Kicking the Tires:
Biomarker Testing in Stomach Cancer

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CURING STOMACH CANCER

HARVARD MEDICAL SCHOOL

Disclosures

- Consulting/Advisory: Eli Lilly, Merck, Bristol Myers Squibb, Foundation Medicine Inc., Natera, Pieris
- Stock/Equity: Turning Point Therapeutics
- Other: Patriots fan (YES, even this year)
- Medical Advisory Board: Debbie's Dream Foundation, Hope for Stomach Cancer

Overview

- Background on molecular testing: How, why, questions to ask your doctor
- Current biomarker testing: what you need to know about your tumor and why
- Emerging targets: EBV, CLDN18.2, FGFR2b, Refining HER2
- The future: Sequence, Treat, Repeat

A Brief Overview of DNA, RNA, and Proteins

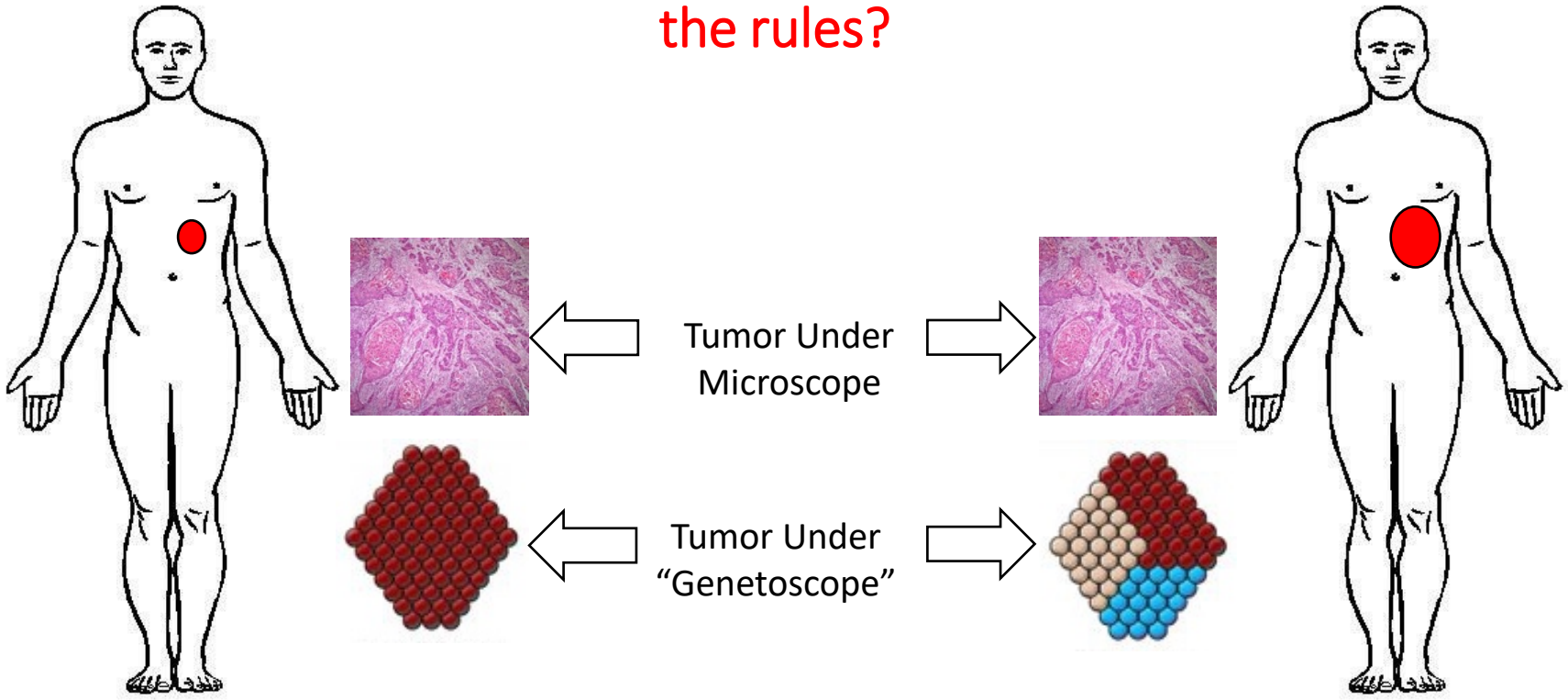
Cancer is the end result of cumulative influence from environmental risk factors, innate host features, and acquired errors in the genome

From the Clinic to the Bench to the Clinic

RESPONDER

NON-RESPONDER

Why don't both tumors follow the rules?



NO CCNE1 amplification, EGFR amplified population

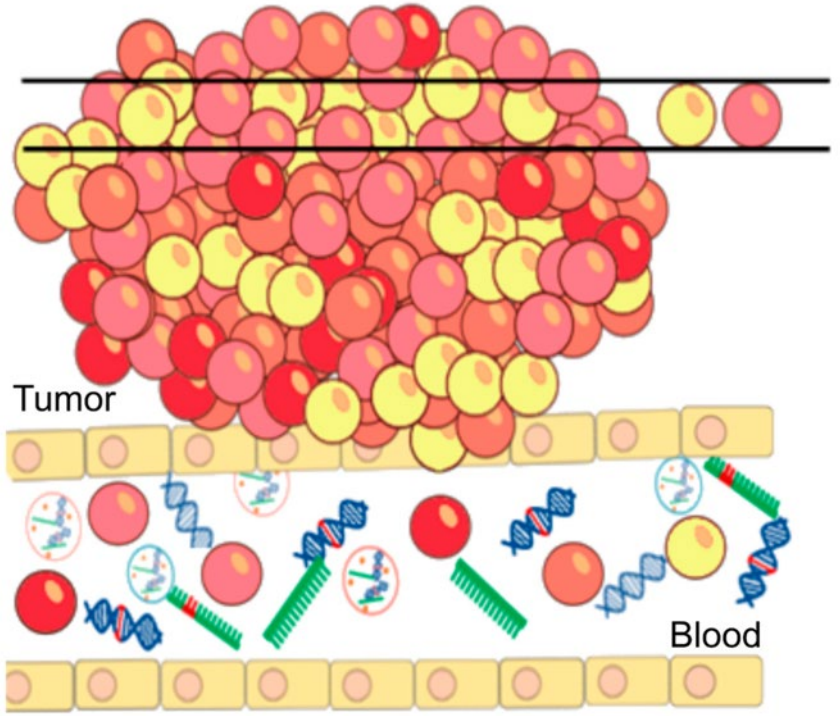
CCNE1 amplified population, some cells lost Her2, EGFR co-amplification etc

Types of Molecular Profiling Used in Stomach Cancer

- Tissue based – “DNA sequencing”, “Genomic Profilng”, etc.
  - Larger panel of genes examined (150-500)
  - Requires biopsy or surgical sample
  - Only examines the changes occurring in the biopsy area
  - 2-4 week turnaround for results
  - Still “gold standard” for biomarker testing

- Blood based – “Liquid biopsy”, “circulating tumor DNA (ctDNA)”
  - Smaller panel of genes (50-80), but getting better
  - 1-2 tubes of blood
  - Reflects tumor makeup more broadly
  - 7-14 day turnaround

- Germline – “Genetic testing”
  - Blood or normal tissue (saliva, cheek swab)
  - Examines normal cell DNA for changes all cells have
  - Used to test for changes you were inherited and influence cancer risk
  - Often used as comparator for tumor testing



Definitions and Concepts

Current Standard Molecular Testing: The Bare Minimum

- **HER2 (ERBB2):** All stage IV patients at diagnosis. Testing is positive in 12-20% of patients. Associated with benefit from trastuzumab (Herceptin)

- **PD-L1:** All stage IV patients at diagnosis. Positive to varying degrees in 50-70% of patients. Associated with benefit from immune checkpoint inhibitors like pembrolizumab and nivolumab (Keytruda and Opdivo)

- **MMR or MSI testing:** All stage IV patients at diagnosis, favor for all stage II-III at diagnosis. Positive in 3-5% of stage IV and 10-20% stage II-III. Associated with even greater benefit from immune checkpoint inhibitors like pembrolizumab (Keytruda). Also predicts lack of benefit from chemo in stage II-III.

