Genomic profiling and new immunotherapies: an oncologist's perspective

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Introduction

- SOC molecular testing in GI cancers
- Promising targeted therapies in GI cancers not yet FDA approved
- Immunotherapies in GI cancer
  - FDA-approved indications
  - Not yet approved (but signals of activity)
  - Clinical trials
- Summary

Introduction

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SOC Molecular testing and implications

Colon cancer: EGFR, RAS and BRAF

- Anti-EGFR Ab therapy
  - Cetuximab FDA-approval 2004
  - Approved as single-agent or combination with irinotecan
  - **EGFR-expressing**, refractory to irinotecan
  - Randomized trial cetuximab alone vs cetuximab + irinotecan
    - RR 11% vs 23%
    - DCR 32% vs 55%
    - HR PFS 0.54 (TTP 1.5 mos vs 4.1 mos)

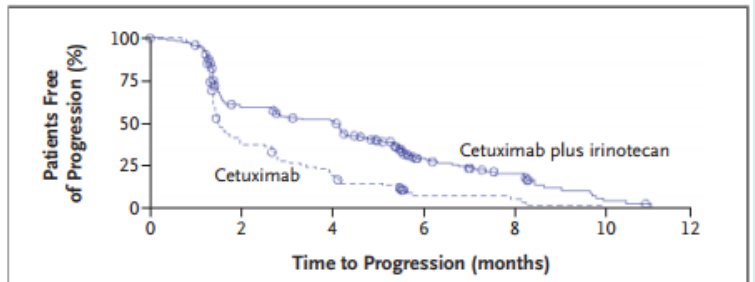


Figure 2. Time to Disease Progression in the Two Study Groups.
The hazard ratio for disease progression in the combination-therapy group as compared with the monotherapy group was 0.54 (95 percent confidence interval, 0.42 to 0.71) (P<0.001 by the log-rank test). The points on the curves represent the dates on which a patient's data were censored.

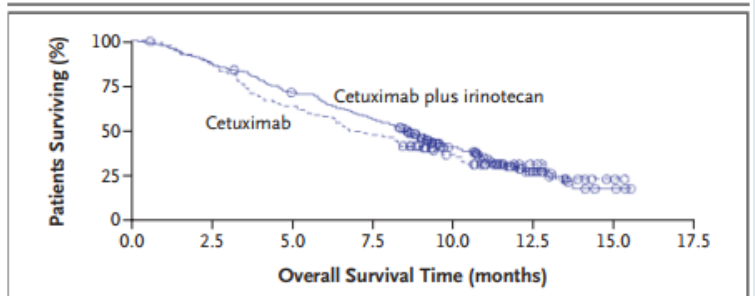
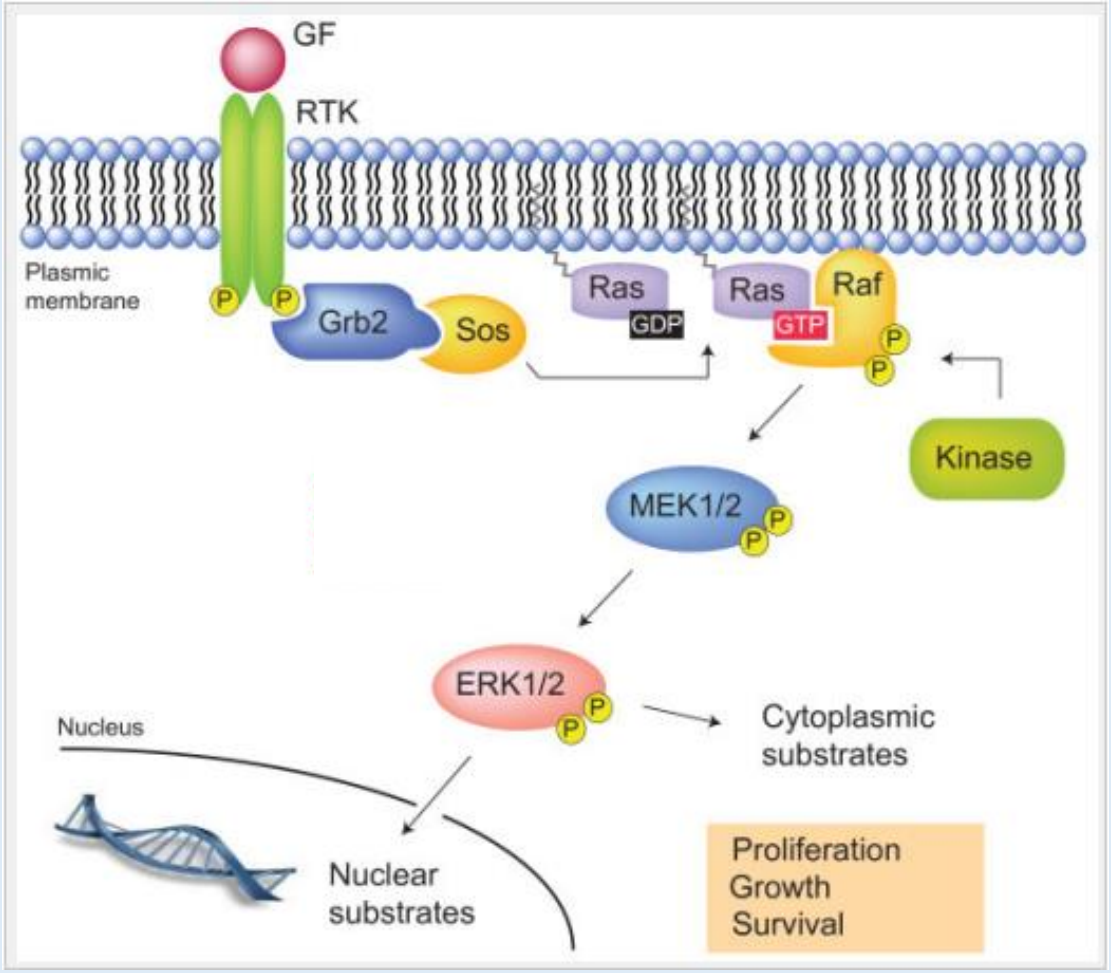


Figure 3. Overall Survival in the Two Study Groups.
The hazard ratio for death in the combination-therapy group as compared with the monotherapy group was 0.91 (95 percent confidence interval, 0.68 to 1.21) (P=0.48 by the log-rank test). The points on the curves represent the dates on which a patient's data were censored.

Cunningham NEJM 2004

SOC Molecular testing and implications

- Colon cancer: EGFR, RAS and BRAF
  - ~ 2008: multiple trials retrospectively look at role of kras mutations (exon 2)
    - Kras mutations identified in approximately 40% of patients
    - Kras mut – RR 1% vs kras wt RR up to 40%
    - No difference in outcomes in kras mut treated w/ cetuximab vs supportive care
    - 2012: FDA indication includes frontline with FOLFIRI, **kras wt**



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  - 2014: "*extended RAS testing*" – KRAS exons 2, 3, 4 & NRAS all predict lack of benefit to anti-EGFR antibody therapy (additional 10-15% of patients identified)
  - 2015: BRAF V600 mutations (5-10%) also suggest lack of response

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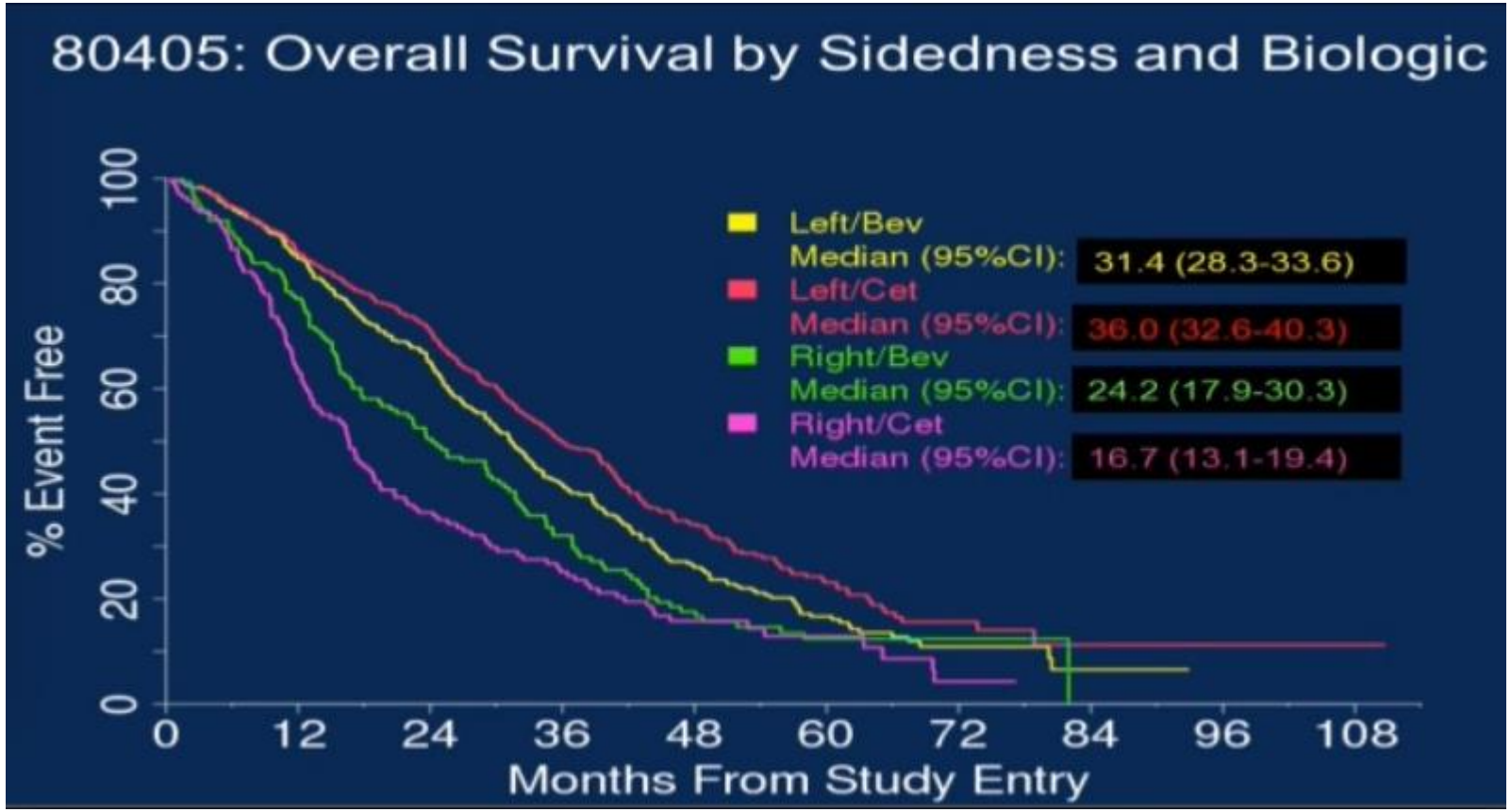
  - 2016: "sidedness" – right-sided colon cancer with apparently no benefit with anti-EGFR antibody therapy (maybe fare worse?)

SOC Molecular testing and implications



"Sidedness"

- Marked survival difference
- Detrimental effect with cetuximab?
- Midgut vs hindgut
- Molecular determinants?

SOC Molecular testing and implications

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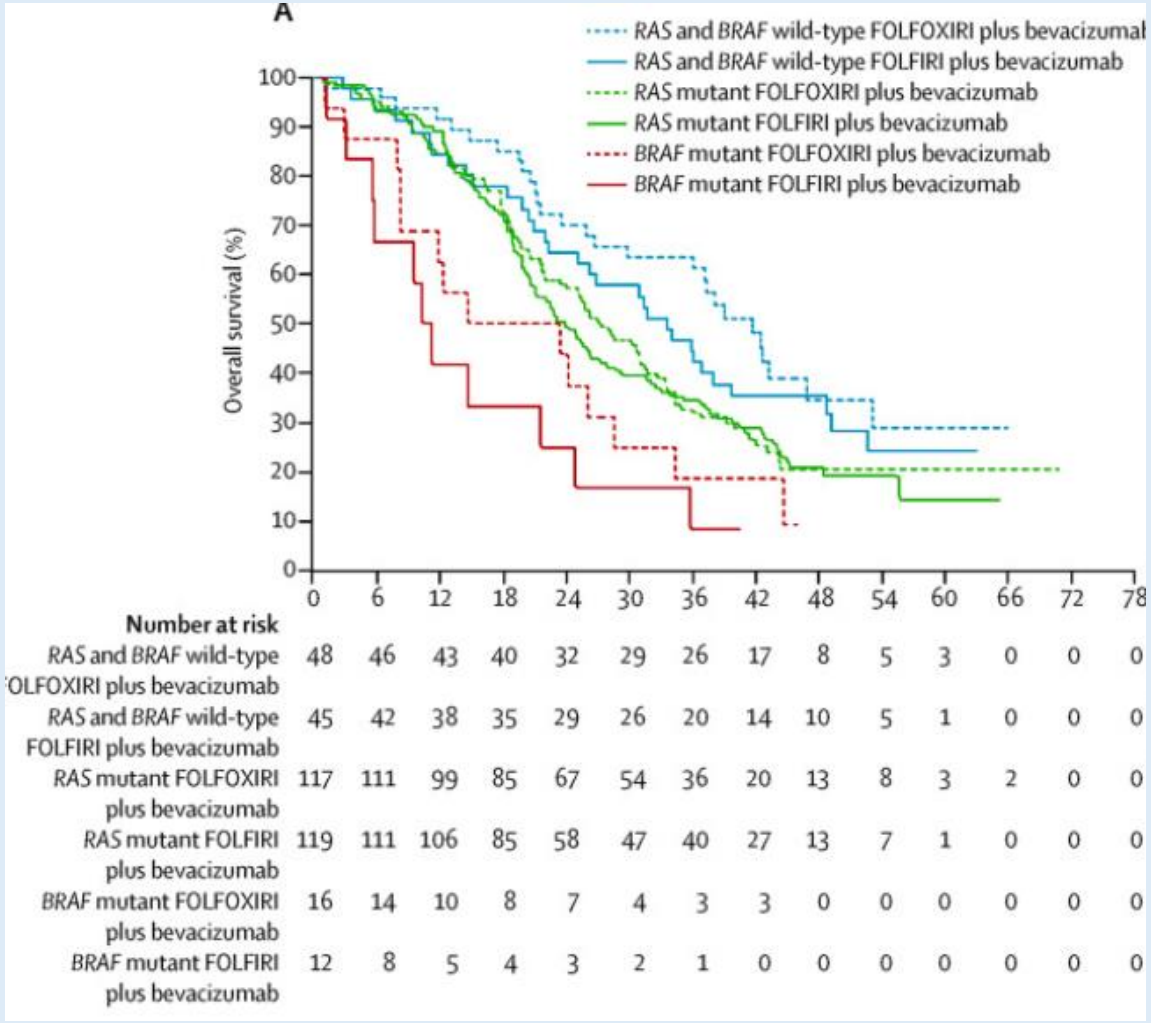
  - 2016: "sidedness" – right-sided colon cancer with apparently no benefit with anti-EGFR antibody therapy (maybe fare worse?)
  - *Current status*: **extended RAS testing and BRAF mutations** - ~60% will have biomarker suggesting lack of benefit with anti-EGFR antibody therapy (this is *not* reflected in PI/FDA-approvals). Additionally with questionable benefit, potential harm in patients with right-sided primary tumors

