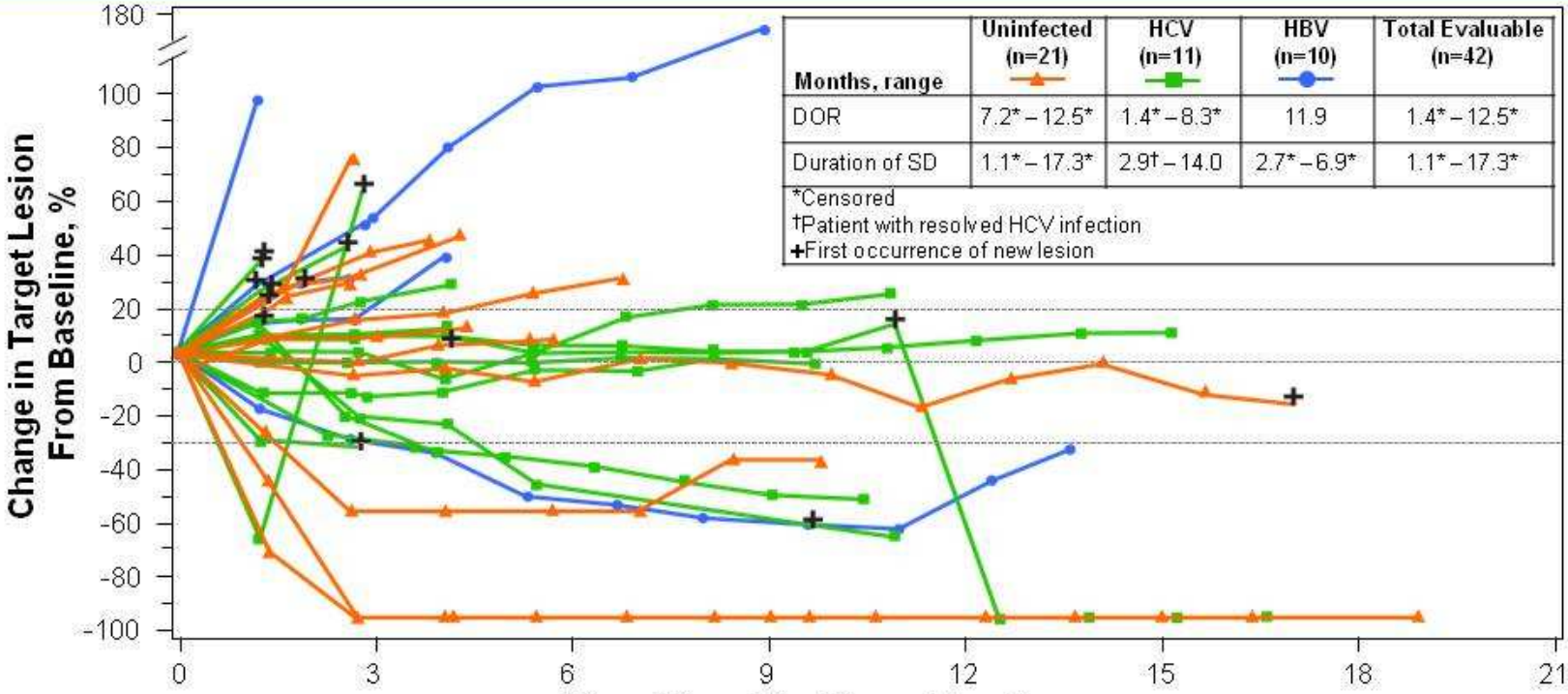
Nivolumab in HCC

Response Kinetics



16

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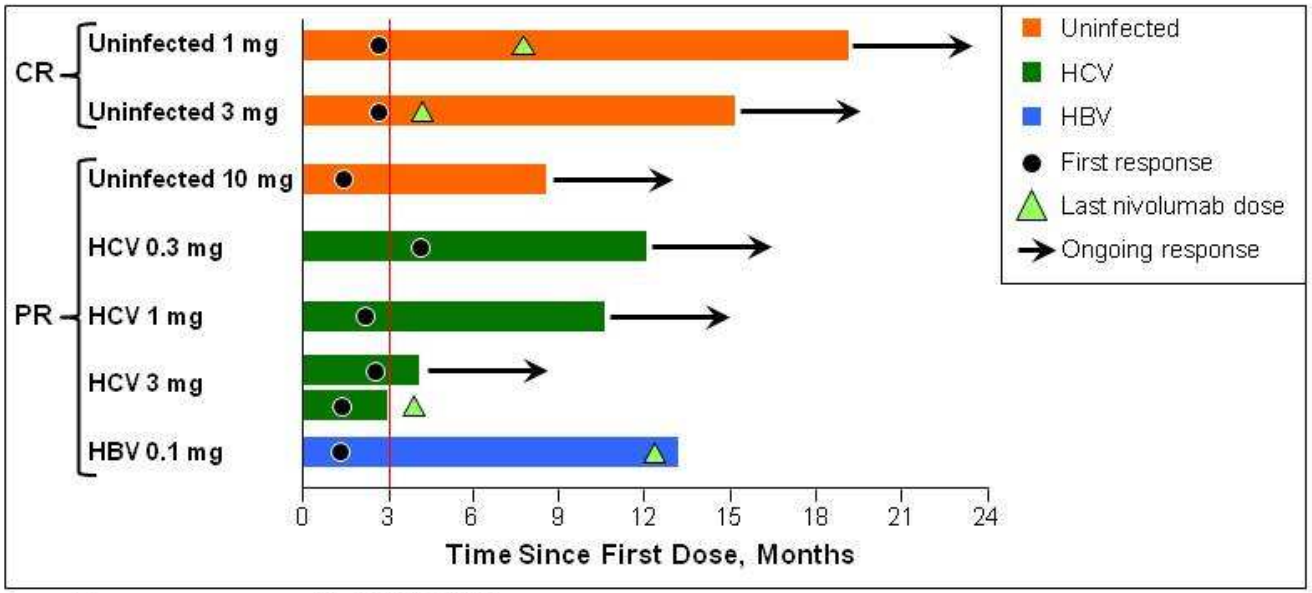
Nivolumab in HCC

Time to and Durability of Response



- 7/8 patients responded within 3 months of beginning treatment
- Responses ongoing in 6/8 patients, including 2 patients who discontinued treatment due to CR

Responses assessed by RECIST 1.1

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El-Khoueiry, *et al*. ASCO 2015 Annual Meeting (abstract # LBA101)