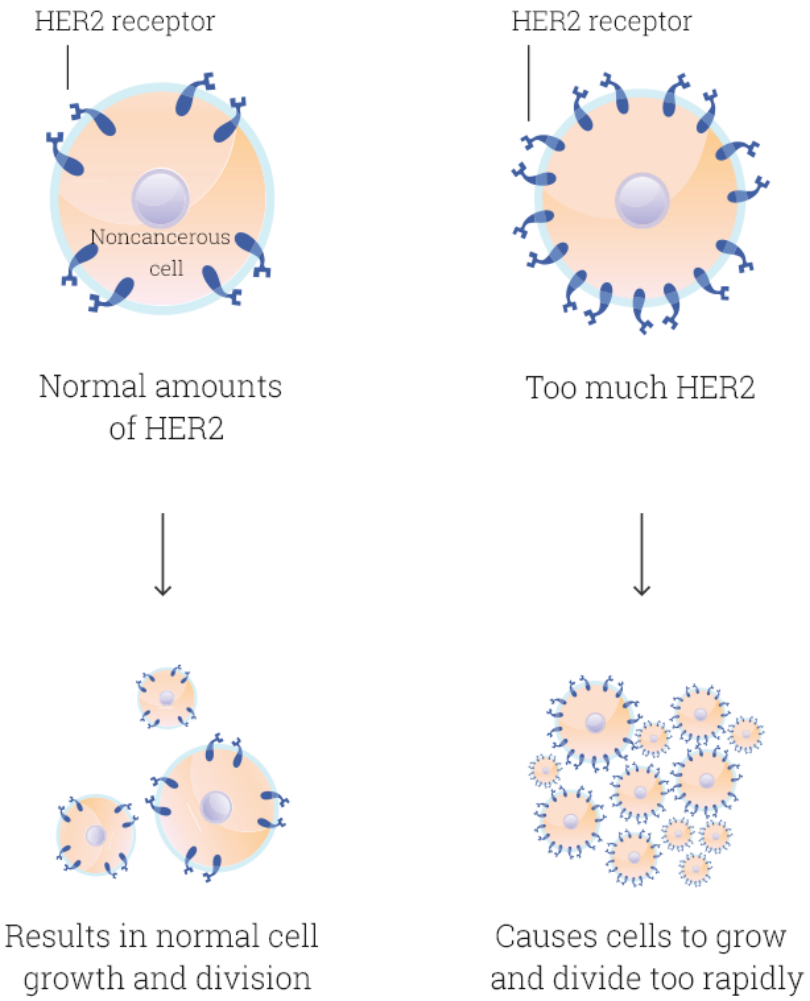
Questions for Your Care Team

1. What are the biomarker results for my tumor?
2. Should we consider more extended tumor testing?
3. Should we consider genetic testing?
4. Is there a role for liquid biopsy?

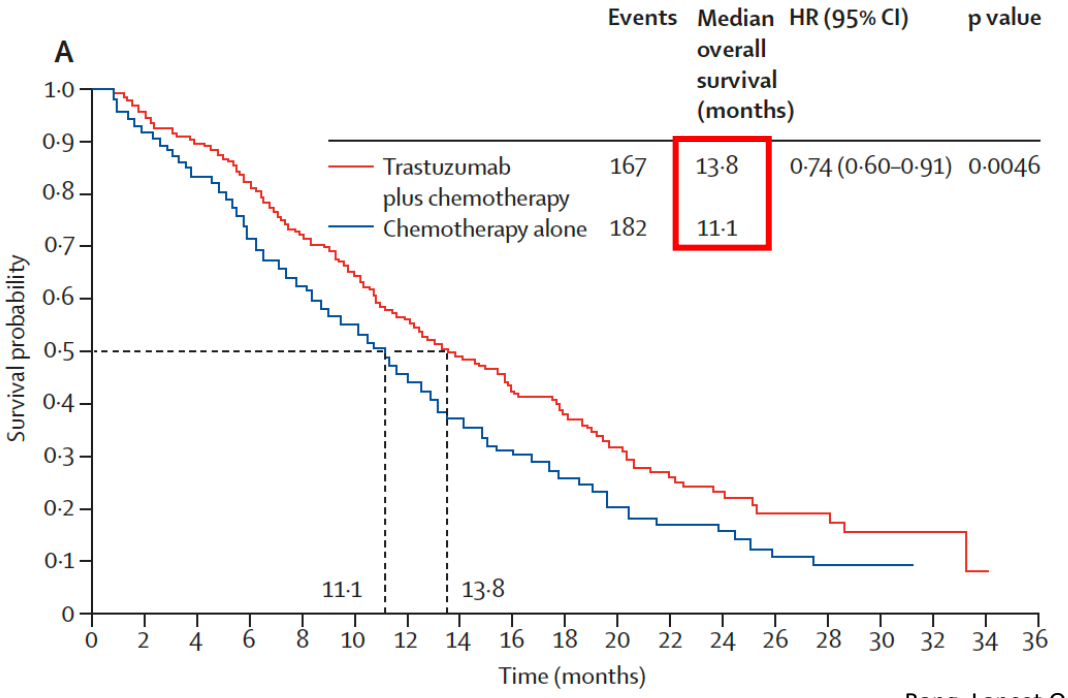
PART II: CURRENT TARGETS

The Economist, 6/7/2007

HER2 Testing and Trastuzumab Benefit



Too much HER2 can be tested by looking at the protein and/or the number of gene copies

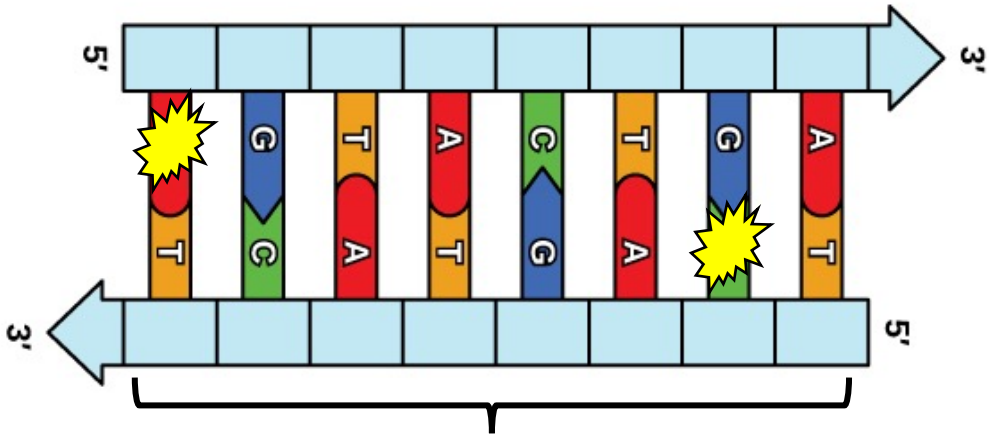


Bang, Lancet Oncol 2014

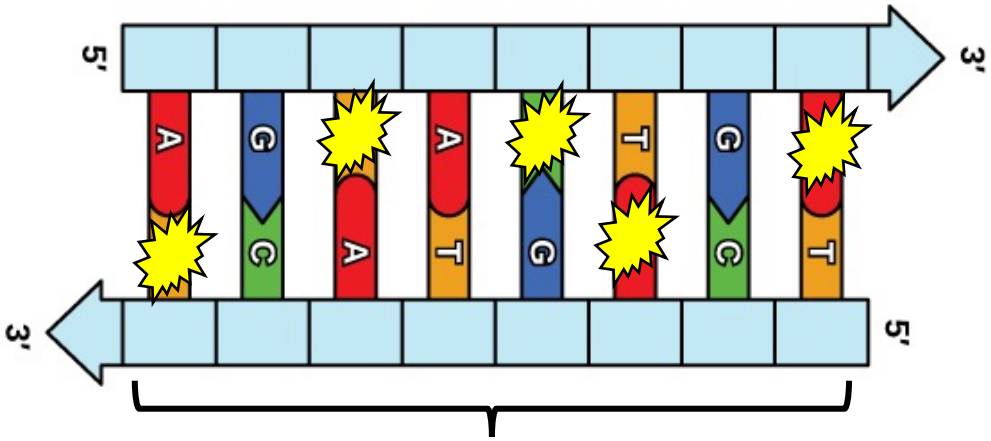
- **Drug approval is linked to biomarker testing**
- **Addition of biologic drug trastuzumab improved survival**
- **Response rates improved from 35 to 47% with addition of trastuzumab**
- **Adding <3 months of life not good enough**

