Unmet Needs in GI Cancers

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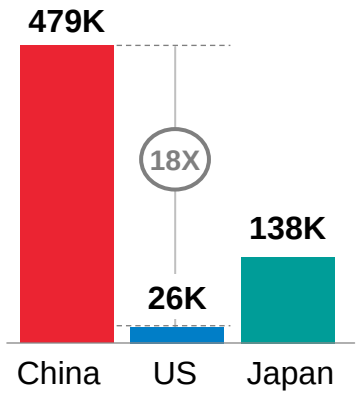
zai lab

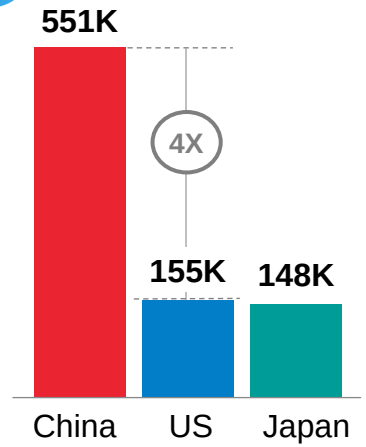
China Has World's Highest Prevalence of GI Malignancies with Extremely Poor Prognosis

New Cases of GI Cancers Significantly Higher vs. US/Japan[1]

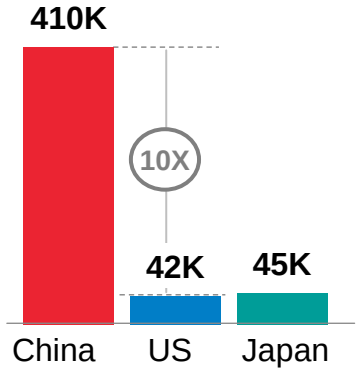
Gastric Cancer



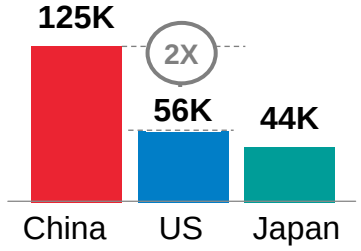
Colorectal Cancer



Liver Cancer

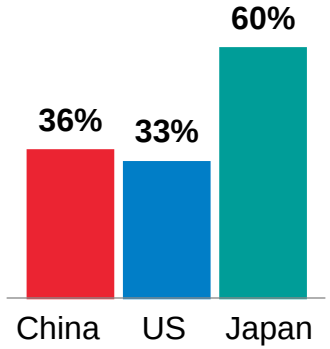


Pancreatic Cancer

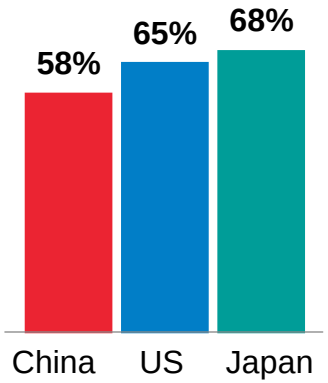


Five-Year Survival (%) (2010–2014)[2]