SOC Molecular testing and implications

- Colon cancer: **BRAF**
  - Poor prognosis (OS ~14 - 18 mos vs > 30 mos if BRAF wt)
  - More common R (15%) vs L (5%)
  - ? better outcomes with FOLFOXIRI
  - No apparent benefit with anti-EGFR antibody therapy
  - Really no response to available BRAF inhibitors

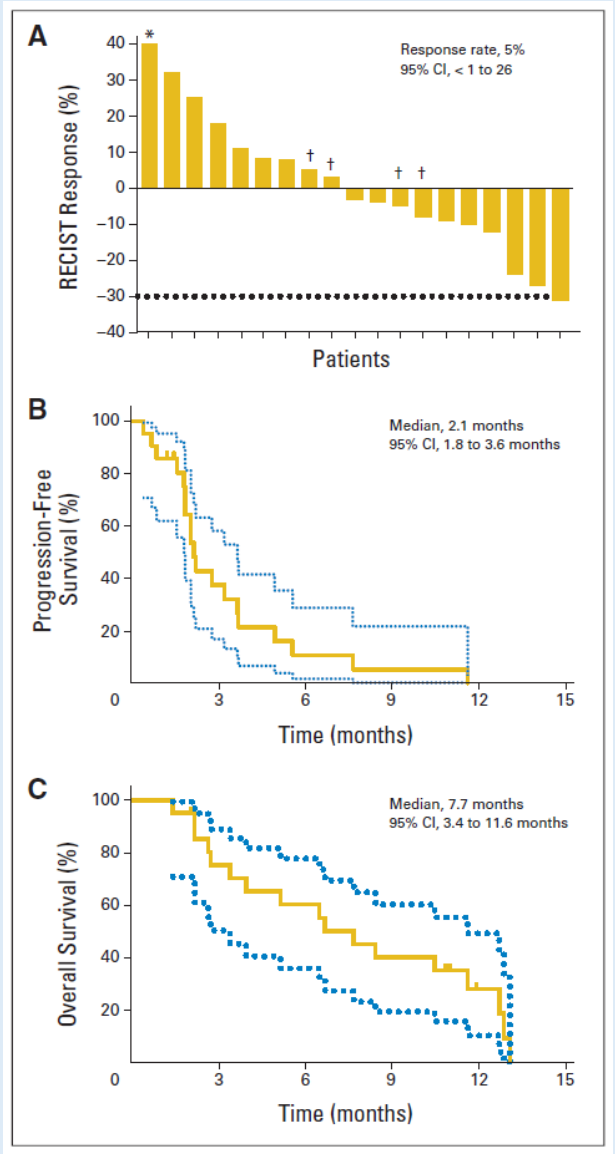


Cremolini Lancet 2015

SOC Molecular testing and implications

- Colon cancer: **BRAF**
  - JCO 2015 – Vemurafenib in BRAF-mutated colorectal cancer
  - 21 patients
  - PFS 2.1 mos, RR 5% (one patient)

  - WHY? – paradoxical MAPK activation
    - RAS activation → CRAF activation, heterodimerization of BRAF-CRAF
    - Re-accumulation of P-ERK → CRAF activation
    - Increase in RTK phosphorylation (EGFR, HER2, MET, etc)



Kopetz
JCO 2015

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  - ? better outcomes with FOLFOXIRI
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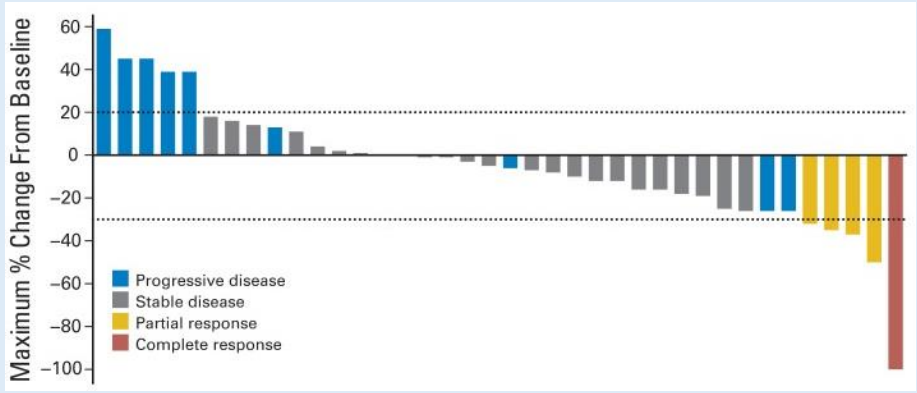
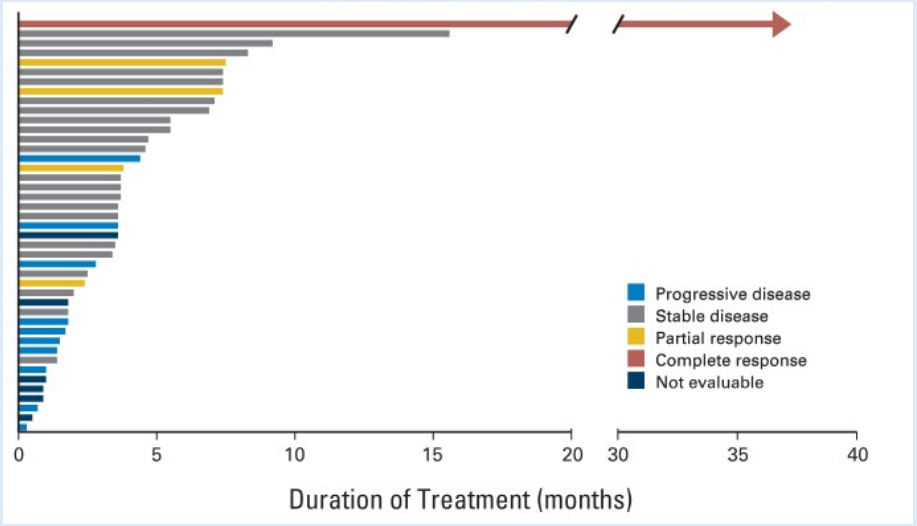
  - Really no response to available BRAF inhibitors
  - 2018 NCCN guidelines to include some targeted treatment
    - Dual targeted therapy braf + mek inhibition
    - Triple therapy braf + mek + EGFR inhibition
  - Association with MSI-H – candidates for immunotherapy





SOC Molecular testing and implications

- Colon cancer: summary
  - SOC to check extended RAS, BRAF
  - SOC to check MSI status
  - Everything else probably not SOC (but rare actionable findings – HER2 amplification, POLE mutations, ATM mutations, etc, unclear significance of PTEN loss, PIK3CA mutations)
  - BRAF mutations are a big problem

SOC Molecular testing and implications

- Esophagogastric cancer: Her2
  - Approximately 20% of gastric cancer overexpress Her2
  - Rare overexpression in diffuse-type gastric cancer
  - Pathology issues:
    - More heterogeneity than with breast cancer – higher false negative rate
    - Tends to spare digestive luminal membrane
    - CAP/ASCP/ASCO panel guidelines

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  - Approximately 20% of gastric cancer overexpress Her2
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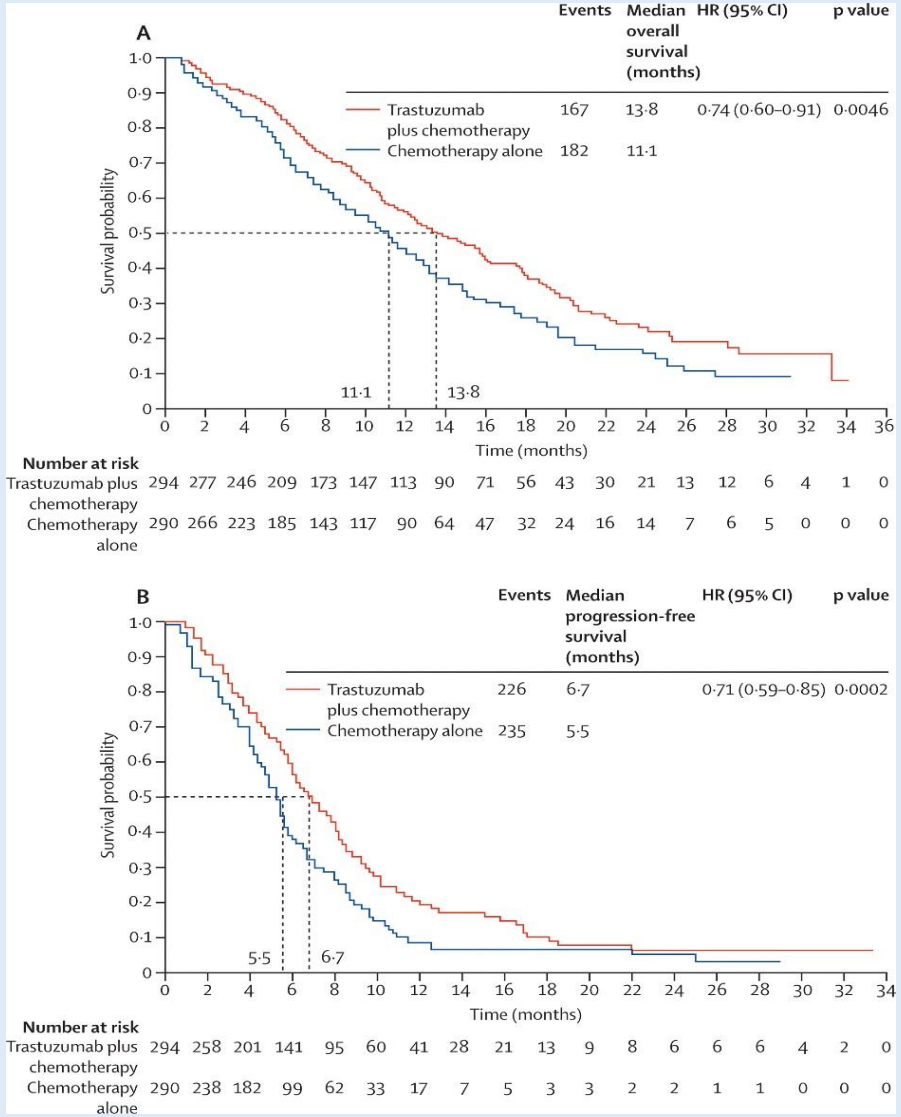
  - Pathology issues:
    - More heterogeneity than with breast cancer – higher false negative rate
    - Tends to spare digestive luminal membrane
    - CAP/ASCP/ASCO panel guidelines
  - Clinical data: TOGA trial
    - Randomized phase III trial (2010)
    - 5FU + cisplatin +/- trastuzumab
    - RR 47 % vs 35%
    - OS 14 vs 11 mos
    - Higher ratio / gene copy number more likely to benefit