MMR/MSI in Stage IV and Immunotherapy Benefit

MSI-Low Stomach Cancer



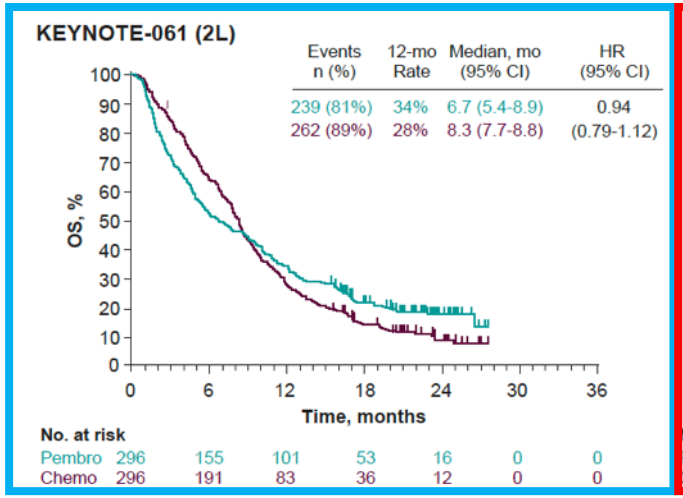
MSI-High Stomach Cancer

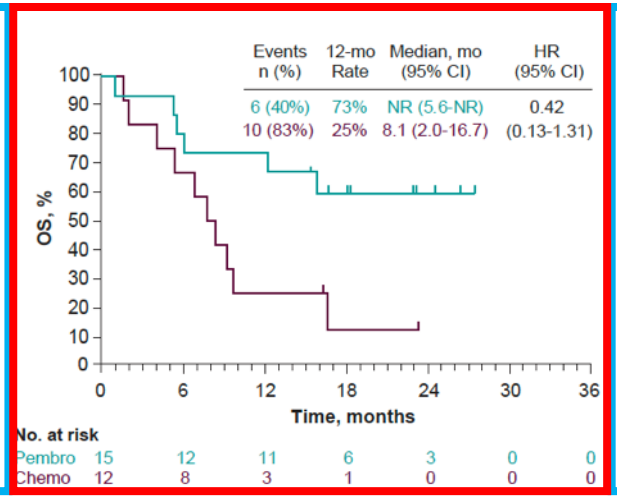


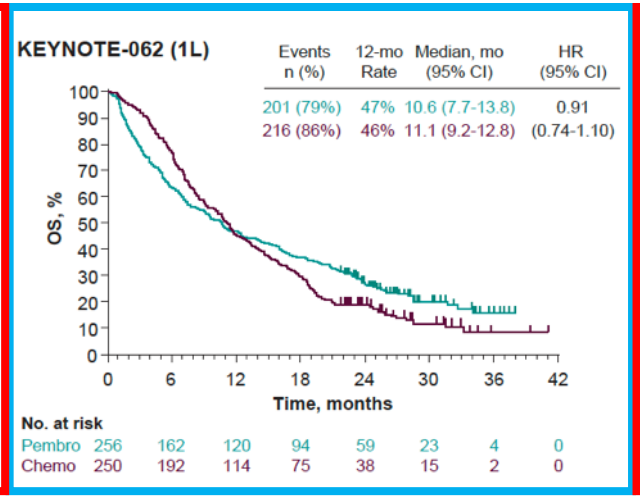
Trial	Drug	MSI - High Response	MSI-Low Response	DOR
KN-059	Pembro	57%	9%	NR vs 8.4
Nature Med	Pembro	86%	~17%	-
KN-061	Pembro	47%	<20%	NR vs -

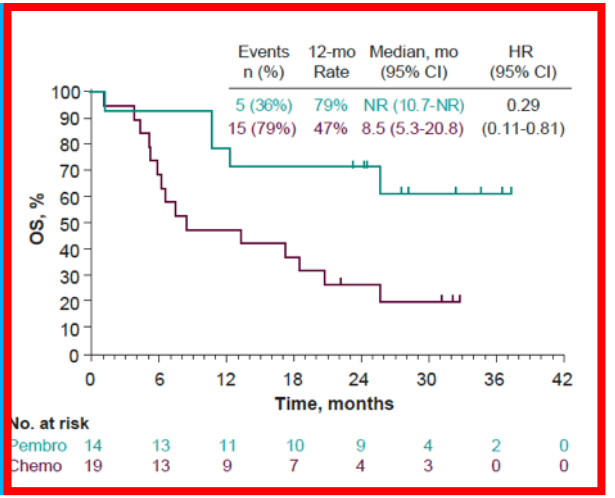
- Biomarker testing linked to drug access
- Biomarker able to identify subgroup (3-5%) of stage IV gastric cancer patient more likely to benefit from immune therapy
- Standard testing from protein or PCR sequencing
- Can also be tested from blood or by broader genomic profiling

Immunotherapy Effective Across Treatment Lines in MSI-H





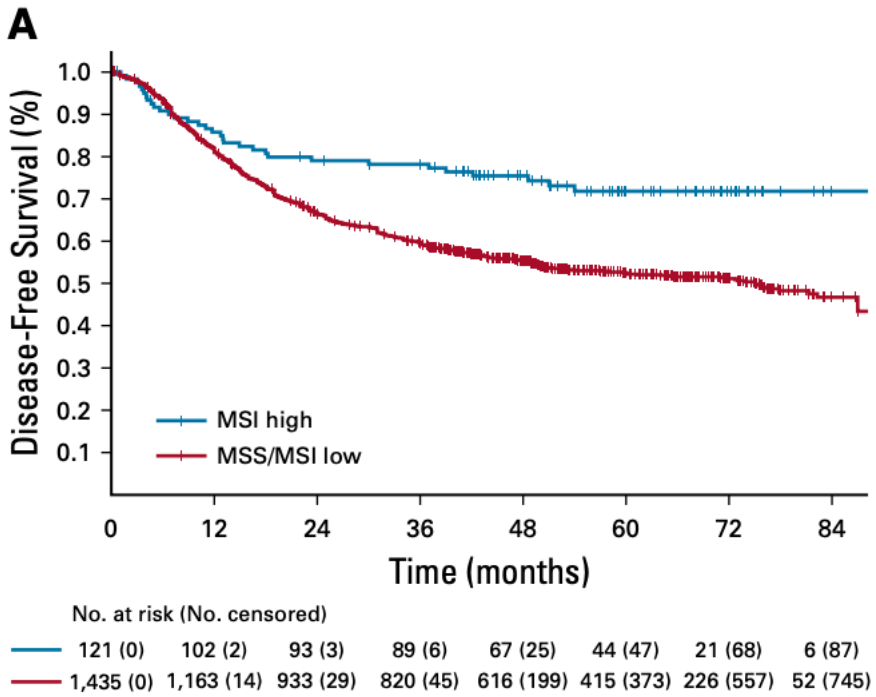


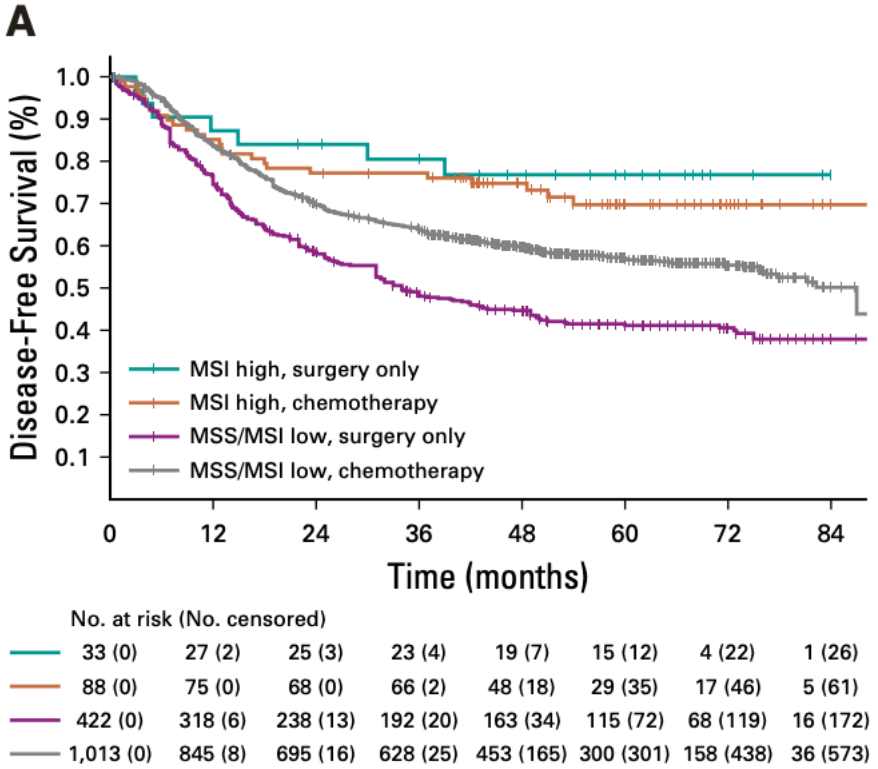


Response	KEYNOTE-059 (3L+)	KEYNOTE-061 (2L)		KEYNOTE-062 (1L)	
	Pembro n = 7	Pembro n = 15	Chemo n = 12	Pembro n = 14	Chemo n = 19
ORR, n (%)	4 (57)	7 (47)	2 (17)	8 (57)	7 (37)
Median DOR, mo (range)	Not reached (20.0+ to 26.8+)	Not reached (5.5 to 26.0+)	Not reached (2.2+ to 12.2+)	21.2 (1.4+ to 33.6+)	7.0 (2.0 to 30.4+)

- MSI-H or dMMR is strongly associated with improved outcomes with immune checkpoint inhibitor therapy
- Activity is independent of the line of therapy
- Stomach cancer patients NEED to know this about their cancer