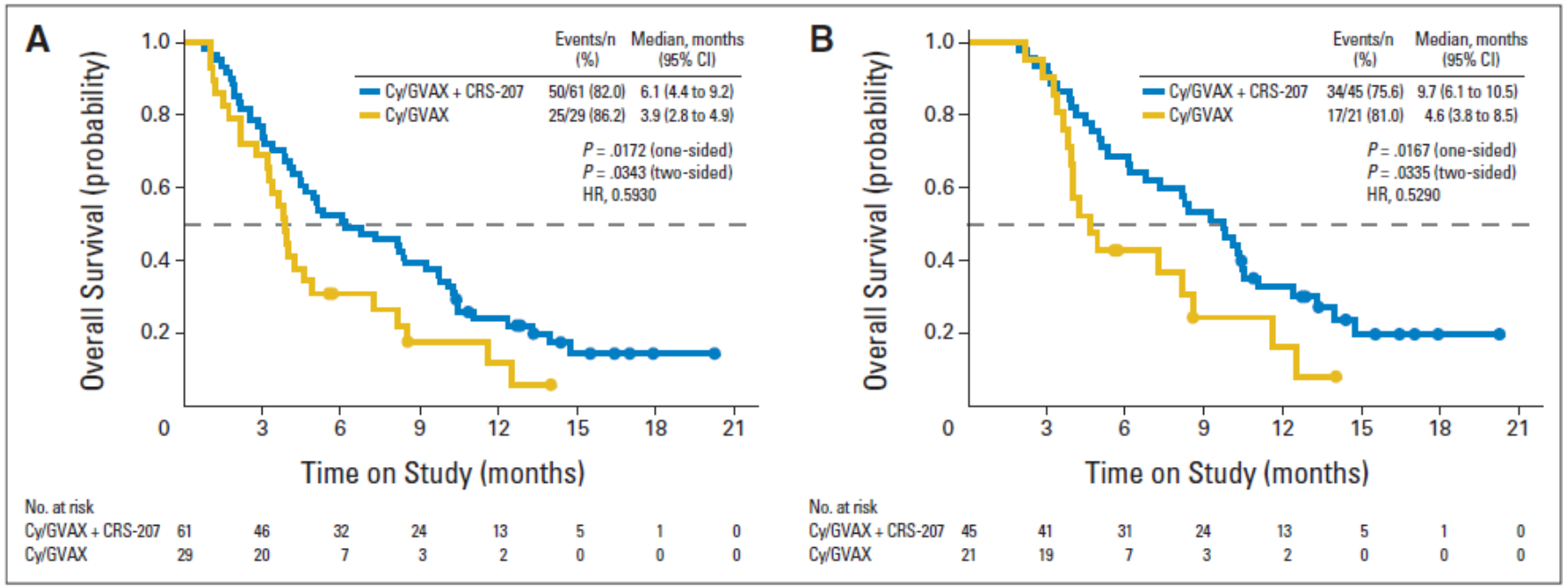
Vaccines in pancreatic cancer

- CEA-vac: carcinoembryonic antigen (CEA) peptide emulsified in Montanide and GM-CSF, given every 2 weeks (Geynisman DM, *et al*. *J Immunother Cancer*. 2013)
  - 7 of 19 pts with survival > 32 months (3 with unresectable disease)
- GVAX: two irradiated GM-CSF secreting allogeneic pancreatic cancer cell lines administered 24 hours after treatment with low-dose cyclophosphamide to inhibit regulatory T cells
- CRS-207: a recombinant live-attenuated *Listeria monocytogenes* engineered to secrete mesothelin (a tumor-associated antigen) into the cytosol of infected APCs

Vaccines in pancreatic cancer

Intention-to-treat analysis

Per-protocol analysis



Le D, *et al*. *J Clin Oncol.* 33: 1325-33, 2015.

Vaccines in pancreatic cancer

- A Phase 2B, Randomized, Controlled, Multicenter, Open-Label Study of the Efficacy and Immune Response of GVAX Pancreas Vaccine (With Cyclophosphamide) and CRS 207 Compared to Chemotherapy or to CRS-207 Alone in Adults With Previously-Treated Metastatic Pancreatic Adenocarcinoma
- NCT02004262(clinicaltrials.gov)
- Estimated start/end dates: 1/2014 – 12/2016

Immunotherapy in pancreatic cancer: next steps

- Combination studies with checkpoint inhibitors
  - Ibrutinib (BTK inhibitor) + MEDI4736 (anti-PD-L1) (NCT02403271)
  - GVAX/Cy + CRS-207 +/- nivolumab (NCT02243371)

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David Geary, RN

Thank you!

Questions/comments/referrals:

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Antibodies that target immune checkpoints have shown preliminary evidence of efficacy in each of the following GI malignancies except which one?

A. Gastric cancer

B. MMR deficient colorectal cancer

C. MMR proficient colorectal cancer

D. Hepatocellular carcinoma

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To date, the immunotherapy strategy that has shown the most promise in pancreatic cancer is which of the following?

A. Anti-PD-1 antibody therapy

B. Anti-CTLA4 antibody therapy

C. Chimeric antigen receptor (CAR) T-cell therapy

D. Vaccines composed of tumor antigens

E. Tumor-infiltrating lymphocytes (TILs)

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