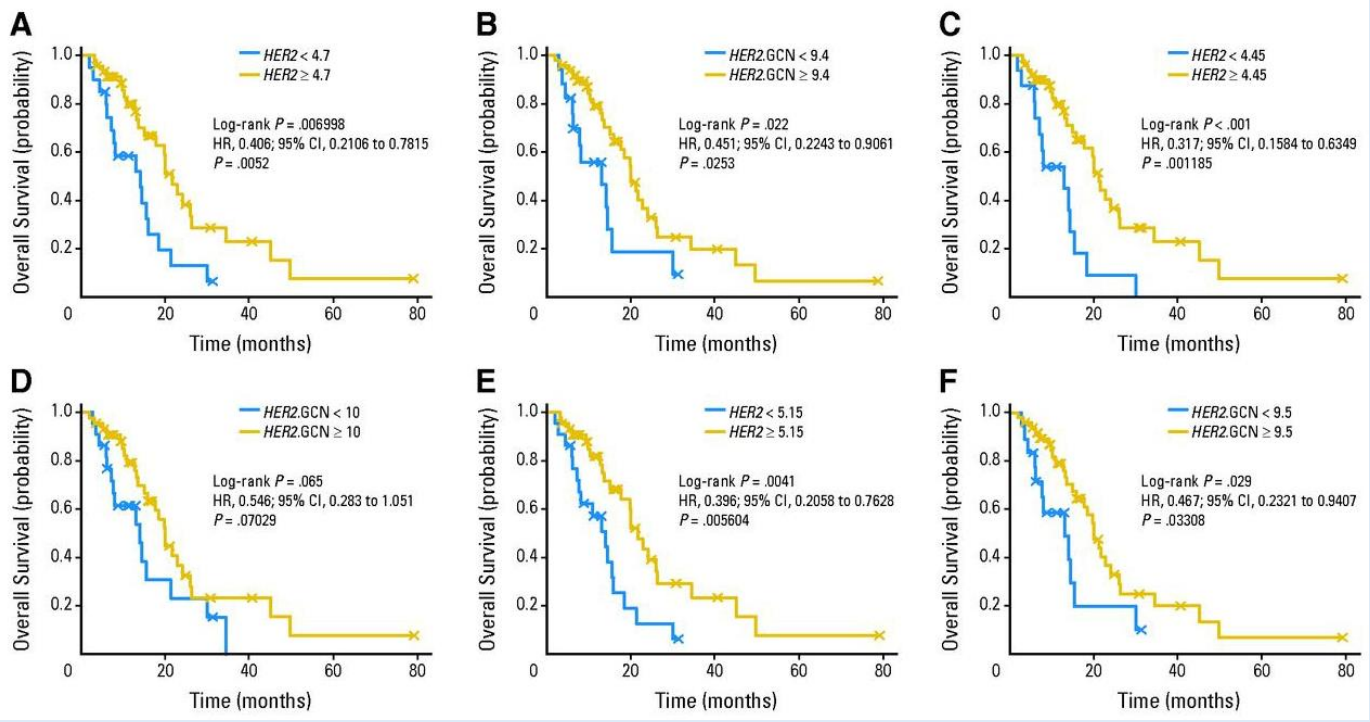


Bang, Lancet 2010

SOC Molecular testing and implications

TOGA

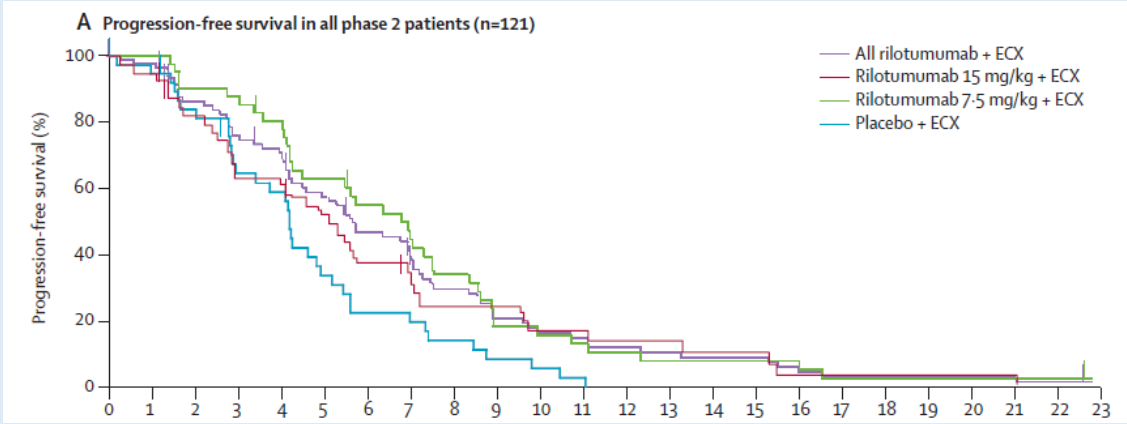
- Her2/CEP17 ratio and gene copy number predictive of benefit
  - Small retrospective analysis suggests ration of 4.7 as optimal cutoff discriminating benefit
    - Ratio > 4.7 = “sensitive” (median OS 21 vs 14 mos)
    - Ratio > 5.1 → OS > 16 mos (median OS 28 vs 14 mos)



Gomez-Martin, JCO 2013

SOC Molecular testing and implications

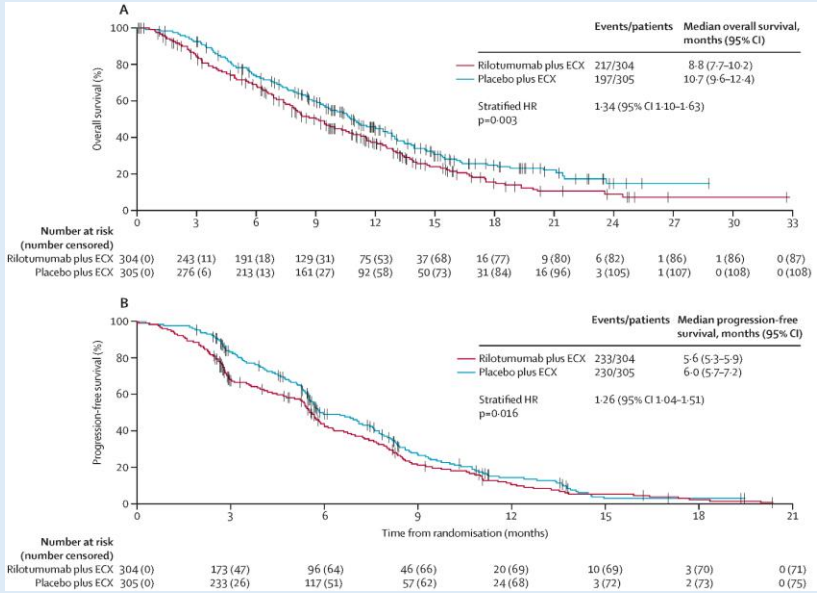
- Esophagogastric cancer: **MET**
  - MET expression in 25 – 75%
  - MET amplification ~ 5%
  - Randomized phase 2 trial evaluating ECX +/- rilotumumab (anti-hepatocyte growth factor / ligand-blocking)
    - Median PFS 5.7 vs 4.2 mos
    - Median OS 10.6 vs 8.9 mos

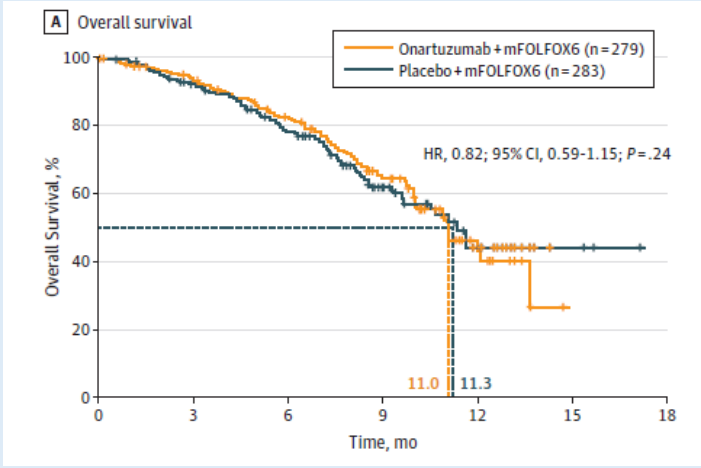


Iveson, Lancet Oncology 2014

SOC Molecular testing and implications

- Randomized phase 3 trials:
  - ECX +/- rilotumumab (RILOMET-1)
    - Median OS 8.8 vs 10.7 mos
  - FOLFOX +/- onartuzumab (METGastric)
    - Median OS 11 vs 11.3 mos
    - PFS 6.8 vs 6.7 mos
  - **WHY?**
    - Early discontinuation (toxicity)
    - Wrong biomarker (expression vs amplification vs mutation, etc)
    - Bad target





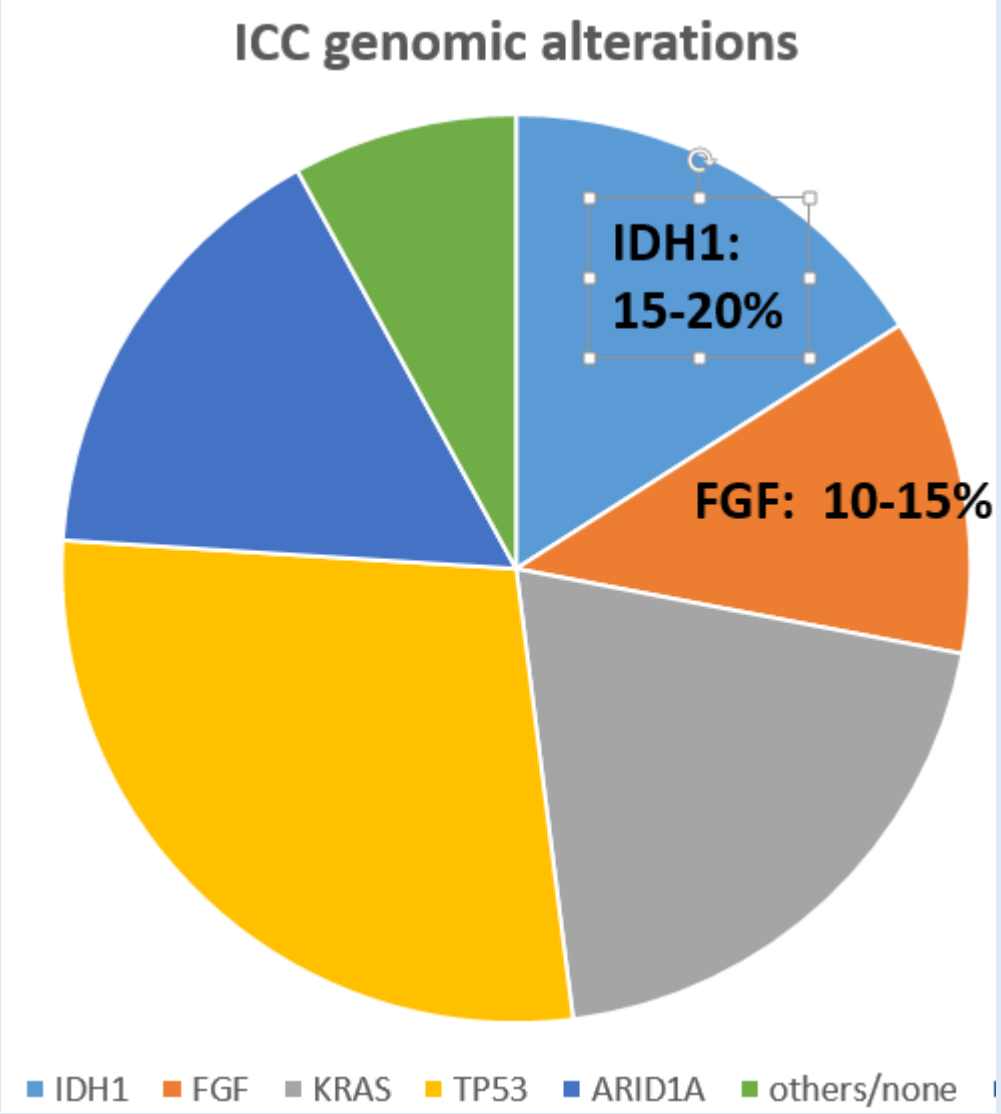
Catanecci, Lancet Oncology 2017; Shah JAMA Oncology 2017

SOC Molecular testing and implications

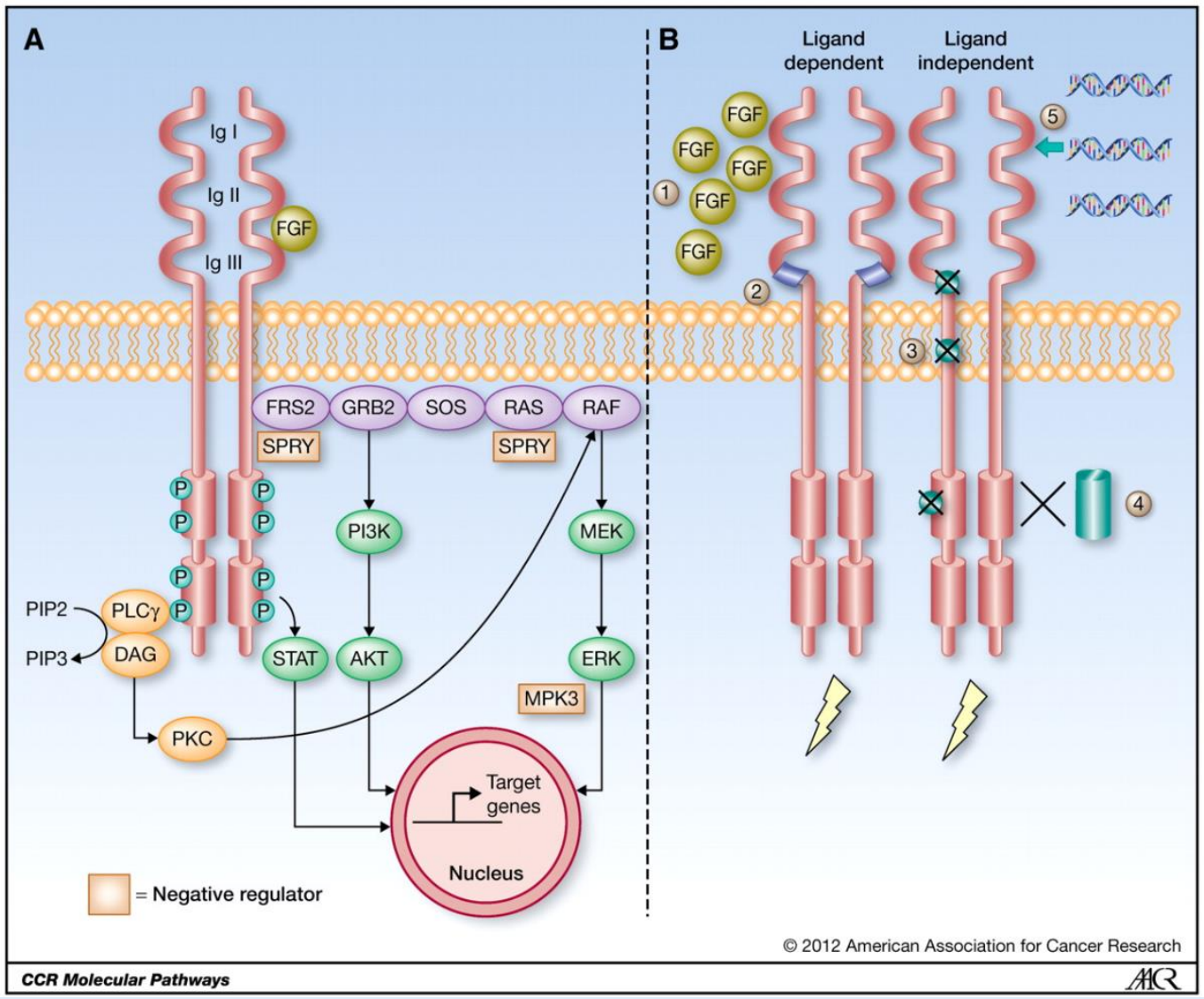
- Gastric cancer: summary
  - SOC to check Her2 amplification
  - Her2 ratio / GCN predictive of benefit
  - MET started out promising, ended up a flop
  - SOC to check MSI status
  - Everything else probably not SOC

Promising molecular testing and implications

- Intrahepatic cholangiocarcinoma
  - Actionable genetic alterations identifiable in ICC
    - FGF alterations
    - IDH1 mutations
    - Other (EPHA2, BAP1, BRCA, KRAS, ERBB family, PTEN, ARID1A, SMAD4, etc)