MSI Testing Needs to Be Considered Earlier

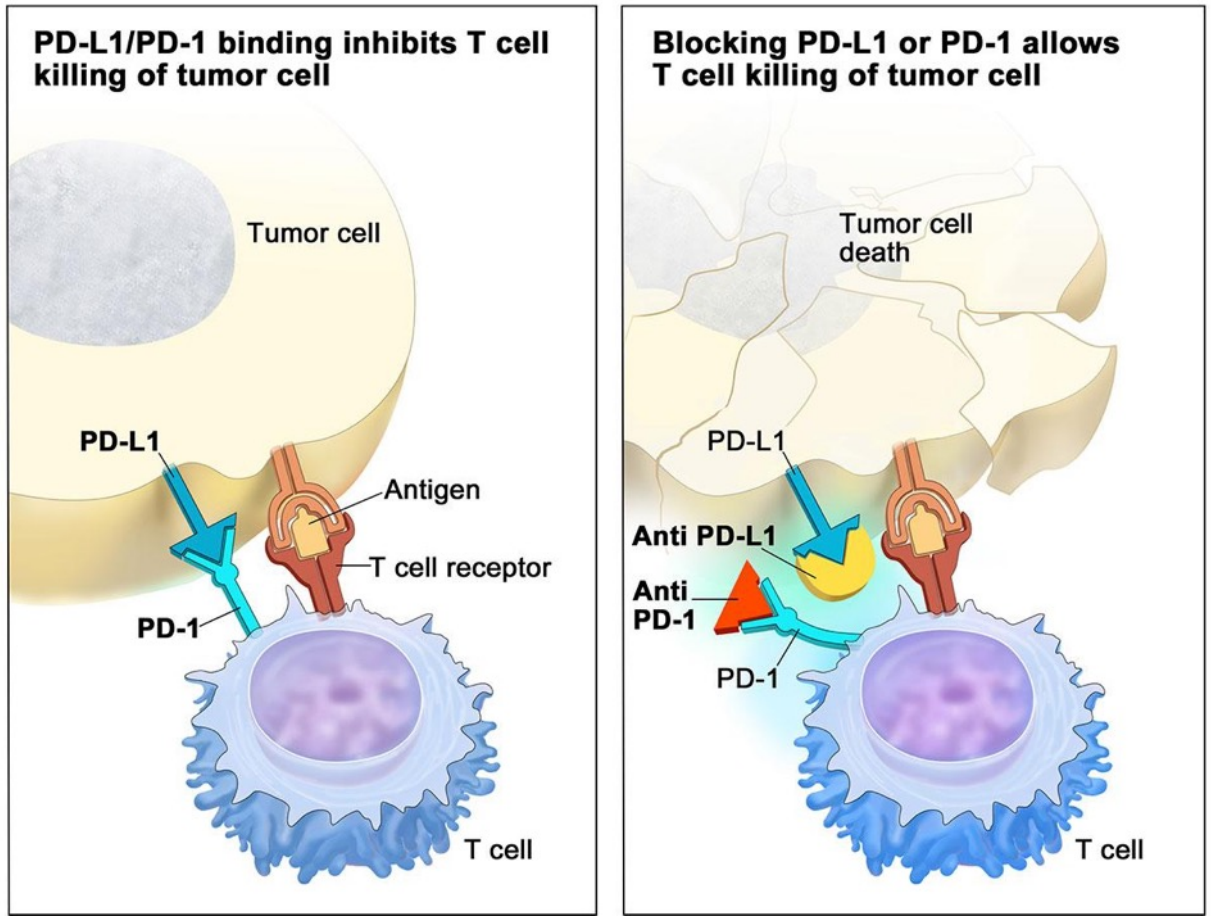




- Patients with locoregional disease who are MSI-High have longer disease-free duration than patients who are MSS/MSI-low
- Patients with MSI-H tumors may not get any benefit, and could be harmed, with our standard chemotherapy-based approaches
- Anywhere from 8-20% of non-metastatic gastric cancers are reported to be MSI-H

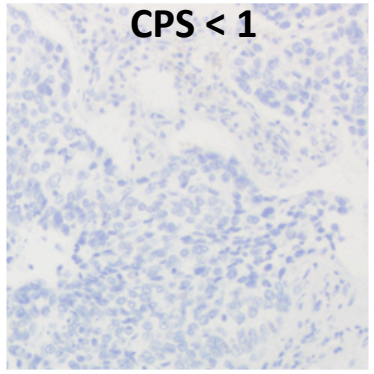
JCO 2019;37:epub

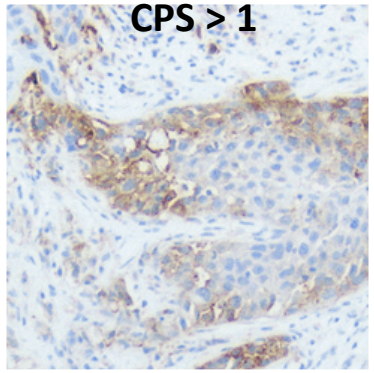
A Word on PD-L1

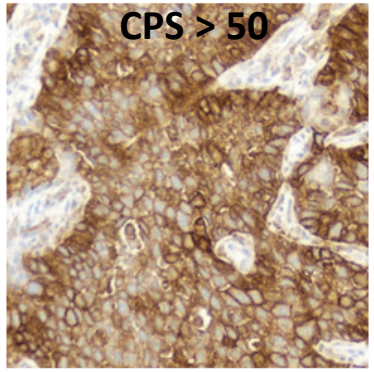


Credit: NCI/Terese Winslow

- Tumor cells have evolved ways to avoid being killed by our immune system
- One common way is using a stop signal called PD-L1

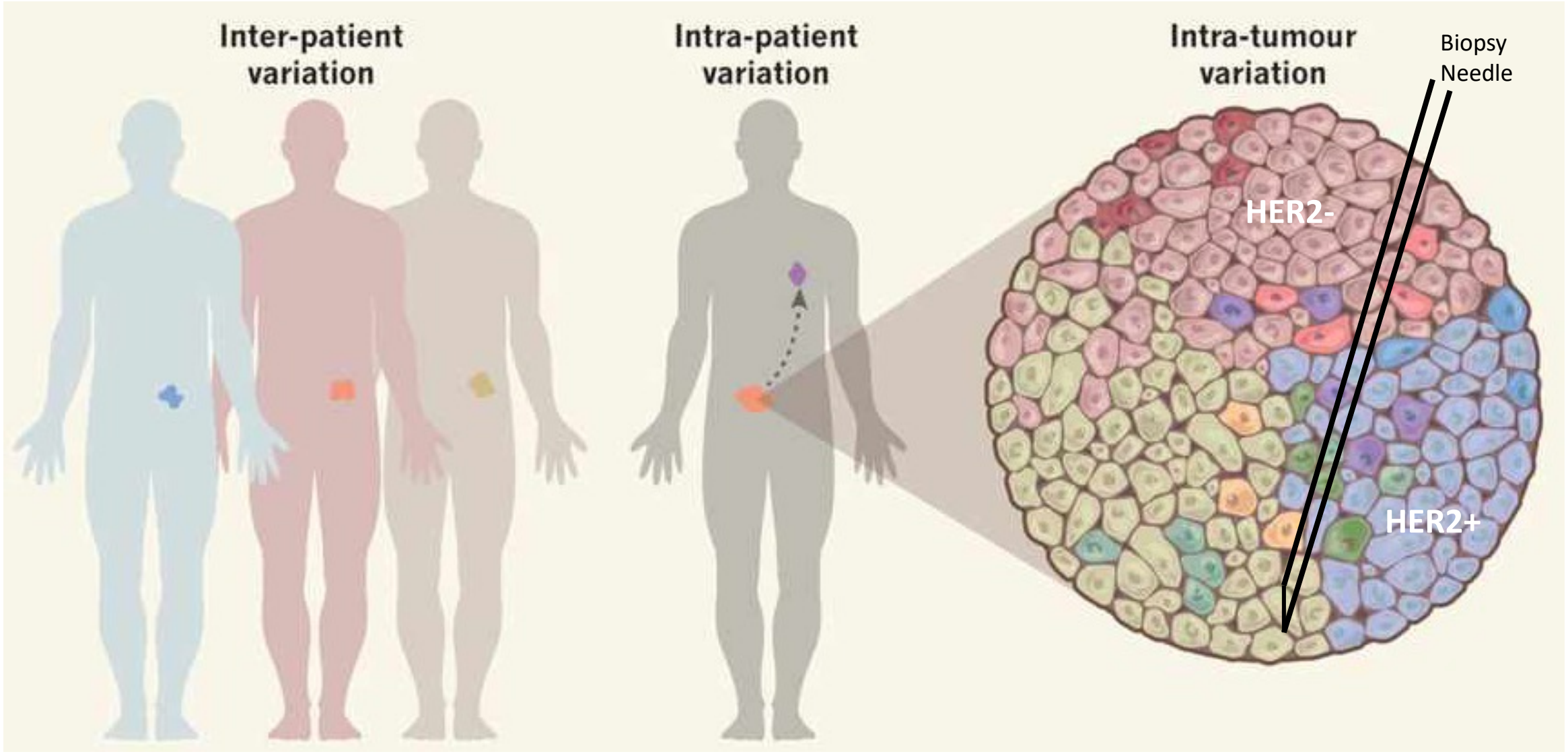






- Tested from a biopsy sample
- A protein test that is widely available
- Between 50-75% of stomach cancers test positive
- Degree of positive may be related to chance of benefit
- Positive test linked to drug access in stomach, GEJ and esophageal cancer in the US
- Result may change over time, sometimes need to consider repeat biopsy

