# 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

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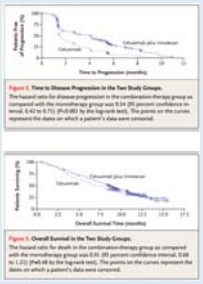
## SOC Molecular testing and implications

**Colon cancer: EGFR, RAS and BRAF**

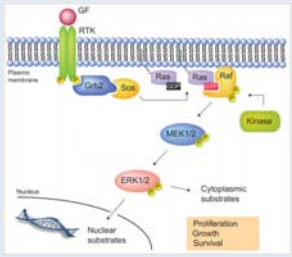
- Anti-EGFR Ab therapy
  - Cetuximab FDA-approval 2004
  - Approved as single-agent or combination with irinotecan
  - **EGFR-expressing**, refractory to irinotecan
  - Randomized trial cetuximab alone vs cetuximab + irinotecan
    - RR 11% vs 23%
    - DCR 32% vs 55%
    - HR PFS 0.54 (TTP 1.5 mos vs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



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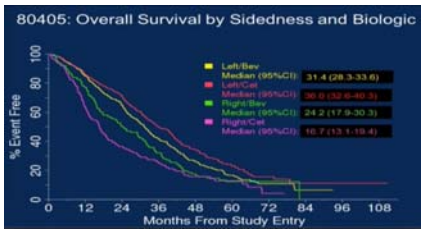
  - 2016: "sidedness" – right-sided colon cancer with apparently no benefit with anti-EGFR antibody therapy (maybe fare worse?)

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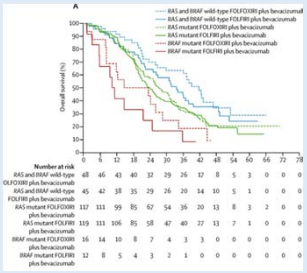
  - 2016: "sidedness" – right-sided colon cancer with apparently no benefit with anti-EGFR antibody therapy (maybe fare worse?)
  - *Current status*: **extended RAS testing and BRAF mutations** - ~60% will have biomarker suggesting lack of benefit with anti-EGFR antibody therapy (this is *not* reflected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

## SOC Molecular testing and implications

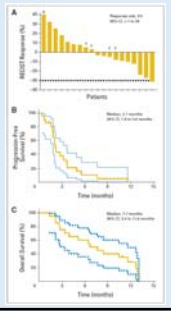
- Colon cancer: **BRAF**
  - Poor prognosis (OS ~14 - 18 mos vs > 30 mos if BRAF wt)
  - More common R (15%) vs L (5%)
  - ? better outcomes with FOLFOXIRI
  - No apparent benefit with anti-EGFR antibody therapy
  - Really no response to available BRAF inhibitors



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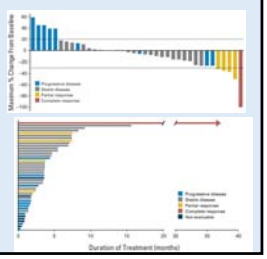
  - Really no response to available BRAF inhibitors
  - 2018 NCCN guidelines to include some targeted treatment
    - Dual targeted therapy braf + mek inhibition
    - Triple therapy braf + mek + EGFR inhibition
  - Association with MSI-H – candidates for immunotherapy



## 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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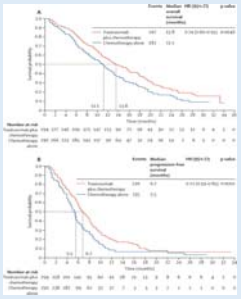
    - Tends to spare digestive luminal membrane
    - CAP/ASCP/ASCO panel guidelines
  - Clinical data: TOGA trial
    - Randomized phase III trial (2010)
    - 5FU + cisplatin +/- trastuzumab
    - RR 47 % vs 35%
    - OS 14 vs 11 mos
    - Higher ratio / gene copy number more likely to benefit