Targeting FGF alterations in Intrahepatic CC

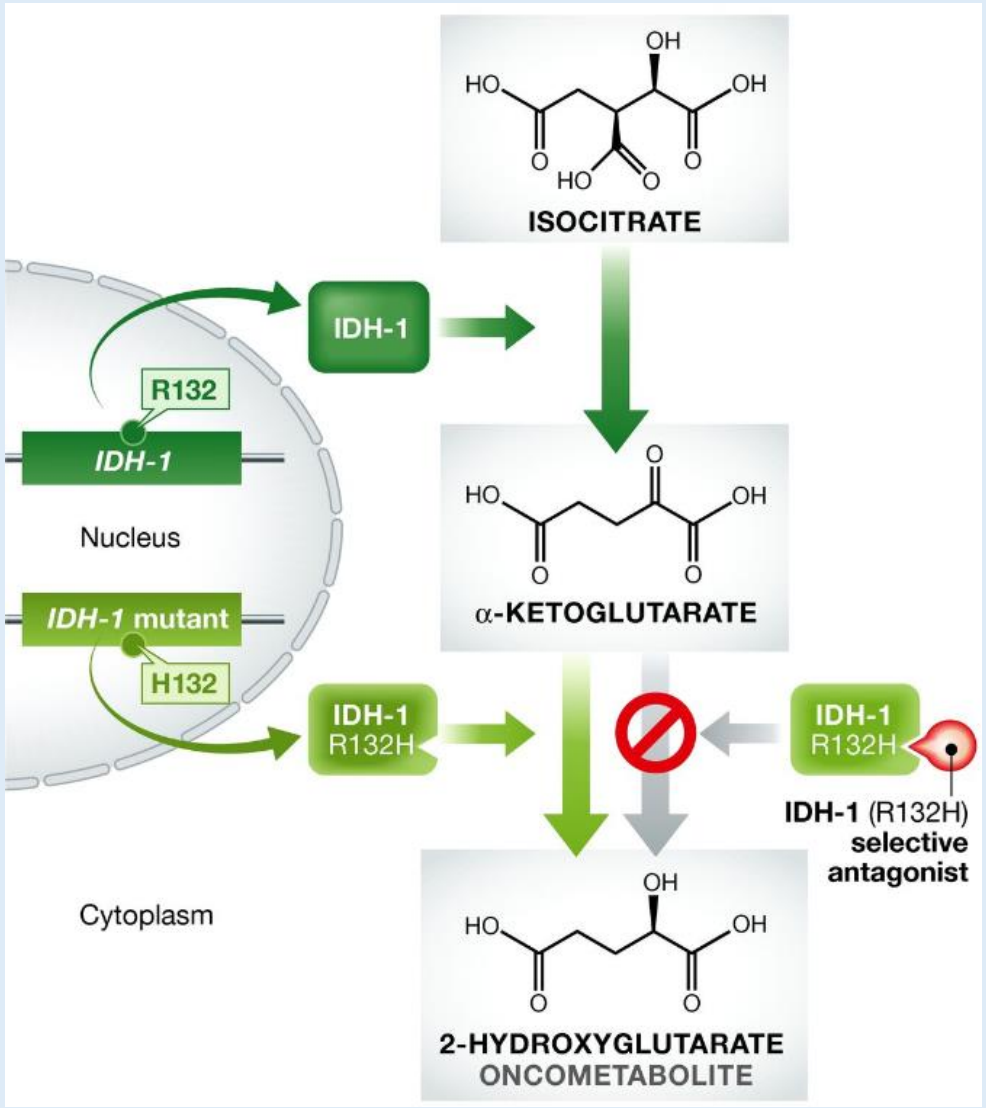


Targeting FGF alterations in Intrahepatic CC

- Multiple FGFR inhibitors under study
  - ORR 15 - 30% (almost always with FGFR2 fusions)
  - DCR > 50% (range 50-90%)
  - Median PFS 4-6 months, median duration of response 1 year
  - Well-tolerated – fatigue, dry mouth, stomatitis, asthenia, dysgeusia *hyperphosphatemia*

- Multiple ongoing trials, phase 2 and phase 3

Targeting IDH1 in Intrahepatic CC



IDH1 Mutations

- IDH1 normal function catalyzes decarboxylation of isocitrate to alpha-KG, ultimately a major source of NADPH production
- Somatic point mutations (R132-) prevent conversion of isocitrate to alpha-KG, AND acquire neomorphic activity enabling IDH-1 to convert alpha-KG to 2HG
- 2HG accumulation induces epigenetic deregulation → DNA and histone hypermethylation → block differentiation, promote proliferation

Targeting IDH1 in Intrahepatic CC

- AG-120 – phase 1 study
  - Dose escalation 3+3 design
  - 73 patients with IDH1 mutated CC
  - Toxicity:
    - Very well tolerated. No DLT
  - Efficacy:
    - ORR 5%, SD 56%
    - 6 months PFS 38.5%
    - 12-month PFS 21% (8 patients on therapy > 1 year)
- Ongoing international phase 3 trial (ClarIDHy)

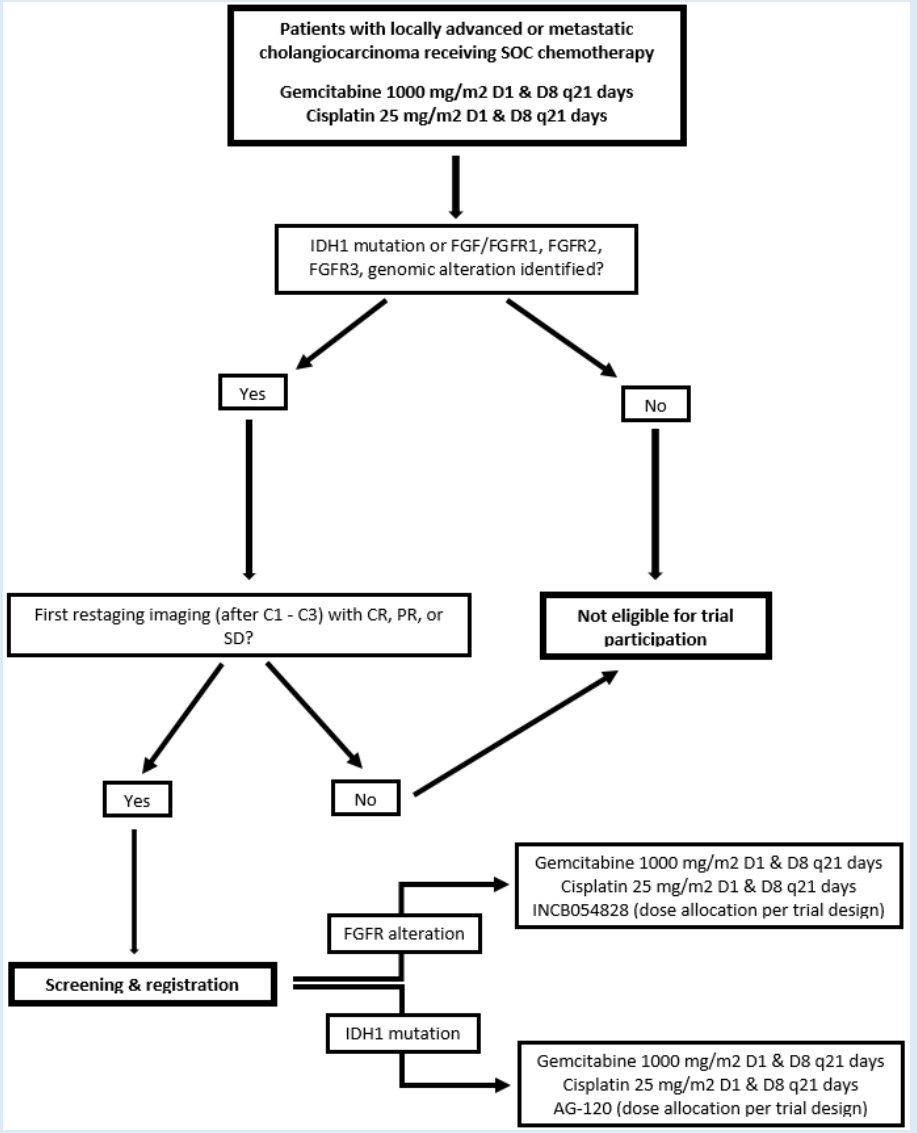
Most Common Drug-Related AEs, n (%)	Pts With CC (n = 73)
Fatigue	18 (25)
Nausea	14 (19)
Diarrhea	9 (12)
Vomiting	9 (12)

- 4 pts (5%) had grade ≥ 3 drug-related AEs at 500 mg QD (n = 2) and 1200 mg QD (n = 2)
  - 500 mg QD: fatigue (n = 1), increased blood alkaline phosphatase (n = 1)
  - 1200 mg QD: fatigue (n = 1), decreased blood phosphorous (n = 1)

Best Overall Response,* n (%)	AG-120 Dosing			All Pts With CC (n = 73)
	< 500 mg QD (n = 6)	500 mg QD (n = 62)	> 500 mg QD (n = 5)	
PR	1 (17)	3 (5)		4 (5)
SD	3 (50)	36 (58)	2 (40)	41 (56)
PD	1 (17)	21 (34)	2 (40)	24 (33)
Not assessed†	1 (17)	2 (3)	1 (20)	4 (5)

Promising molecular testing and implications

- Intrahepatic cholangiocarcinoma
  - Multiple phase 2 trials evaluating role of FGFR inhibitors
  - Phase 3 trial evaluating role of IDH-1 inhibition with AG-120 (ClarIDHy)
  - ? Potentially move it up to first-line setting
    - avoid chemotherapy
    - lag time for NGS results
    - add-on —> toxicity

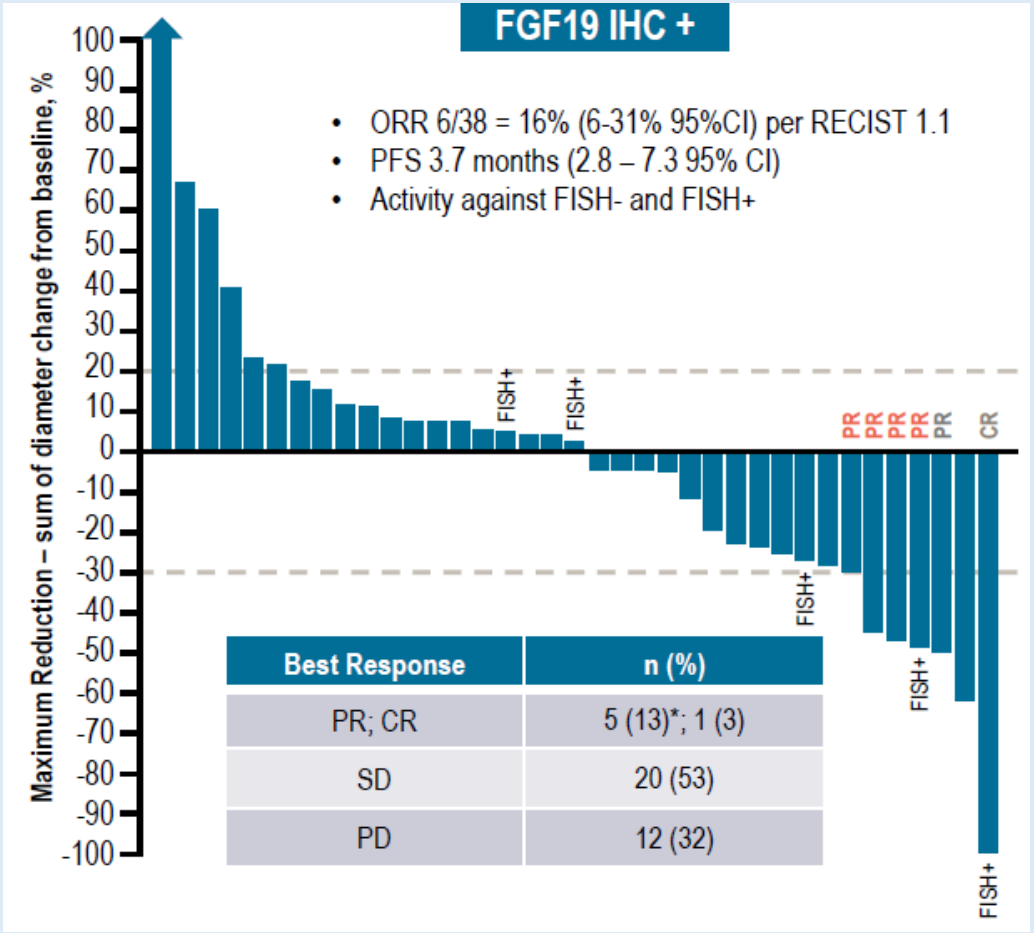


Promising molecular testing and implications

- Cholangiocarcinoma cancer: summary
  - No FDA-approved targeted therapy
  - SOC to check MSI status
  - Given early data suggesting benefits with targeted therapies, would strongly consider genomic profiling (with clinical trial enrollment)
  - Other uncommon mutations potentially targetable
    - DDR (eg BRCA, ATM, POLE, CHEK2, PALB2, etc)
    - mTOR - PTEN, STK11, TSC1, TSC2
    - MAK - BRAF, NF1

Molecular testing and implications

- Hepatocellular carcinoma
  - 2 FDA-approved drugs (“targeted”) – sorafenib and regorafenib
    - Modest benefits
    - Moderate toxicity
    - No biomarker
  - BLU-554 – potent, highly selective FGFR4 inhibitor
    - FGF19 signals via FGFR4, aberrant expression appears to drive HCC
    - FGF19 expression ~25-30%
  - Nivolumab – no biomarker



Molecular testing and implications

- Pancreas cancer
  - Rare actionable mutations
    - BRCA2 – platinum sensitivity, PARP inhibitors
    - NTRK fusions
    - ROS1 fusions
  - MSI

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Genomic profiling – clinical trials and off-label treatment

- Genomic alterations with emerging evidence of benefit:
  - BRCA1, BRCA2
  - other DDR genes (e.g. PALB2, ATM, CHEK2, POLE, BAP1, etc)
  - IDH1 (CC)
  - FGFR2 fusions (CC)
  - Her2 (not gastric)
    - Colon
    - EHCC (mutations)
  - NTRK, ROS1 fusions

Genomic profiling – clinical trials and off-label treatment

- DNA Damage Response genes (BRCA1, BRCA2, PALB2, ATM, CHEK2, POLE, etc)
  - Pancreas, colon, CC, gastric
  - ? Higher response to platinum agents
  - Role of PARP inhibitors
    - Pancreas →
      - Gem + cis + veliparib, PR 66%, DCR 88%
      - Cisplatin, olaparib in mice → cisplatin active, better w/ addition of olaparib
      - ongoing trials w/ veliparib, rucaparib, olaparib
    - Colon → not active in unselected patients, case reports with activity
  - Role of immunotherapy
  - Implications for germline testing, etc.