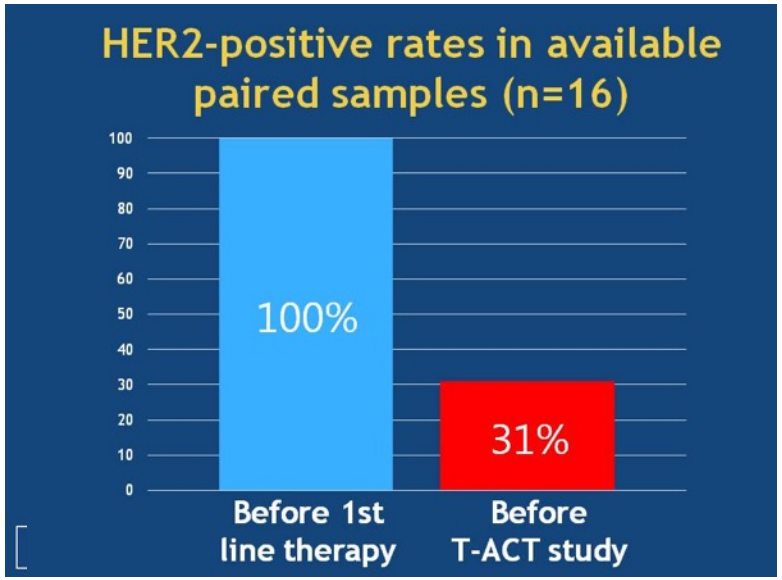
Heterogeneity and Biomarker Testing



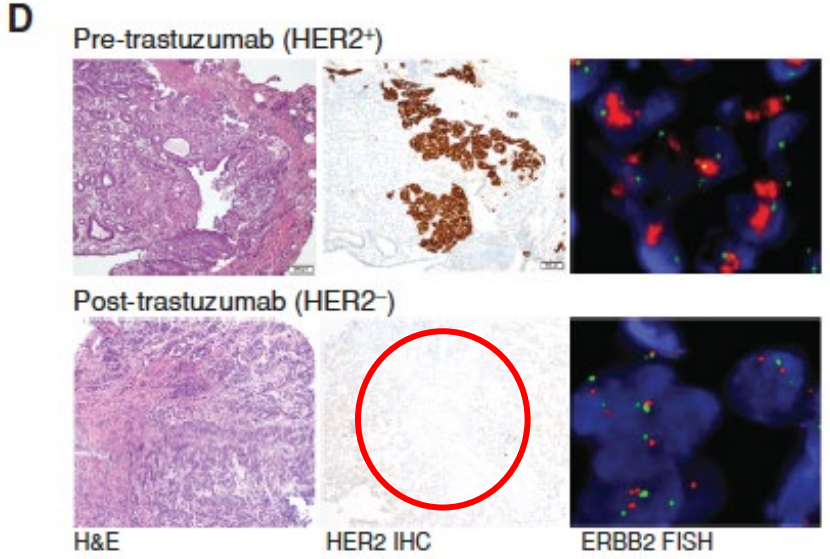
Nature 2014;512:143-144

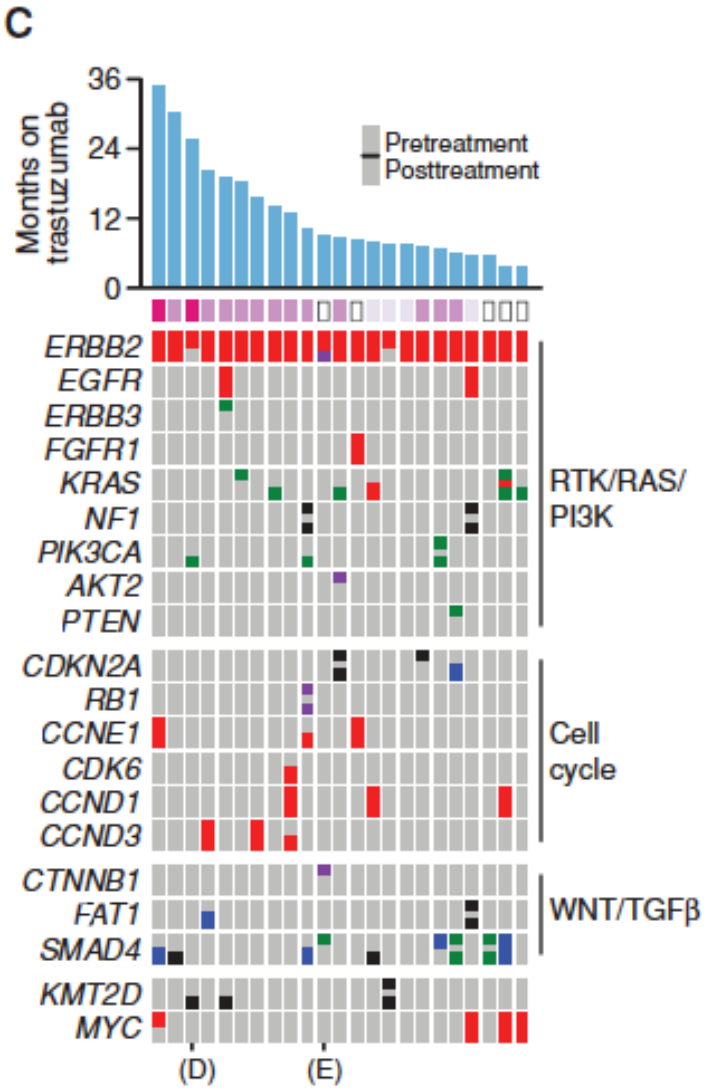
Biomarker Changes May Impact Treatment Outcomes

- **HER2 testing results vary in time and space**
- **HER2 positive tumors can evolve over time**
- **We should consider repeat biopsy and testing in patients who progress, especially on targeted therapies**



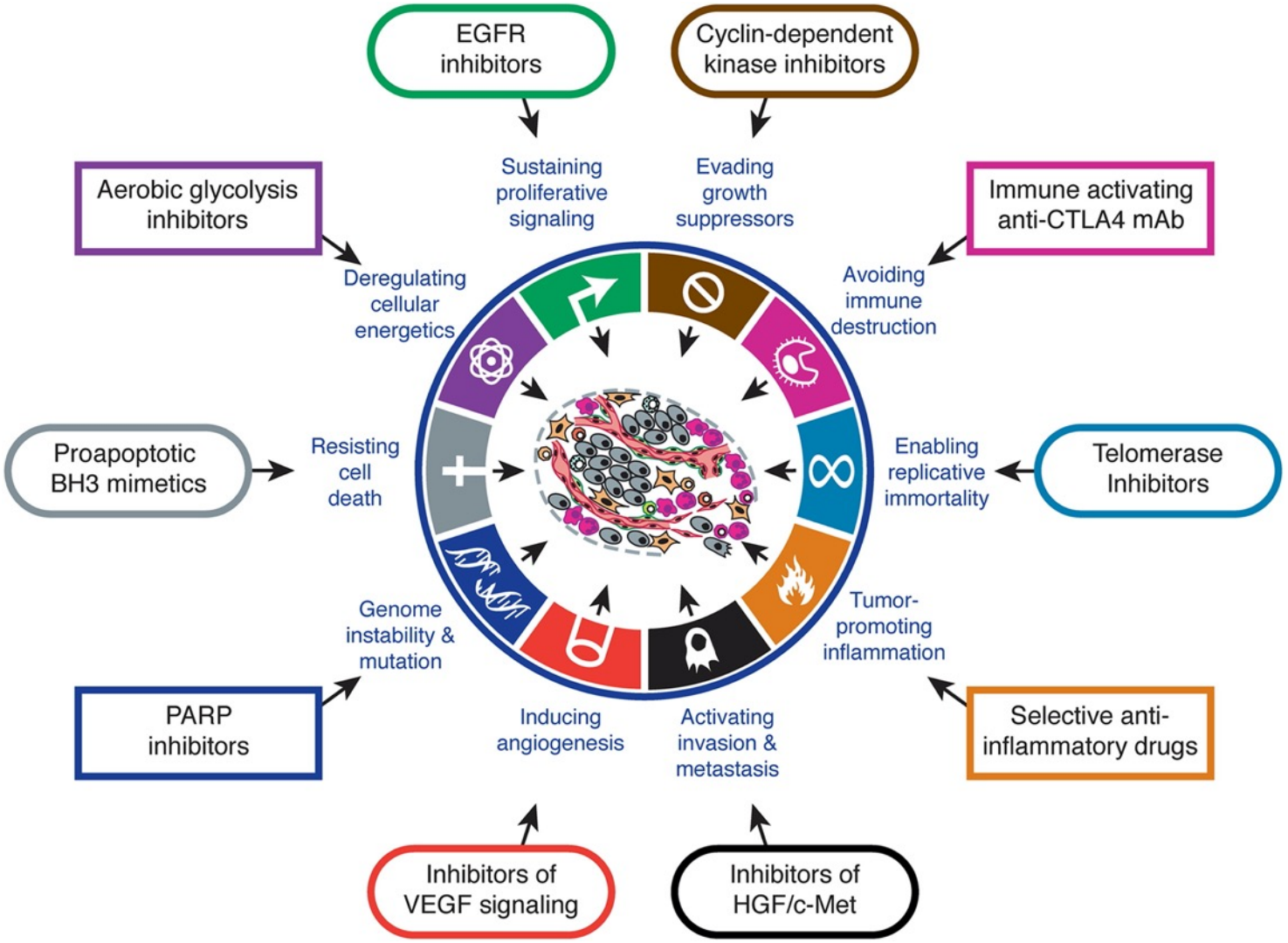
Makiyama et al., phase II T-ACT trial, ASCO 2018