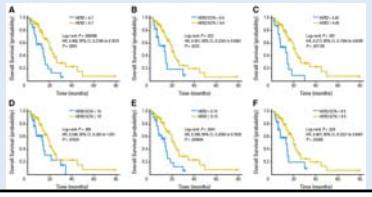


Bang, Lancet 2010

## SOC Molecular testing and implications

**TOGA**

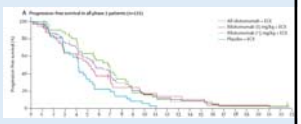
- Her2/CEP17 ratio and gene copy number predictive of benefit
  - Small retrospective analysis suggests ration of 4.7 as optimal cutoff discriminating benefit
    - Ratio > 4.7 = "sensitive" (median OS 21 vs 14 mos)
    - Ratio > 5.1 → OS > 16 mos (median OS 28 vs 14 mos)



Gomez-Martin, JCO 2013

## SOC Molecular testing and implications

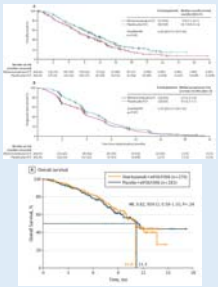
- Esophagogastric cancer: **MET**
  - MET expression in 25 – 75%
  - MET amplification ~ 5%
  - Randomized phase 2 trial evaluating ECX +/- rilotumumab (anti-hepatocyte growth factor / ligand-blocking)
    - Median PFS 5.7 vs 4.2 mos
    - Median OS 10.6 vs 8.9 mos



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



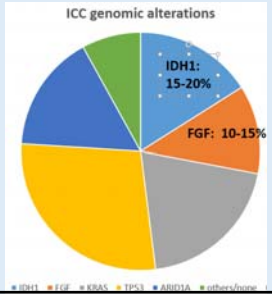
Catanecci, Lancet Oncology 2017; Shah JAMA Oncology 2017

## SOC Molecular testing and implications

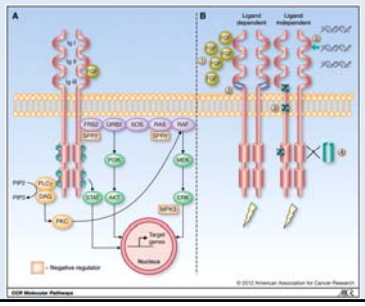
- Gastric cancer: summary
  - SOC to check Her2 amplification
  - Her2 ratio / GCN predictive of benefit
  - MET started out promising, ended up a flop
  - SOC to check MSI status
  - Everything else probably not SOC

## 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)



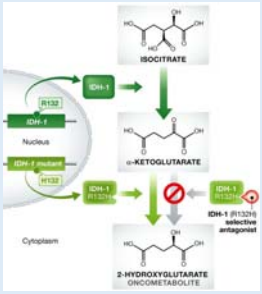

## Targeting FGF alterations in Intrahepatic CC



## 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 phosphorus (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

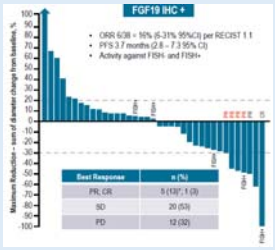
- Intrahepatic cholangiocarcinoma
  - Multiple phase 2 trials evaluating role of FGFR inhibitors
  - Phase 3 trial evaluating role of IDH-1 inhibition with AG-120 (ClarIDHy)
  - ? Potentially move it up to first-line setting
    - avoid chemotherapy
    - lag time for NGS results
    - add-on —> toxicity

## 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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  - MSI

## 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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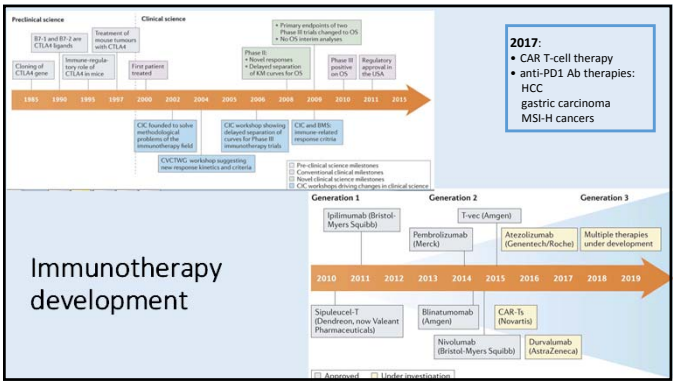
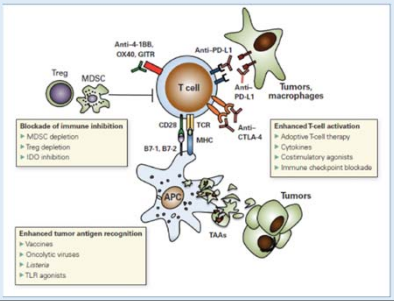
## Immunotherapy development