SOC Molecular testing and implications

- Summary:
  - Colorectal: extended ras, braf, MSI
  - Gastroesophageal: Her2
  - Pancreas: not much
  - Cholangiocarcinoma: promising early data
  - Hepatocellular carcinoma: not much (FGFR4/FGF19)
  - Orphans:
    - Neuroendocrine tumor / neuroendocrine carcinoma
    - Small bowel tumors (extrapolate from colon / ampullary / pancreas cancer)
    - Appendix cancer (extrapolate from colon cancer)
    - Anal cancer
  - ? MSI in everyone

Genomic profiling – clinical trials and off-label treatment

- What do we do?
- NGS –
  - Foundation Medicine
  - Others: Caris, Tempus, Guardant, ARUP, etc
- MSI
- Practical issues:
  - Reimbursement / payment
  - Tumor samples
  - Repeat biopsies
  - Liquid biopsies

Ongoing issues w/ genomic profiling

- Oncogene addiction
- Driver mutations, passenger mutations, co-mutations, resistance mutations
  - adding multiple medications —> overlapping toxicity, *contracts / budgets*
- Sub-clonal populations, tumor heterogeneity
- Germline vs somatic mutations

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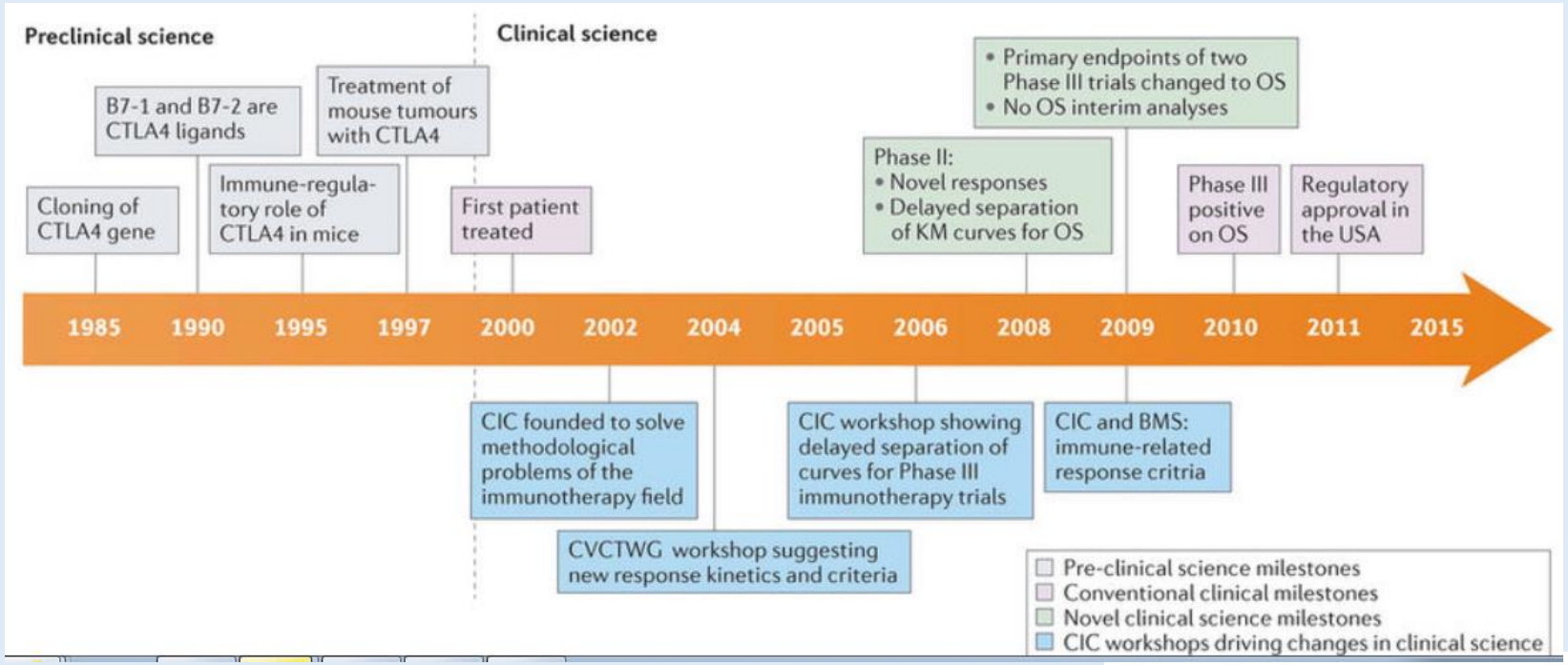
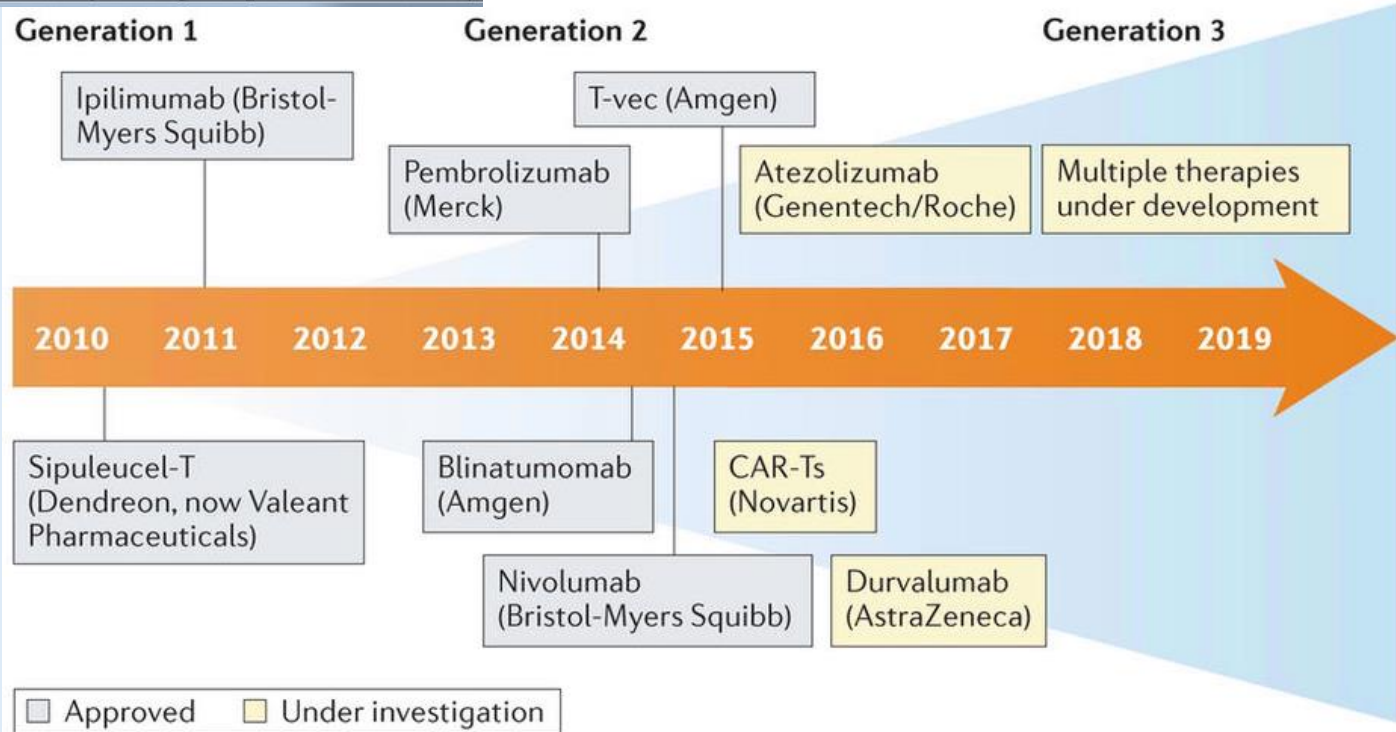


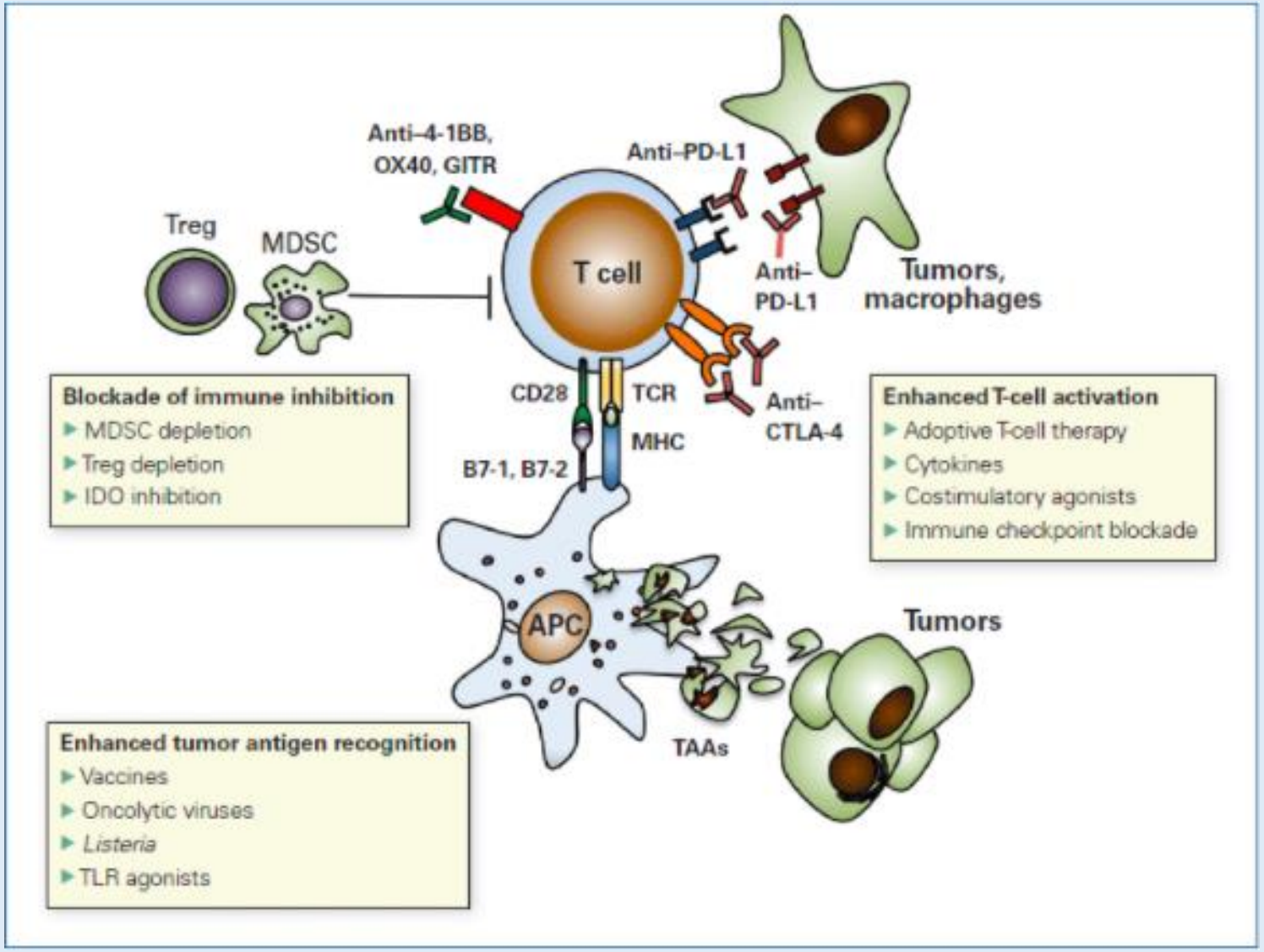
2017:

- CAR T-cell therapy
- anti-PD1 Ab therapies:
  HCC
  gastric carcinoma
  MSI-H cancers

Immunotherapy development

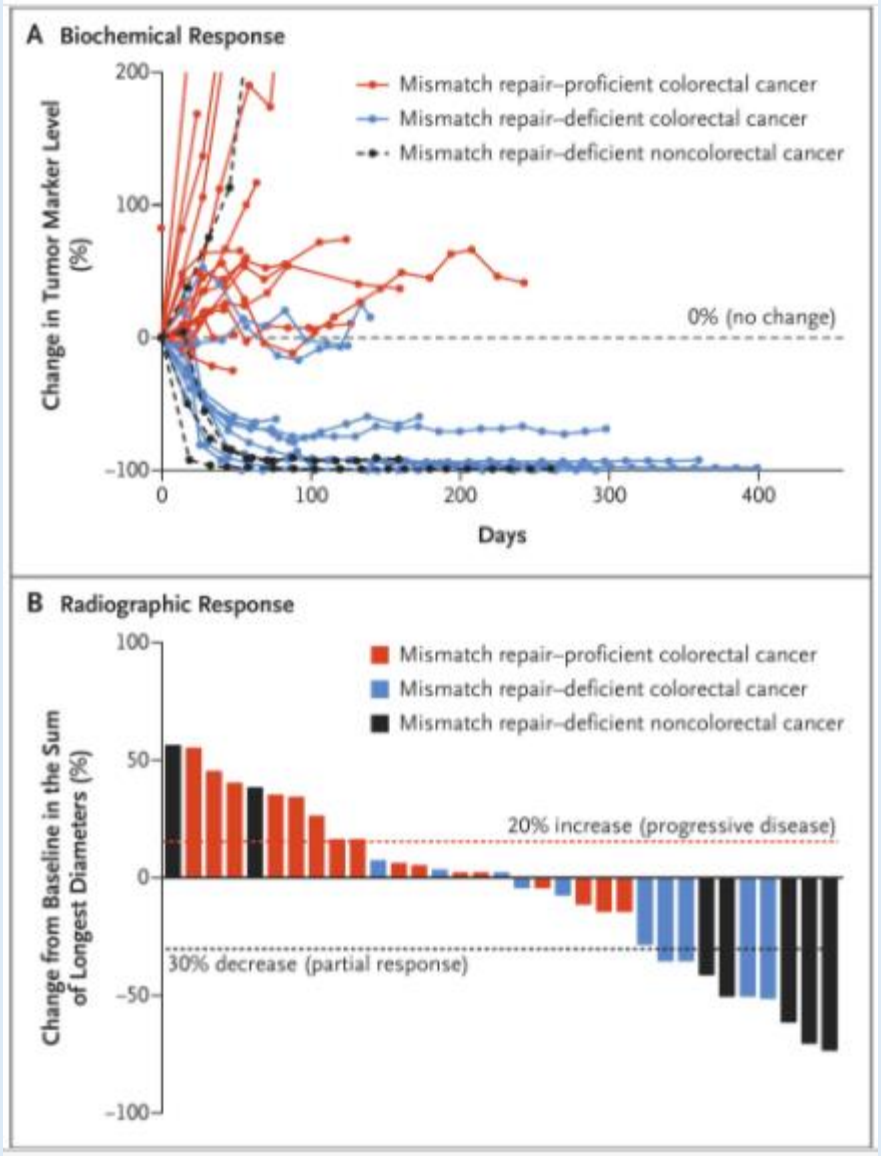


Cancer immunotherapy



Immunotherapy: MSI-H ("tissue agnostic")