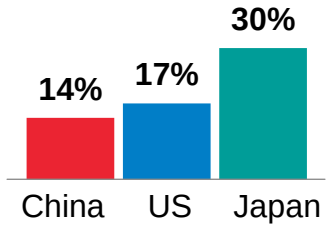
Gastric Cancer



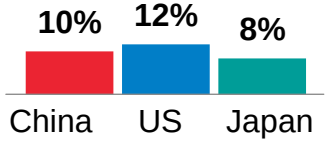
Colorectal Cancer



Liver Cancer



Pancreatic Cancer

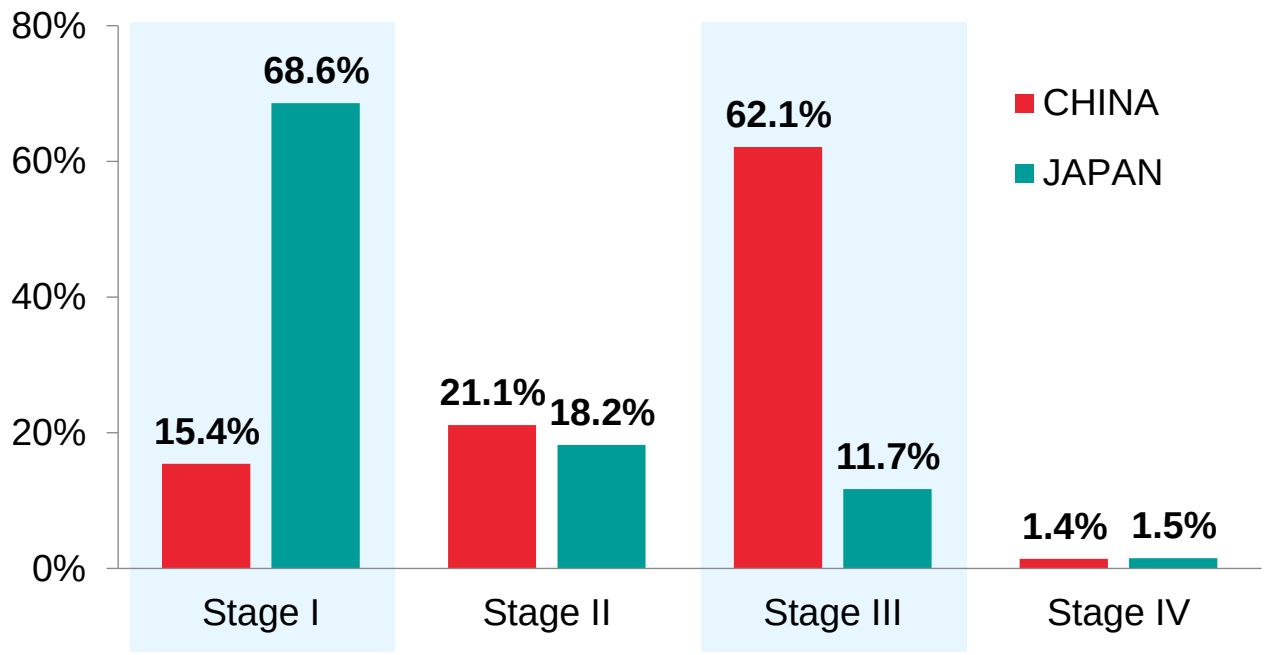


Source: (1) GLOBOCAN 2020; (2) Allemani, C., et al. Lancet, 2018.

Gastric Cancer
Significant Burden for China with High Mortality and Late Diagnosis

- **3rd largest** cancer in China, in terms of both incidence rate and mortality rate
  - Unhealthy dietary habits
  - High incidence of H. pylori infection
  - Smoking
- **Lower rate of early diagnosis** in China vs. Japan
- **Lower rate of gastroscope** in China vs. Japan
- Huge disease burden of advanced gastric cancer patients in China

60–70% of Patients Diagnosed at Advanced Stage with Poor Prognosis[1]



For advanced/metastatic gastric cancer:

- **5%~20%** 5-year survival rate
- mOS of approx. **one year**

Source: (1) Liu D, et al. Yonago Acta Medica 2019.

Compared to US, China Has Limited Effective Therapies Approved in Metastatic Gastric Cancer

Metastatic, Advanced GC/GEJ Cancers

CSCO

	HER2- 88.8%	HER2+ 11.2%
1L	chemotherapy	trastuzumab + chemotherapy
	nivolumab + chemotherapy (PD-L1 CPS≥5)[1]	chemotherapy
2L	chemotherapy	chemotherapy
		trastuzumab + chemotherapy
≥3L	apatinib	
	nivolumab	

NCCN National Comprehensive Cancer Network®

Not recommended by CSCO guidelines in China

	HER2- 77.9%	HER2+ 22.1%
1L	chemotherapy	trastuzumab + chemotherapy
	nivolumab + chemotherapy (PD-L1 CPS≥5/CPS 1-4)	trastuzumab+ pembrolizumab+ chemotherapy
2L	chemotherapy	chemotherapy
	ramucirumab (VEGFR2) ± chemotherapy	ramucirumab (VEGFR2) ± chemotherapy
	entrectinib or larotrectinib for NTRK+	fam-trastuzumab deruxtecan-nxki
≥3L	chemotherapy	