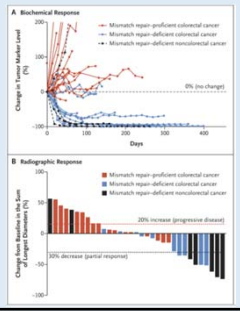

**2017**:
- CAR T-cell therapy
- anti-PD1 Ab therapies:
  HCC
  gastric carcinoma
  MSI-H cancers

## 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

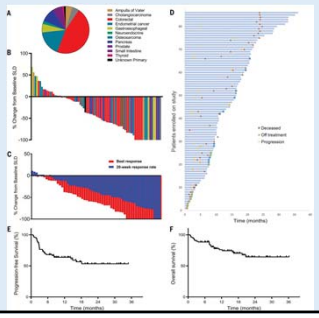
## Immunotherapy: MSI-H ("tissue agnostic")

**FDA Announcement**

Release Date: May 22, 2017
Announcement: FDA approves first cancer treatment for any solid tumor with a specific genetic feature

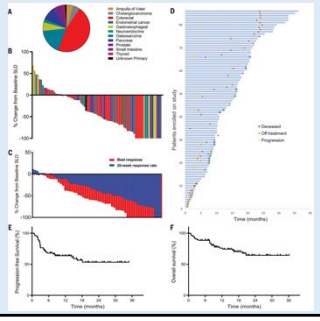
- 5 uncontrolled single arm trials
- 149 patients
- RR 40%
- response duration - 78% responses > 6 months

## Immunotherapy: MSI-H ("tissue agnostic")



Le Science 2017

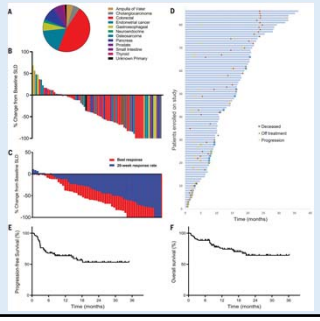
## Immunotherapy: MSI-H ("tissue agnostic")



***Who to test?***

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

## Immunotherapy: MSI-H ("tissue agnostic")

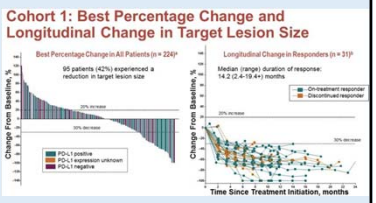


***Who to test?***

- 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

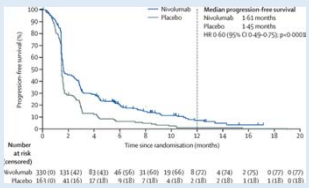
## Immunotherapy: gastroesophageal cancer

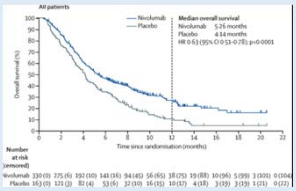
**FDA grants accelerated approval to pembrolizumab for advanced gastric cancer**

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

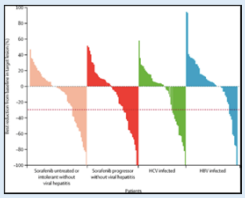



Kang Lancet 2017

## 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

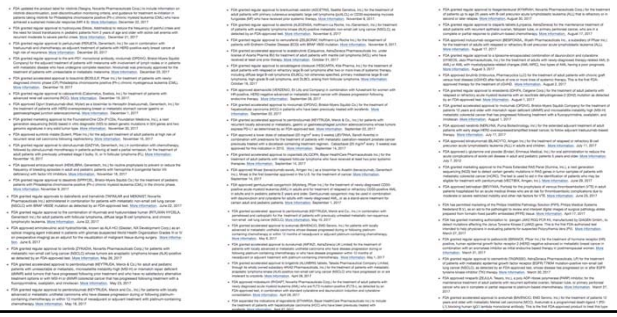
Vyxeos (daunorubicin and cytarabine) ; Jazz Pharma; For the treatment of newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes, Approved August 2017

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



## Genomic profiling and immunotherapies: HCI trials

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

*fin*