- phase 2 trial: refractory cancers
  - MSI-H colorectal (n=11)
  - MSS colorectal (n=21)
  - MSI-H non-colorectal (n=9)
- MSI-H CRC
  - ORR 40%
  - 20-wk PFS 78%
- MSI-H non-CRC
  - ORR 71%
  - 20-wk PFS 67%



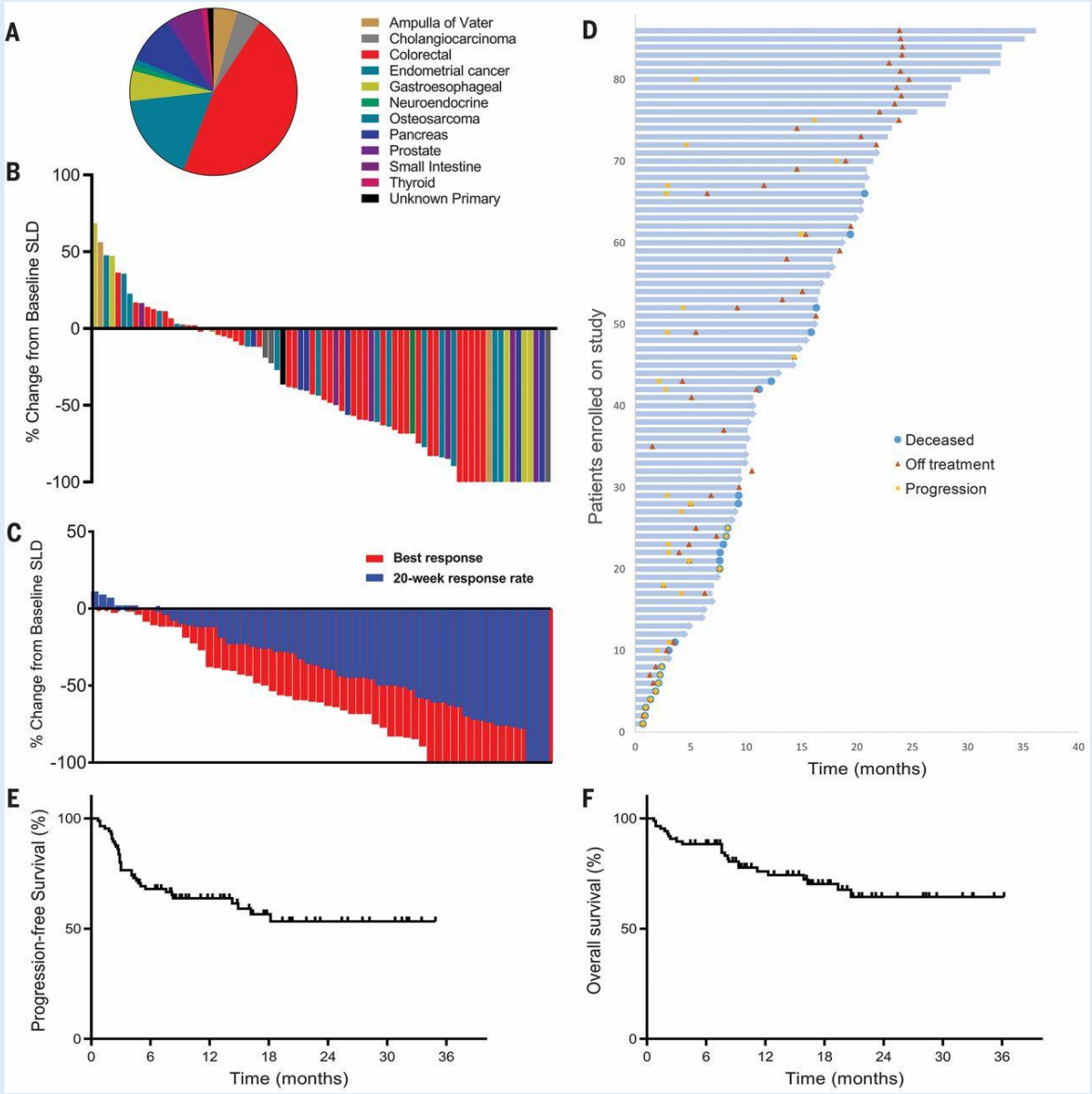
Le NEJM 2015

Immunotherapy: MSI-H (“tissue agnostic”)

- 5 uncontrolled single arm trials
- 149 patients
- RR 40%
- response duration -

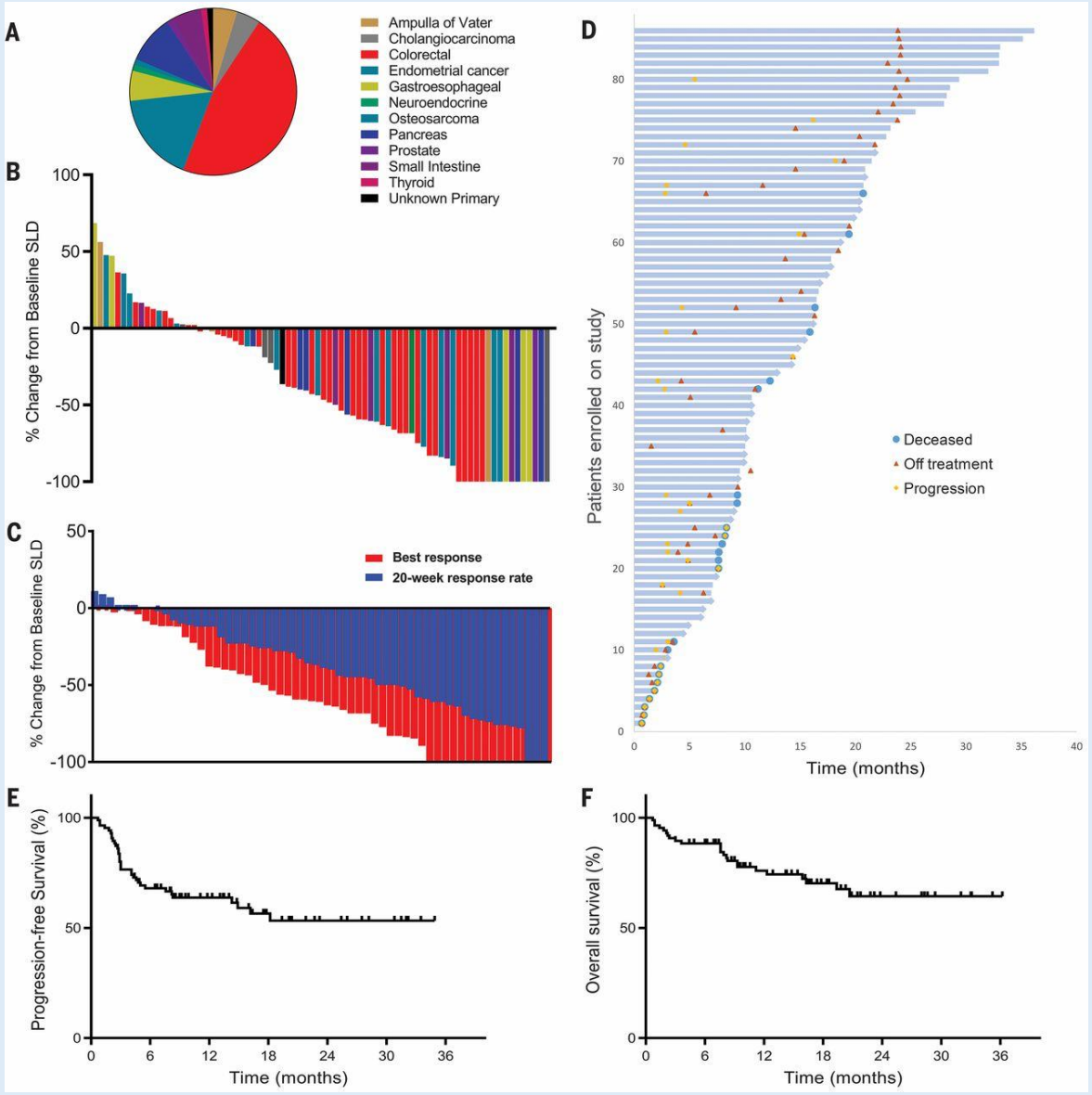
  78% responses > 6 months

Immunotherapy: MSI-H ("tissue agnostic")



Le Science 2017

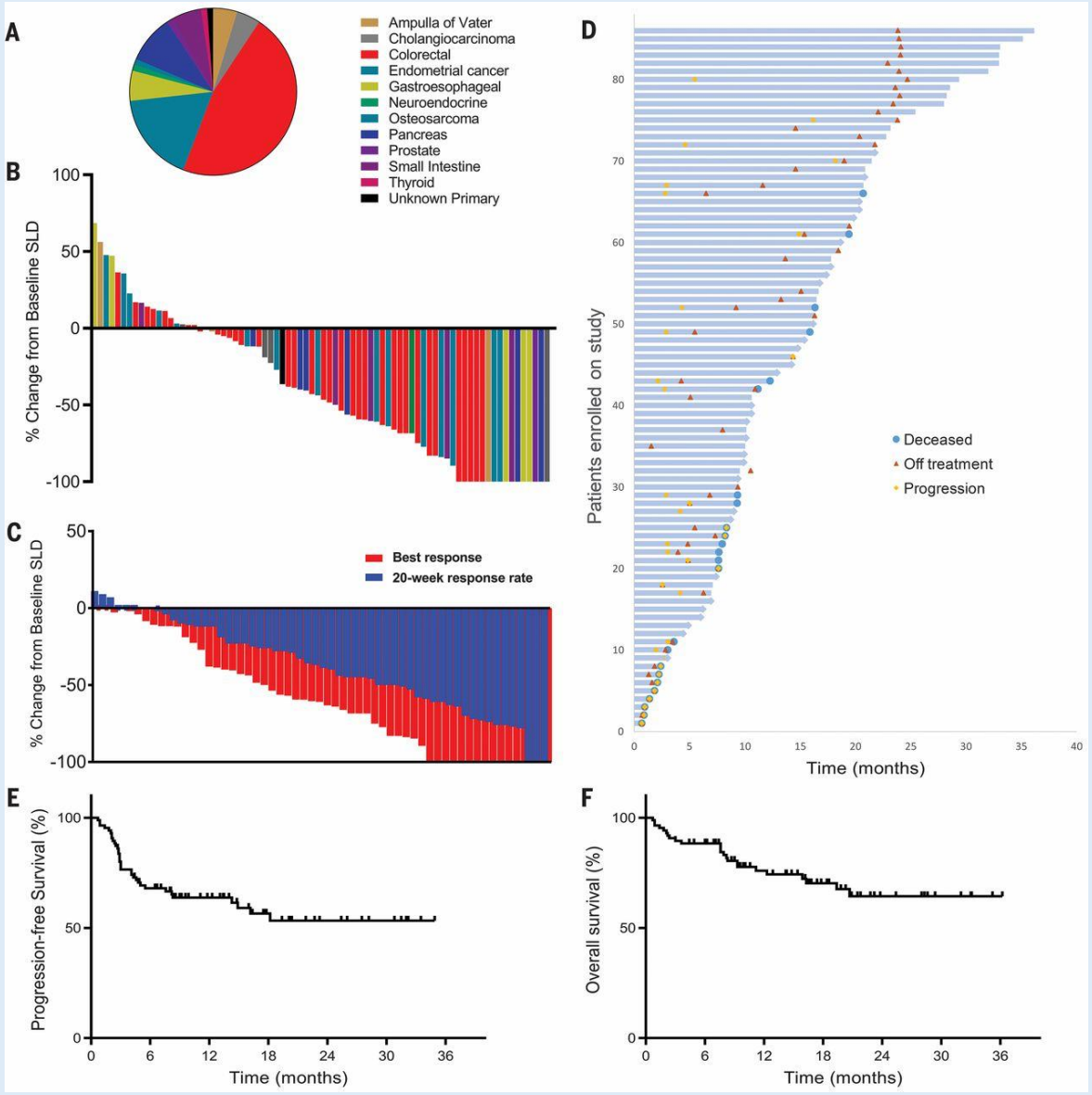
Immunotherapy: MSI-H (“tissue agnostic”)



Who to test?

- all colon cancers?
- all GI cancers?
- other cancers?