- For MSI-high/PD-L1 CPS≥1, GC/GEJ patients: pembrolizumab is recommended in recurrent setting in China, same as US; for HER2-, trastuzumab and pembrolizumab is III level recommendation in 1L in CSCO guideline

Source: Version4.2021 NCCN Guideline; 2021 CSCO Guideline (Published in July 2021); Miaozhen Qiu, et al. BMC Cancer 2014; Eric Van Cutsem, et al. Gastric Cancer 2015 Jul.

Precision Medicine in Gastric Cancer

Before

Gastric Cancer as ONE DISEASE

- Prior to 2012, chemotherapy was **only treatment** for advanced gastric cancer
- For the recent decade, HER2 is **only target** for gastric cancer

Molecular Pathology

Genomic Alterations as Therapeutic Targets[1]

Gene	Alteration	Prevalence in GC
ERRB2 (HER2)	Amplification/Overexpression	10%–20%
VEGFR2	Overexpression	~50%
VEGF	Overexpression	40%–50%
EGFR	Amplification/Overexpression	6%–27%
MET	Amplification/Overexpression	5%–40%
FGFR2	Amplification/Overexpression	4%–12%
ATM	Loss (Protein)	60%
PIK3CA	Mutation	5%–10%
CDK4/6	Amplification	6%–15%
PD-L1/L2	Amplification/Overexpression	15% of EBV-positive GC
MSI (Microsatellite Instability)	Mutation	15%–20%
ARID1A	Mutation	8%–10%

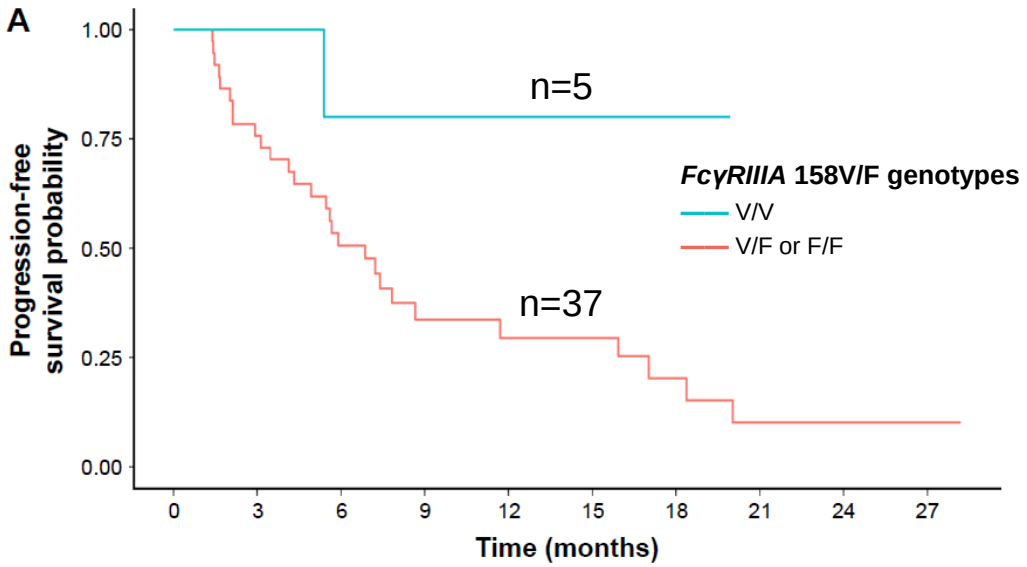
Zai Lab's current gastric cancer portfolio

Source: (1) Patrick Tan, et al. Genetics and Molecular Pathogenesis of Gastric Adenocarcinoma, Gastroenterology (2015).