Janjigian YY et al., Cancer Discovery 2017

PART III: EMERGING TARGETS

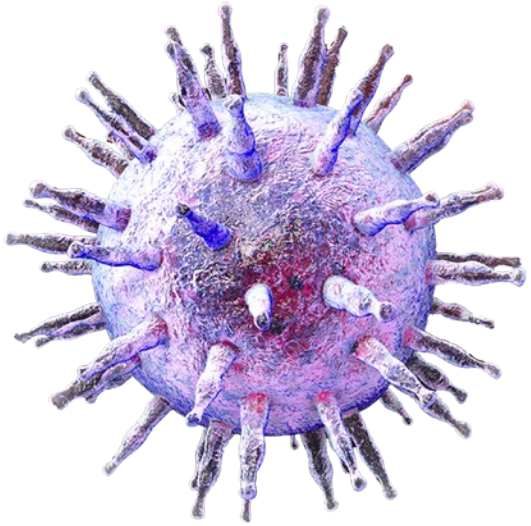


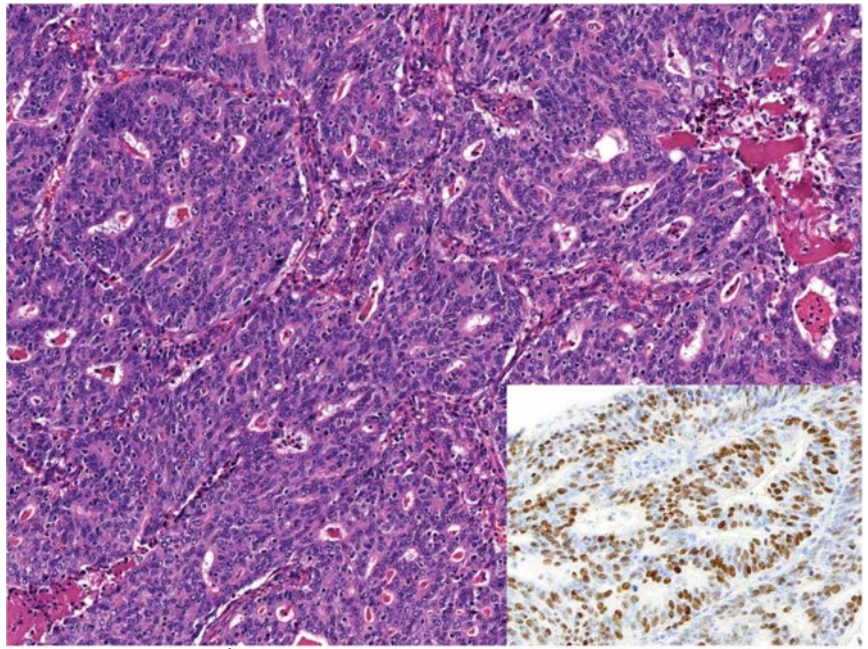
Cell 2011;144:646-674

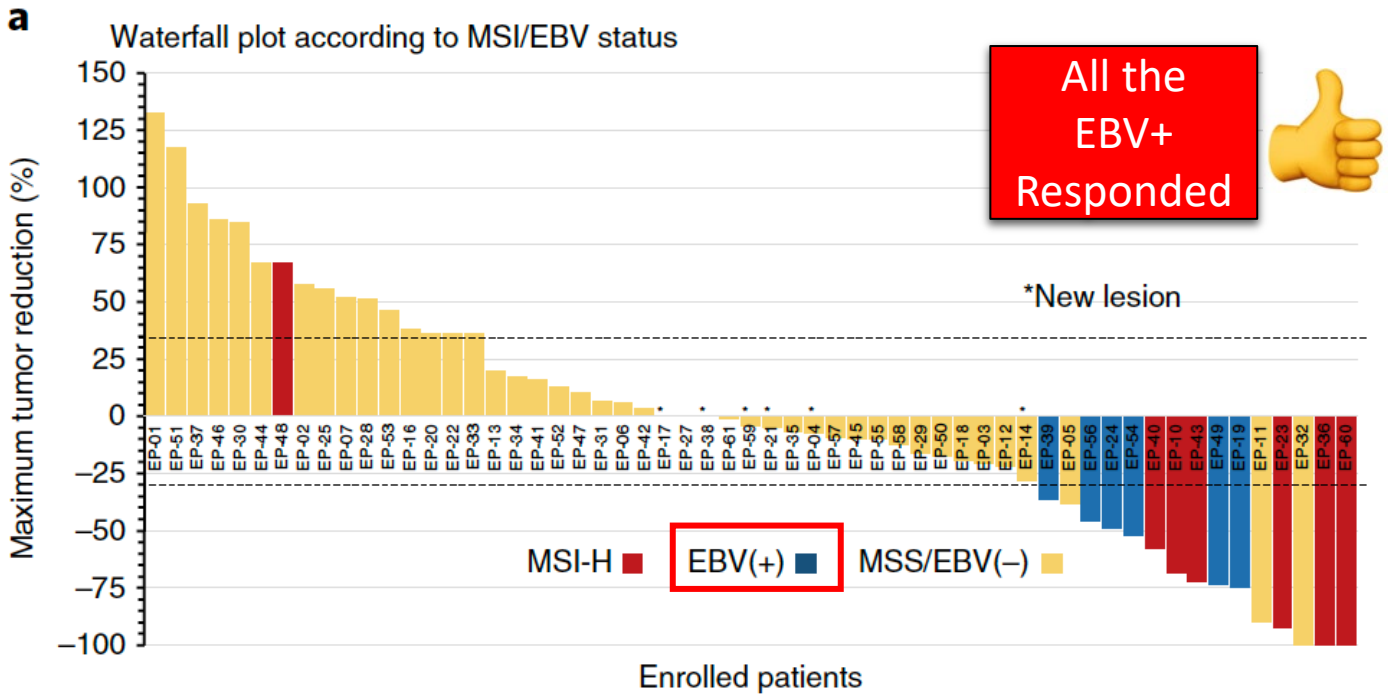
Emerging Targets and Biomarkers

- EBV
- FGFR2
- CLDN18.2
- Revisiting HER2

EBV: Connecting a Virus to Some Stomach Cancers





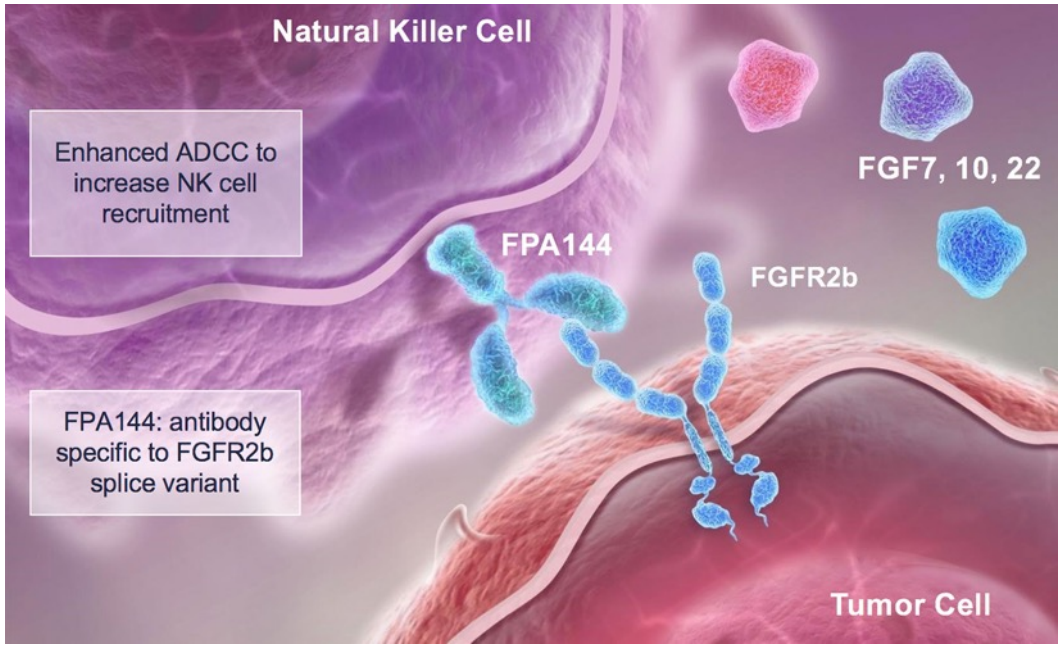


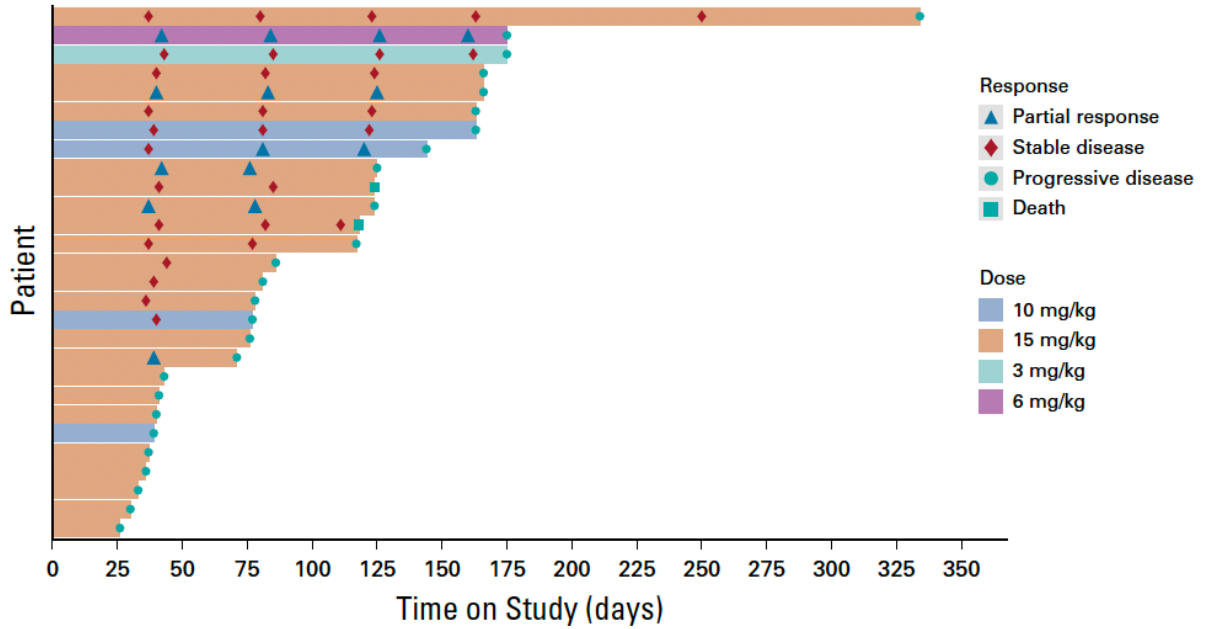
- One of the most common human viruses, majority are infected at some point
- Up to 8-11% of stomach cancers are associated with EBV
- Relatively straightforward testing available in many pathology labs
- Associated with increased response to immune therapies