Immunotherapy: MSI-H ("tissue agnostic")

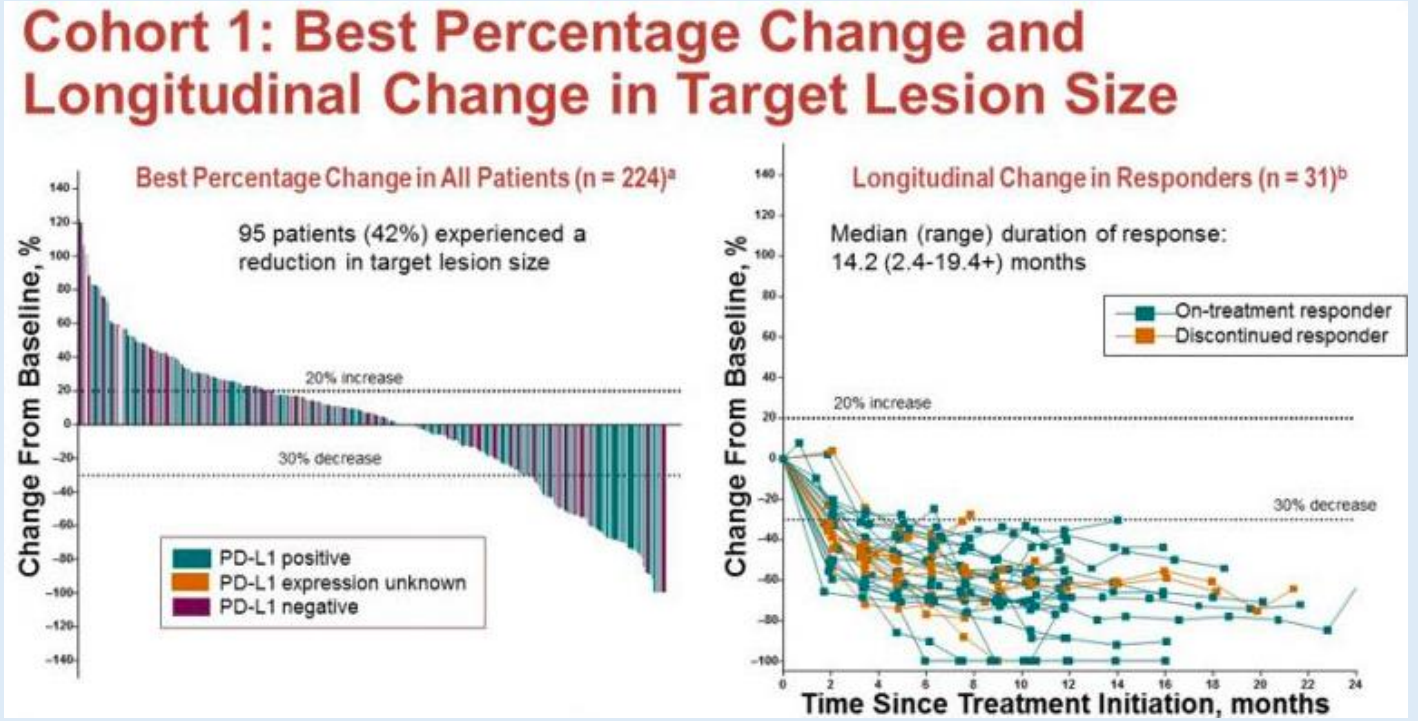


Who to test?

- all colon cancers? - yes
- all GI cancers? - yes ?
- other cancers? - ???

Immunotherapy: gastroesophageal cancer

- Keynote 059 — phase 2 trial gastric/GEJ (refractory)
  - 259 patients — 57% PDL1+ (>/=1%, 223C)
  - ORR PDL1+ 16% vs PDL1- 6%
  - Median duration of response: 14 mos
  - 1st line ORR 26%



Wainberg ESMO 2017

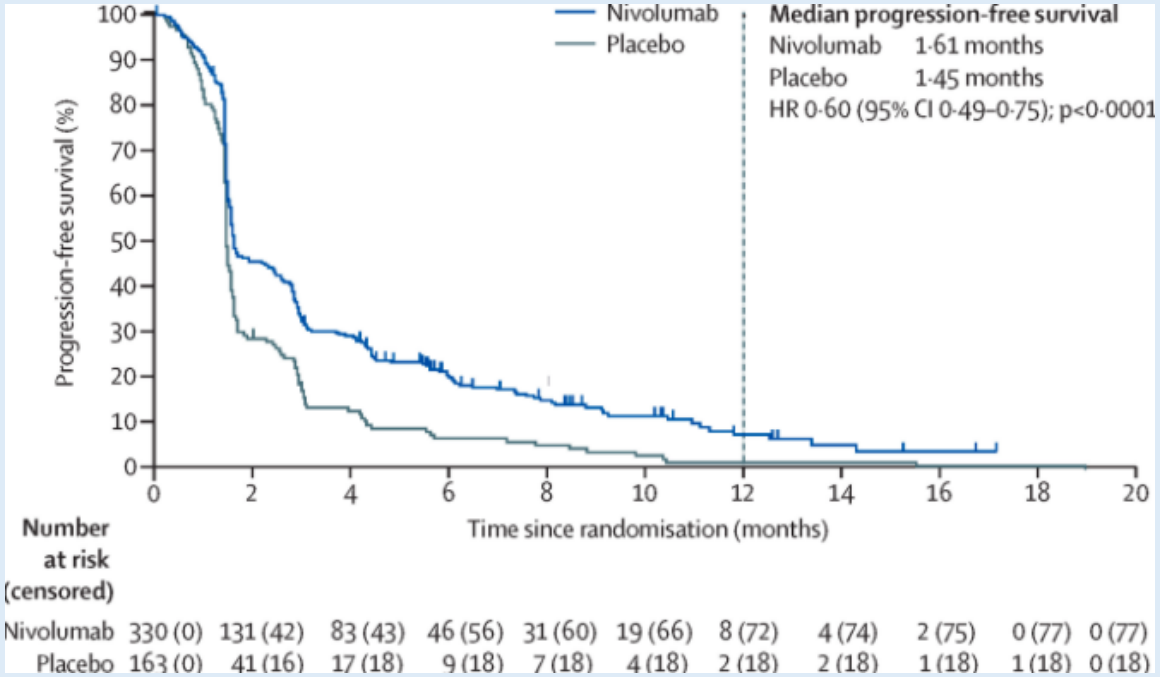
Immunotherapy: gastroesophageal cancer

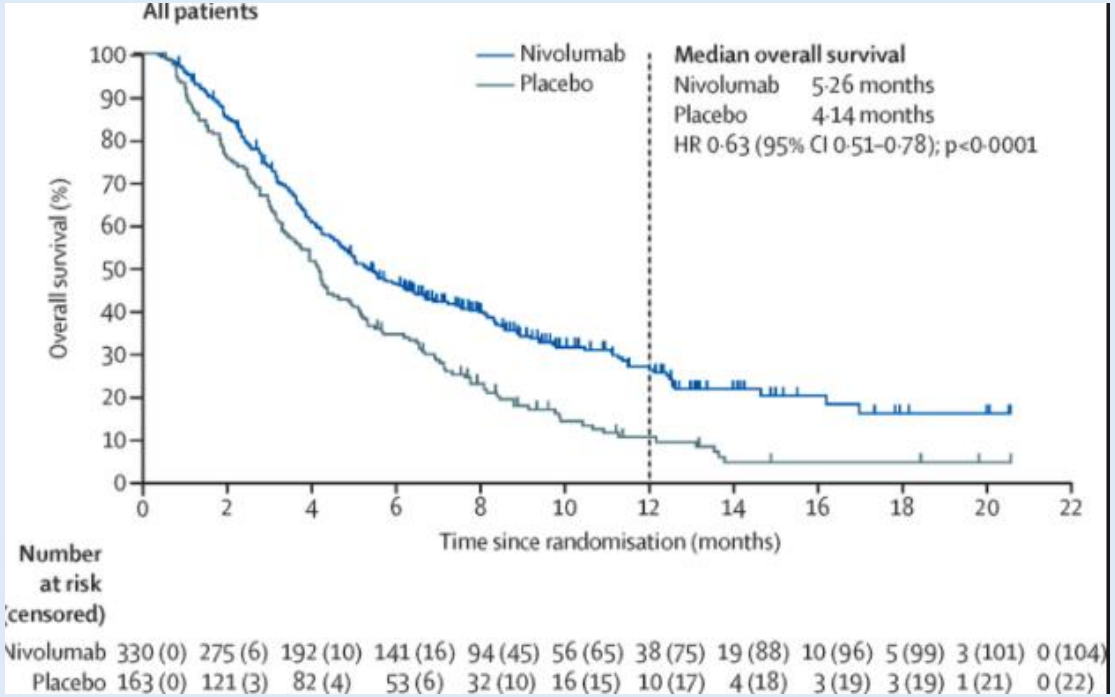
FDA grants accelerated approval to pembrolizumab for advanced gastric cancer

On September 22, 2017, the Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test. Patients must have had disease progression on or after two or more prior systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy.

Immunotherapy: gastroesophageal cancer

ATTRACTION-2: Japan, salvage setting with nivolumab

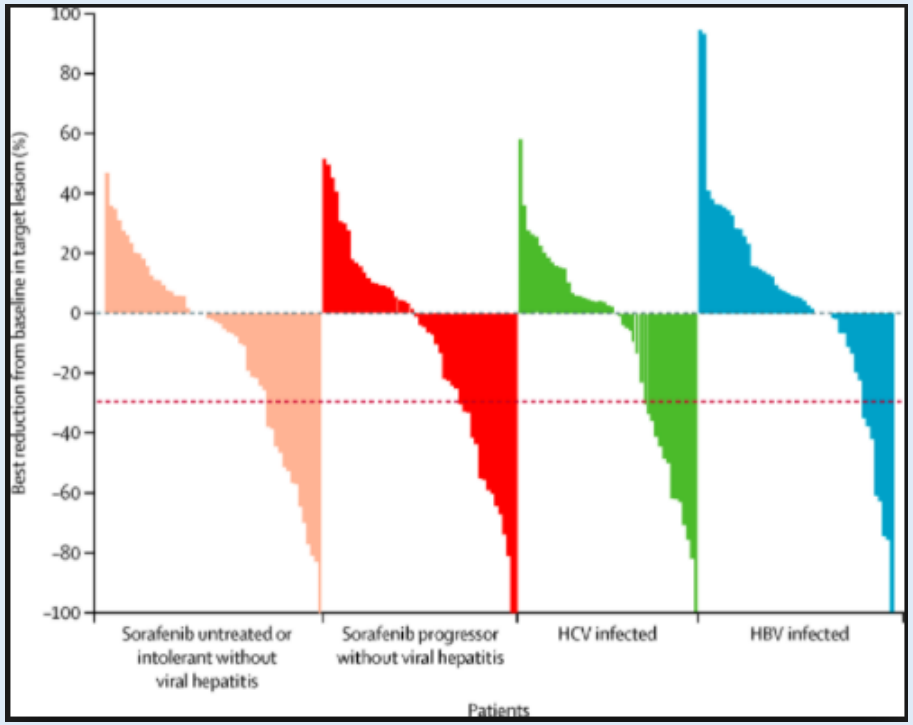




Kang Lancet 2017

Immunotherapy: hepatocellular carcinoma

- CHECKMATE-040
- phase 1/2
- child-pugh A, sorafenib failure
- 262 patients
  - 159 sorafenib failure
  - 80 sorafenib naive
- ORR 20% in expansion, DCR 56%
- OS 16 mos, 29 mos if sorafenib naive



6-month PFS 37%
9-month PFS 28%

El-Khoueiry Lancet 2017

Immunotherapies: signals of activity

- Biliary tract cancers
  - KEYNOTE 026 — 17% response rate
  - KEYNOTE 158 — 100 cases cholangiocarcinoma, results pending this year
- Neuroendocrine carcinoma (high grade)
  - Merkel cell carcinoma, SCLC, case reports with high grade NET/NEC
- What about colon?
  - Generally disappointing
  - Multiple ongoing trials evaluating immunotherapy combinations
  - anti-PDL1 Ab + MEK inhibitor with responses

Immunotherapies: clinical trials

- anti-PD1 Ab + “drug X”
  - second immunomodulatory agent
    - second checkpoint inhibitor (eg CTLA4, LAG, etc)
    - costimulatory agonist (OX40, GITR, etc)
    - anti-VEGF
    - oncolytic virus
    - other (eg IDO, mTOR, p53 stabilizer, chemokine, cytokine)
  - chemotherapy (with antigen release)
  - abscopal effect —> add RT, SIRT

Immunotherapy: summary

- MSI-H cancers ("tissue agnostic")
  - 40% ORR
  - 50% durable control (>2 years?)
- PDL1+ gastroesophageal carcinomas
  - RR 10-15%
  - Duration of response > 1 year
- Hepatocellular carcinoma
  - RR 20%
  - impressive OS (> 2 years in TKI naive patients)
- ? Promising: cholangiocarcinoma, ? high grade NET/NEC
- Problems: MSS CRC, pancreas cancer
- **Need better biomarker / predictors**
  - **TMB, immune infiltrate, PDL1 status, gamma-IFN signature**

New cancer drugs approved by the FDA in 2017

Aliqopa (copanlisib); Bayer; For the treatment of follicular lymphoma , Approved September 2017

Alunbrig (brigatinib); Ariad Pharmaceuticals; For the treatment of advanced ALK-positive metastatic non-small cell lung cancer, Approved April 2017

Bavencio (avelumab) ; EMD Serono/Pfizer; For the treatment of Merkel cell carcinoma , Approved March 2017

Besponsa (inotuzumab ozogamicin); Pfizer; For the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia, Approved August 2017

Calquence (acalabrutinib); Acerta Pharmaceuticals; For the treatment of mantle cell lymphoma , Approved November 2017

IDHIFA (enasidenib); Celgene; For the treatment of relapsed or refractory acute myeloid leukemia with IDH2 mutation , Approved August 2017

Imfinzi (durvalumab); AstraZeneca; For the treatment of advanced or metastatic urothelial carcinoma, Approved May 2017

Kisqali (ribociclib); Novartis; For the treatment of breast cancer, Approved March 2017

Kymriah (tisagenlecleucel); Novartis; For the treatment of refractory B-cell precursor acute lymphoblastic leukemia , Approved August 2017

Nerlynx (neratinib); Puma Biotech; For the treatment of HER2 breast cancer, Approved July 2017

Rydapt (midostaurin); Novartis; For the treatment of FLT3 positive acute myeloid leukemia and mastocytosis , Approved April 2017

Verzenio (abemaciclib); Eli Lilly; For the treatment of HR+, HER2- breast cancer, Approved September 2017

Vyxeos (daunorubicin and cytarabine) ; Jazz Pharma; For the treatment of newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes, Approved August 2017

Xermelo (telotristat ethyl); Lexicon Pharmaceuticals; For the treatment of carcinoid syndrome diarrhea, Approved February 2017

Yescarta (axicabtagene ciloleucel); Kite Pharmaceuticals; For the treatment of relapsed or refractory large B-cell lymphomas, Approved October 2017

Zejula (niraparib); Tesaro; For the treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer , Approved March 2017