Targeting FcγRIIIA (CD16A) Is Potential Strategy to Improve Treatment Outcome of HER2+ Cancer Patients

PFS Analysis by CD16A Genotype[1]

- Retrospective study examined 42 Her2-positive patients receiving fluorouracil and platinum-based chemotherapy and trastuzumab; FcγRIIIA (CD16A) polymorphisms were assessed
- Trastuzumab showed better treatment outcome in FcγRIIIA (CD16A)158V/V patients, while in **majority of 158V/F or F/F patients, treatment outcome of trastuzumab was poor**



ADCC Effect of Trastuzumab Low in 158V/F or F/F[2,3,4]

- The ADCC effect is mediated by FcγRIIIA (CD16A)
- Patients with FcγRIIIA (CD16A) 158V/V genotypes have high binding affinity between Fc portion of antibody and FcγR on immunologic effector cells and lead to high ADCC effect of trastuzumab
- **Increased FcγRIIIA (CD16A) can enhance ADCC effect and can potentially increase efficacy of cancer cell destruction in HER2+ gastric cancer**

Tumor Type	MBC	MBC	BC	MGC
V/V	20.7%	13.6%	11.9%	17.2%
V/F	48.1%	48.4%	41.6%	46.4%
F/F	31.2%	37.9%	46.5%	36.4%

V/F and F/F patients account for majority in different tumor types

High

- Binding affinity
- ADCC effect of trastuzumab

Low

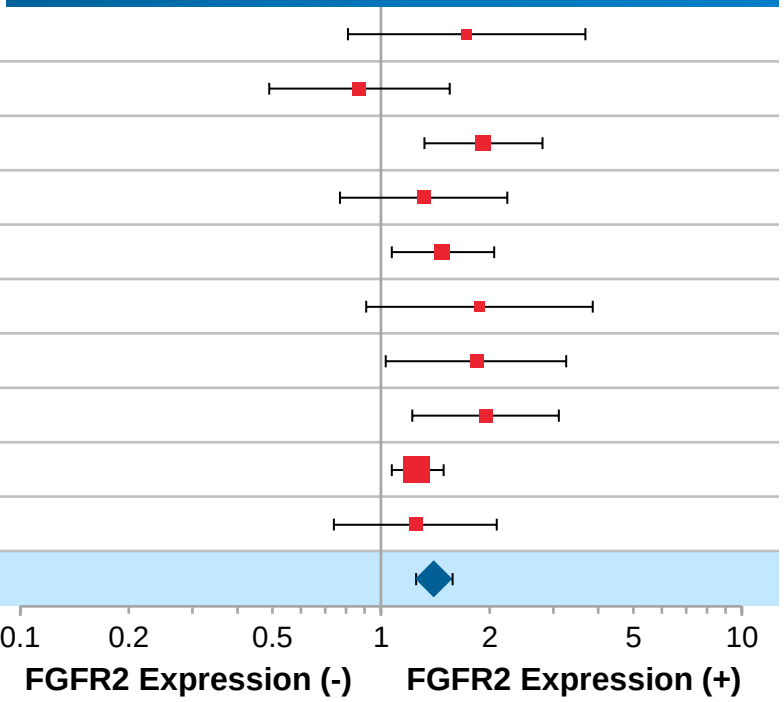
Source: (1) De-Shen Wang, et al. OncoTargets and Therapy 2017; (2) Rugo HS, et al. JAMA Oncol 2021; (3) Musolino A, et al. J Clin Oncol 2008; (4) Patrick G. Gavin, et al. JAMA Oncology 2016.

FGFR2b Overexpression Correlates With Poor Prognosis
Promising Target in HER2-Negative Gastric Cancer

Meta-Analysis Indicated Patients with FGFR2-Overexpressed Gastric Cancer Showed Significantly Worse Survival Than Those with FGFR2-Low Tumors (HR = 1.40, 95% CI: 1.25-1.58, p <0.00001)