Kim S, Nature Medicine, 2018

FGFR2: A Target with a Mixed Record

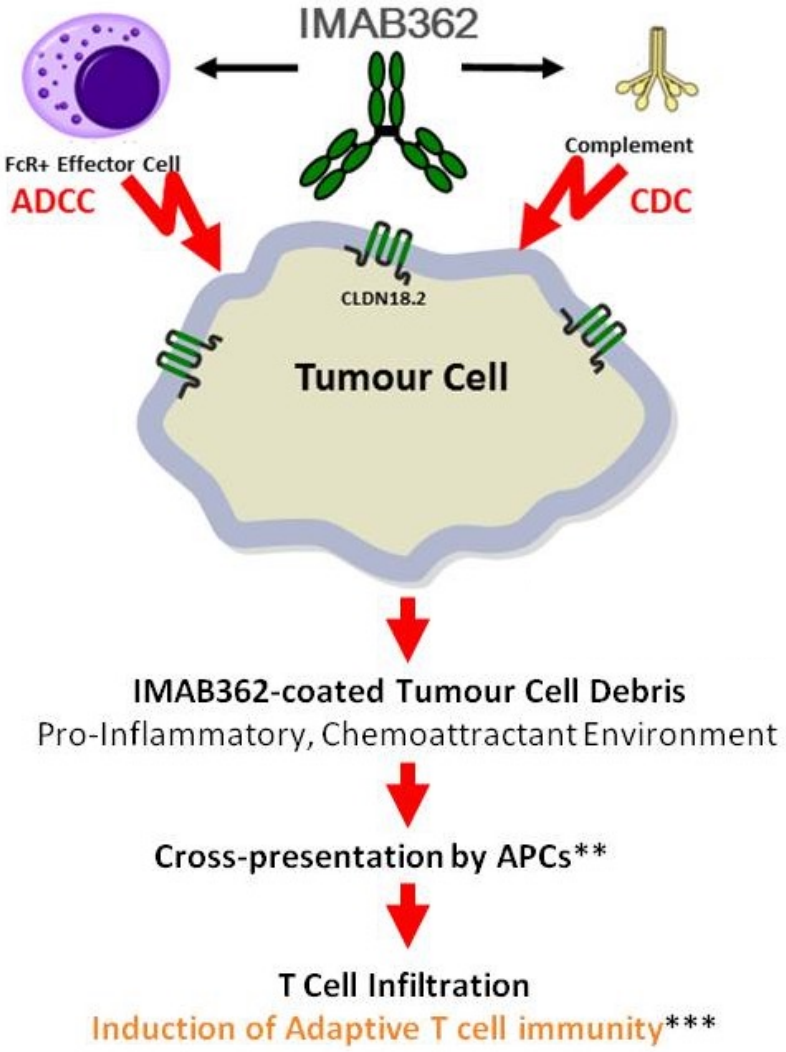
- FGFR2b is overexpressed in up to 30% of non-HER2+ gastroesophageal cancers
- Bemarituzumab is a non-chemo antibody that blocks FGFR2b on cancer cells
- Recent positive phase II data in combination with 1L FOLFOX chemo
- Not yet captured with standard testing, but FGFR2 amplification is



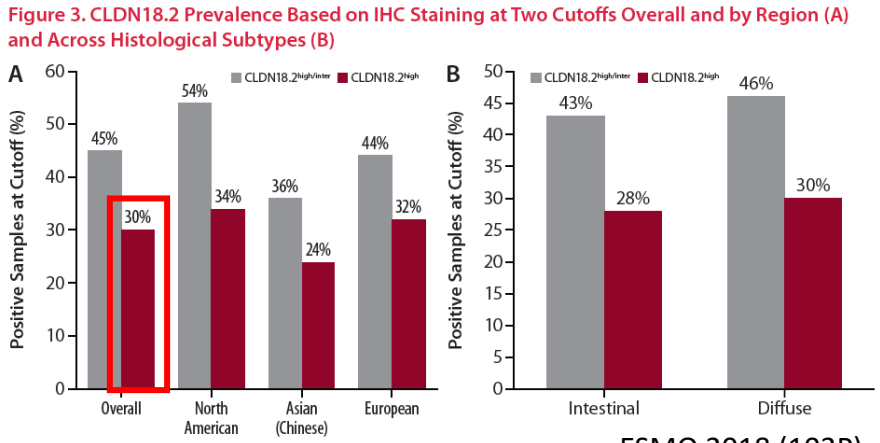


Catenacci et al., JCO 2020

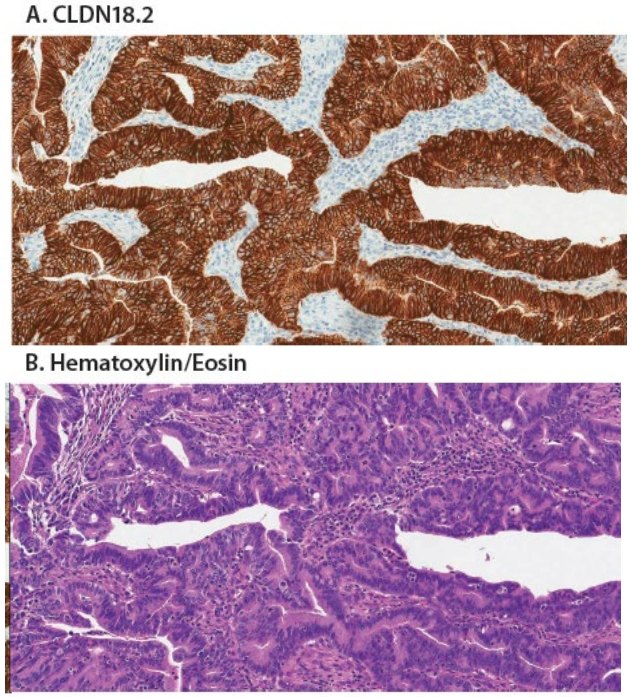
CLDN18.2: Targeting the Ties that Bind



Al-Batran, ASCO 2016 (LBA4001)



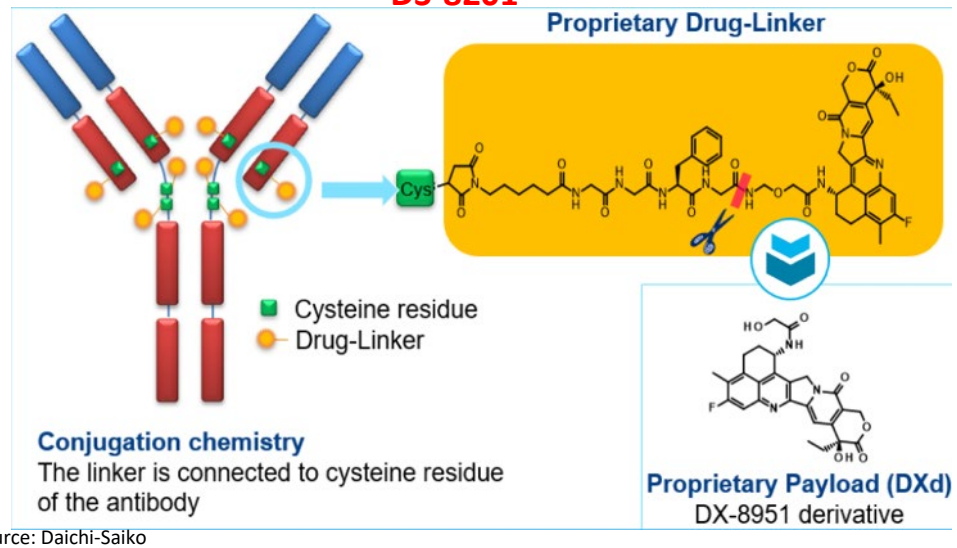
ESMO 2018 (103P)