FDA approvals in oncology: 2017

- FDA updated the product label for nilotinib (Tasigna, Novartis Pharmaceuticals Corp.) to include information on nilotinib discontinuation, post-discontinuation monitoring criteria, and guidance for treatment re-initiation in patients taking nilotinib for Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) who have achieved a sustained molecular response (MR 4.5). More Information. December 22, 2017
- FDA granted regular approval to hydroxyurea (Siklos, Addmedica) to reduce the frequency of painful crises and the need for blood transfusions in pediatric patients from 2 years of age and older with sickle cell anemia with recurrent moderate to severe painful crises. More Information. December 21, 2017
- FDA granted regular approval to pertuzumab (PERJETA, Genentech, Inc.) for use in combination with trastuzumab and chemotherapy as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence. More Information. December 20, 2017
- FDA granted regular approval to the anti-PD1 monoclonal antibody, nivolumab (OPDIVO, Bristol-Myers Squibb Company) for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or in patients with metastatic disease who have undergone complete resection. Nivolumab was previously approved for the treatment of patients with unresectable or metastatic melanoma. More Information. December 20, 2017
- FDA granted accelerated approval to bosutinib (BOSULIF, Pfizer Inc.) for treatment of patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML). More Information. December 19, 2017
- FDA granted regular approval to cabozantinib (Cabometyx, Exelixis, Inc.) for treatment of patients with advanced renal cell carcinoma (RCC). More Information. December 19, 2017.
- FDA approved Ogivri (trastuzumab-dkst, Mylan) as a biosimilar to Herceptin (trastuzumab, Genentech, Inc.) for the treatment of patients with HER2-overexpressing breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma). More Information. December 1, 2017
- FDA granted marketing approval to the FoundationOne CDx (F1CDx, Foundation Medicine, Inc.), a next generation sequencing (NGS) based in vitro diagnostic (IVD) to detect genetic mutations in 324 genes and two genomic signatures in any solid tumor type. More Information. November 30, 2017
- FDA approved sunitinib malate (Sutent, Pfizer Inc.) for the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma following nephrectomy. More Information. November 16, 2017
- FDA granted regular approval to obinutuzumab (GAZYVA, Genentech, Inc.) in combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III, or IV follicular lymphoma (FL). More Information. November 16, 2017
- FDA approved emicizumab-kxwh (HEMLIBRA, Genentech, Inc.) for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. More Information. November 16, 2017
- FDA granted regular approval to dasatinib (SPRYCEL, Bristol-Myers Squibb Co.) for the treatment of pediatric patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the chronic phase. More Information. November 9, 2017
- FDA granted regular approvals to dabrafenib and trametinib (TAFINLAR and MEKINIST, Novartis Pharmaceuticals Inc.) administered in combination for patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test. More Information. June 22, 2017
- FDA granted regular approval to the combination of rituximab and hyaluronidase human (RITUXAN HYCELA, Genentech Inc.) for adult patients with follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia. More Information. June 22, 2017
- FDA approved aminolevulinic acid hydrochloride, known as ALA HCl (Gleolan, NX Development Corp.) as an optical imaging agent indicated in patients with gliomas (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery. More Information. June 6, 2017
- FDA granted regular approval to ceritinib (ZYKADIA, Novartis Pharmaceuticals Corp.) for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. More Information. May 26, 2017
- FDA granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. More Information. May 23, 2017
- FDA granted regular approval to pembrolizumab (KEYTRUDA, Merck and Co., Inc.) for patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. More Information. May 18, 2017
- FDA granted regular approval to brentuximab vedotin (ADCETRIS, Seattle Genetics, Inc.) for the treatment of adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy. More Information. November 9, 2017.
- FDA granted regular approval to alectinib (ALECENSA, Hoffmann-La Roche, Inc./Genentech, Inc.) for treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test. More Information. November 6, 2017
- FDA granted regular approval to vemurafenib (ZELBORAF, Hoffmann-La Roche Inc.) for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation. More Information. November 6, 2017.
- FDA granted accelerated approval to acalabrutinib (Calquence, AstraZeneca Pharmaceuticals Inc. under license of Acerta Pharma BV) for treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. More Information. October 31, 2017
- FDA granted regular approval to axicabtagene ciloleucel (YESCARTA, Kite Pharma, Inc.) for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. More Information. October 18, 2017
- FDA approved abemaciclib (VERZENIO, Eli Lilly and Company) in combination with fulvestrant for women with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy. More Inforrmation. September 28, 2017
- FDA granted accelerated approval to nivolumab (OPDIVO, Bristol-Myers Squibb Co.) for the treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib. More Information. September 22, 2017
- FDA granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co., Inc.) for patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 as determined by an FDA-approved test. More Information. September 22, 2017
- FDA approved a lower dose of cabazitaxel (20 mg/m^2 every 3 weeks) (JEVTANA, Sanofi-Aventis) in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen. Cabazitaxel (25 mg/m^2 every 3 weeks) was approved for this indication in 2010. More Information. September 14, 2017
- FDA granted accelerated approval to copanlisib (ALIQOPA, Bayer HealthCare Pharmaceuticals Inc.) for the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies. More Information. September 14, 2017
- FDA approved Mvasi (bevacizumab-awwb, Amgen Inc.) as a biosimilar to Avastin (bevacizumab, Genentech Inc.). Mvasi is the first biosimilar approved in the U.S. for the treatment of cancer. More Information. September 14, 2017
- FDA approved gemtuzumab ozogamicin (Mylotarg, Pfizer Inc.) for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults and for treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older. Gemtuzumab ozogamicin may be used in combination with daunorubicin and cytarabine for adults with newly-diagnosed AML, or as a stand-alone treatment for certain adult and pediatric patients. More Information. September 1, 2017
- FDA granted accelerated approval to pembrolizumab (KEYTRUDA, Merck and Co., Inc.) in combination with pemetrexed and carboplatin for the treatment of patients with previously untreated metastatic non-squamous non-small cell lung cancer (NSCLC). More Information. May 10, 2017
- FDA granted accelerated approval to avelumab (BAVENCIO, EMD Serono, Inc.) for patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. More Information. May 9, 2017
- FDA granted accelerated approval to durvalumab (IMFINZI, AstraZeneca UK Limited) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. More Information. May 1, 2017
- FDA granted accelerated approval to brigatinib (ALUNBRIG tablets, Takeda Pharmaceutical Company Limited, through its wholly owned subsidiary ARIAD Pharmaceuticals, Inc.) for the treatment of patients with metastatic anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. More Information. April 28, 2017
- FDA approved midostaurin (RYDAPT, Novartis Pharmaceuticals Corp.) for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive (FLT3+), as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. More Information. April 28, 2017
- FDA expanded the indications of regorafenib (STIVARGA, Bayer HealthCare Pharmaceuticals Inc.) to include the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. More Information. April 27, 2017
- FDA granted regular approval to tisagenlecleucel (KYMRIAH, Novartis Pharmaceuticals Corp.) for the treatment of patients up to age 25 years with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. More Information. August 30, 2017
- FDA granted regular approval to olaparib tablets (Lynparza, AstraZeneca) for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy. More Information. August 17, 2017
- FDA approved inotuzumab ozogamicin (BESPONSA,, Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc.) for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). More Information. August 17, 2017
- FDA granted regular approval to a liposome-encapsulated combination of daunorubicin and cytarabine (VYXEOS, Jazz Pharmaceuticals, Inc.) for the treatment of adults with newly-diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC), two types of AML having a poor prognosis. More Information. August 3, 2017
- FDA approved ibrutinib (Imbruvica, Pharmacyclics LLC) for the treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. This is the first FDA-approved therapy for the treatment of cGVHD. More Information. August 2, 2017
- FDA granted regular approval to enasidenib (IDHIFA, Celgene Corp.) for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test. More Information. August 1, 2017
- FDA granted accelerated approval to nivolumab (OPDIVO, Bristol-Myers Squibb Company) for the treatment of patients 12 years and older with mismatch repair deficient (dMMR) and microsatellite instability high (MSI-H) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. More Information. August 1, 2017
- FDA approved neratinib (NERLYNX, Puma Biotechnology, Inc.) for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. More Information. July 17, 2017
- FDA approved blinatumomab (BLINCYTO, Amgen Inc.) for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in adults and children. More Information. July 11, 2017
- FDA approved L-glutamine oral powder (Endari, Emmaus Medical, Inc.) for oral administration to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years and older. More Information. July 7, 2012
- FDA granted marketing approval to the Praxis Extended RAS Panel (Illumina, Inc.), a next generation sequencing (NGS) test to detect certain genetic mutations in RAS genes in tumor samples of patients with metastatic colorectal cancer (mCRC). The test is used to aid in the identification of patients who may be eligible for treatment with panitumumab (VECTIBIX, Amgen, Inc.). More Information. June 29, 2017
- FDA approved betrixaban (BEVYXXA, Portola) for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. More Information. June 23, 2017
- FDA has permitted marketing of the Philips IntelliSite Pathology Solution (PIPS, Philips Medical Systems Nederland B.V.), as an aid to the pathologist to review and interpret digital images of surgical pathology slides prepared from formalin-fixed paraffin embedded (FFPE) tissue. More Information. April 17, 2017
- FDA has granted marketing authorization to ipsogen JAK2 RGQ PCR Kit, manufactured by QIAGEN GmbH., to detect mutations affecting the Janus Tyrosine Kinase 2 (JAK2) gene. This is the first FDA-authorized test intended to help physicians in evaluating patients for suspected Polycythemia Vera (PV). More Information. March 27, 2017
- FDA granted regular approval to palbociclib (IBRANCE, Pfizer Inc.) for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine based therapy in postmenopausal women. More Information. March 31, 2017
- FDA granted regular approval to osimertinib (TAGRISSO, AstraZeneca Pharmaceuticals, LP) for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy. More Information. March 30, 2017
- FDA approved niraparib (ZEJULA, Tesaro, Inc.), a poly ADP-ribose polymerase (PARP) inhibitor, for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. More Information. March 27, 2017
- FDA granted accelerated approval to avelumab (BAVENCIO, EMD Serono, Inc.) for the treatment of patients 12 years and older with metastatic Merkel cell carcinoma (MCC). Avelumab is a programmed death-ligand 1 (PD-L1) blocking human IgG1 lambda monoclonal antibody. This is the first FDA-approved product to treat this type of cancer. More Information. March 23, 2017

Genomic profiling and immunotherapies: HCI trials

Colon Cancer: • FOLFOX +/- PD1 (MSI-H) • FOLFOX + PD1 + IDO • FOLFIRI + VEGF/DLL4 • FOLFIRI + MEK (kras mutated) • BRAF inhibitor ("paradox breaker") • Immunotherapy combinations	**Pancreas Cancer:** • Preoperative chemo • Gem/ABI +/- olaratumab • Gem/ABI + PD1 + IDO • Gem/ABI + BBI668	**Cholangiocarcinoma**: • FGFR inhibitor • IDH1 inhibitor • anti-CD166 ADC ("probody")	**Hepatocellular**: • SBRT (unresectable) • anti-FGFR4/FGF19 • anti-PD1 + bevacizumab
Gastroesophageal: • Chemo +/- PD1 • MEK ADC • Immunotherapy combinations	**Neuroendocrine**: • anti-DLL3 ADC ("Rova-T") • anti-PD1 (high grade) • anti-PD1 + anti-LAG (well-differentiated)	**GIST**: • novel KIT inhibitors	**All-comers:** • immunotherapies: STING anti-TGFb +/- anti-PD1 anti-PD1 "probody" • targeted therapies: NTRK DDR

Genomic profiling and immunotherapies: summary

Standard:

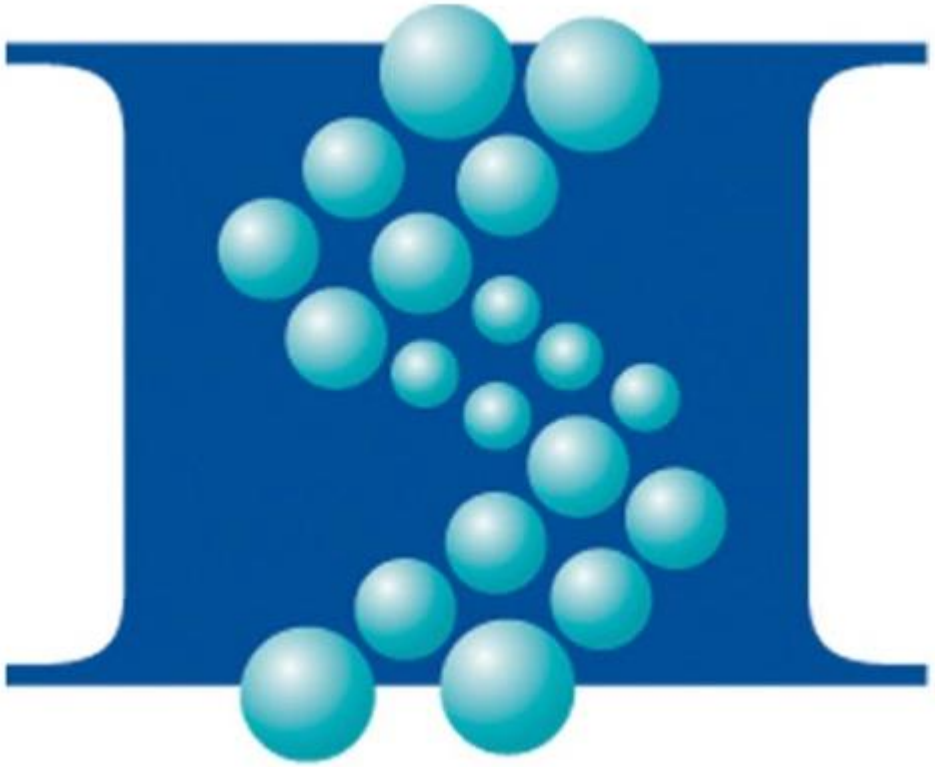
Colon: kras, nras, braf, MSI
Gastric/esophagus: Her2, PDL1
Pancreas:
Biliary:
HCC:
NET:
Other (ampullary, small bowel, appendix, etc.):
ALL: ? MSI

Promising:

Colon: HER2
Gastric/esophagus:
Pancreas: BRCA, NTRK
Biliary: FGFR, IDH1, HER2
HCC: FGFR4/FGF19
NET:
Other (ampullary, small bowel, appendix, etc.):
ALL: MSI

Experimental:

Colon: immunotherapy combinations
Gastric/esophagus: MEK
Pancreas:
Biliary:
HCC:
NET:
Other (ampullary, small bowel, appendix, etc.):
ALL: rare actionable mutations (other DDR, eg ATM, PALB2, POLE, STK11, CHEK2), immunotherapies
PROBLEMS: ras, TP53, APC, braf



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