- Claudin 18.2 (CLDN18.2) protein involved in holding cells closely together
- Overexpressed (>= 75%) in roughly 1/3 patients
- Need to be tested through clinical trial, not standard testing
- Targeted by non-chemo antibody, Zolbetuximab
- Being studied in phase III with chemotherapy (SPOTLIGHT trial)

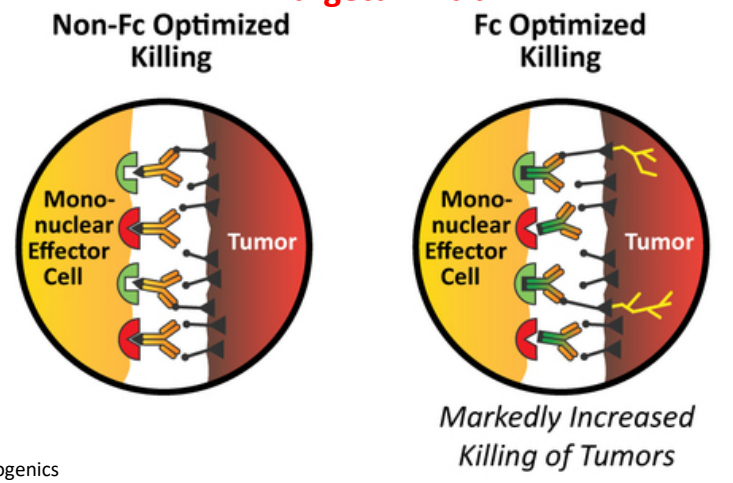
Revisiting HER2: Never Settle

DS-8201



Source: Daichi-Saiko

Margetuximab



Source: Macrogenics

DS-8201 after trastuzumab in gastric cancer

	Total evaluable, n=44	Previously irinotecan treated (post-hoc analysis), n=24
Confirmed objective response, n (%; 95% CI)	19 (43·2%; 28·3–59·0)	10 (41·7%; 22·1–63·4)
Confirmed disease control, n (%; 95% CI)*	35 (79·5%; 64·7–90·2)	19 (79·2%; 57·8–92·9)
Time to response, months†		
n	21‡	12
Median (95% CI)	1·4 (1·3–1·6)	1·5 (1·2–2·6)
Duration of response, months§		
n	21‡	12
Median (95% CI)	7·0 (4·4–16·6)	6·9 (2·9–12·2)
Range	1·4–23·5¶	1·4–12·2
Progression-free survival, months		
Events	30 (68%)	18 (75%)
Median (95% CI)	5·6 (3·0–8·3)	4·1 (2·4–8·3)
Range	1·2–24·6¶	1·2–13·7

Lancet Oncol 2019;20:827-836

Margetuximab + Pembrolizumab after trastuzumab

Efficacy Results in Gastric Cancer Population by Biomarker Expression

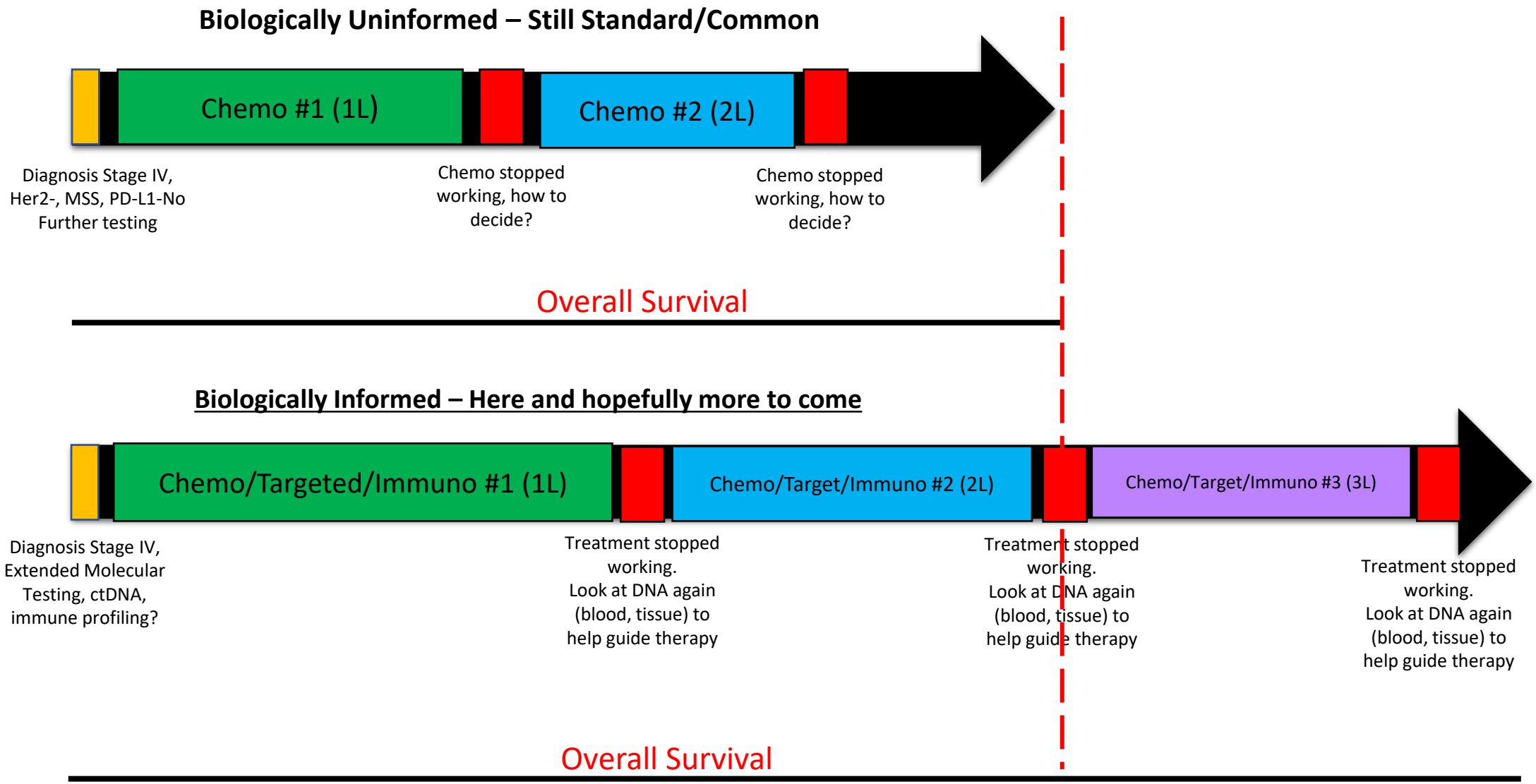
	n	ORR	DCR	mPFS	mOS
Total	61	29.5% (18/61)	65.6% (40/61)	4.07 (2.30, 5.45)	14.62 (9.07, NR)
IHC3+	**55**	**32.7% (18/55)**	**69.1% (38/55)**	**4.70 (2.66, 7.49)**	**NR (12.48, NR)**
ERBB2^{amp}	35	40.0% (14/35)	77.1% (27/35)	4.76 (2.69, 7.59)	14.62 (8.41, NR)
PDL1+	26	46.2% (12/26)	80.8% (21/26)	4.14 (2.60, 7.59)	NR (6.74, NR)
IHC3+/ PDL1+	**23**	**52.2% (12/23)**	**82.6% (12/23)**	**4.14 (2.60, 15.54)**	**NR (6.74, NR)**

ORR=Objective Response Rate; DCR=Disease Control Rate=CR/PR/SD; mPFS=Median Progression Free Survival; mOS=Median Overall Survival

ASCO GI 2019, Abstr #65

- Prior attempts to continue HER2 targeting have failed
- Both DS-8201a (Enhertu) is now approved in Japan, review in US
- Margetuximab being studied with immunotherapy and chemotherapy
- Highlights importance of biomarker selection, and repeat testing after trastuzumab
- Patients on trastuzumab should explore options and care teams plan for future lines

The Future – Serial Testing to Capture Tumor Changes and Adapt Treatment



Adding it All Together: It's Always About Food

1. **You need to know your tumor**
2. **You need to know your tumor**
3. Biomarkers testing can be done from biopsy, blood, or both, discuss with your care team
4. Standard biomarker testing in advanced disease is HER2, MSI/MMR, and PD-L1 at the minimum
5. All advanced patients should discuss more extended testing (my opinion)
6. Repeat biomarker testing should be a discussion at key treatment decision time points. People and tumors can change
7. Clinical trials and collaborative research are the mechanisms to improve survival

Where to Learn More

- Your care team, each other. Ask the questions
- Debbie's Dream Foundation – and other events like this
- NCCN – excellent patient guide, available in Spanish, Korean, Russian, Japanese, Italian, Mandarin
- Count Me In Project – excellent opportunity to participate in research, free at https://escproject.org/home
- Andrea Eidelman (DDF CEO) – here is her cell, 954-STO-MACH

Contact Information

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