Study or Subgroup	Log (Hazard Ratio)	SE	% Weight	Hazard Ratio IV, Fixed, 95% CI
Hattori (1996)	0.5481	0.3851	2.4%	1.73 (0.81, 3.68)
Matsunobu (2006)	-0.1393	0.2947	4.1%	0.87 (0.49, 1.55)
Toyokawa (2009)	0.6523	0.1925	9.6%	1.92 (1.32, 2.80)
Murase (2014)	0.2746	0.2705	4.9%	1.32 (0.77, 2.24)
Nagatsuma (2015)	0.3920	0.1677	12.6%	1.48 (1.07, 2.06)
Han (2015)	0.6254	0.3700	2.6%	1.87 (0.91, 3.86)
Ahn (2016)	0.6076	0.2928	4.1%	1.84 (1.03, 3.26)
Jia (2016)	0.6653	0.2393	6.2%	1.95 (1.22, 3.11)
Tokunaga (2016)	0.2311	0.0857	48.4%	1.26 (1.07, 1.49)
Hosoda (2018)	0.2199	0.2649	5.1%	1.25 (0.74, 2.09)
Total (95% CI)			**100.0%**	**1.40 (1.25, 1.58)**

Hazard Ratio IV, Fixed, 95% CI



Heterogeneity: $CHI^2 = 10.82$, df = 9 (P = 0.29); $I^2 = 17\%$

Test for overall effect: Z = 5.68 (P < 0.00001)

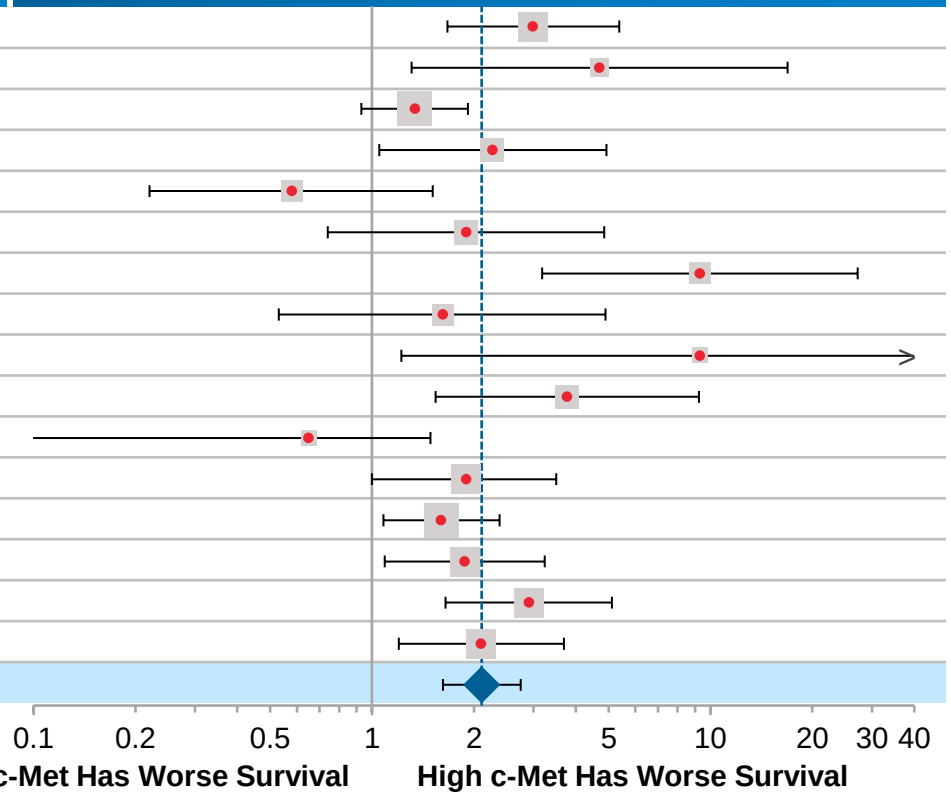
Source: Hyeong Su Kim, et al. Journal of Cancer 2019.

c-Met Status Is Important Factor Affecting Prognosis of Gastric Cancer

Meta-Analysis of HRs Indicated Significantly Poorer OS in Patients with High c-Met Expression (Average HR=2.112, 95% CI: 1.622-2.748)

Forest Plot Showing Meta-Analysis of Hazard Ratio Estimates for Overall Survival

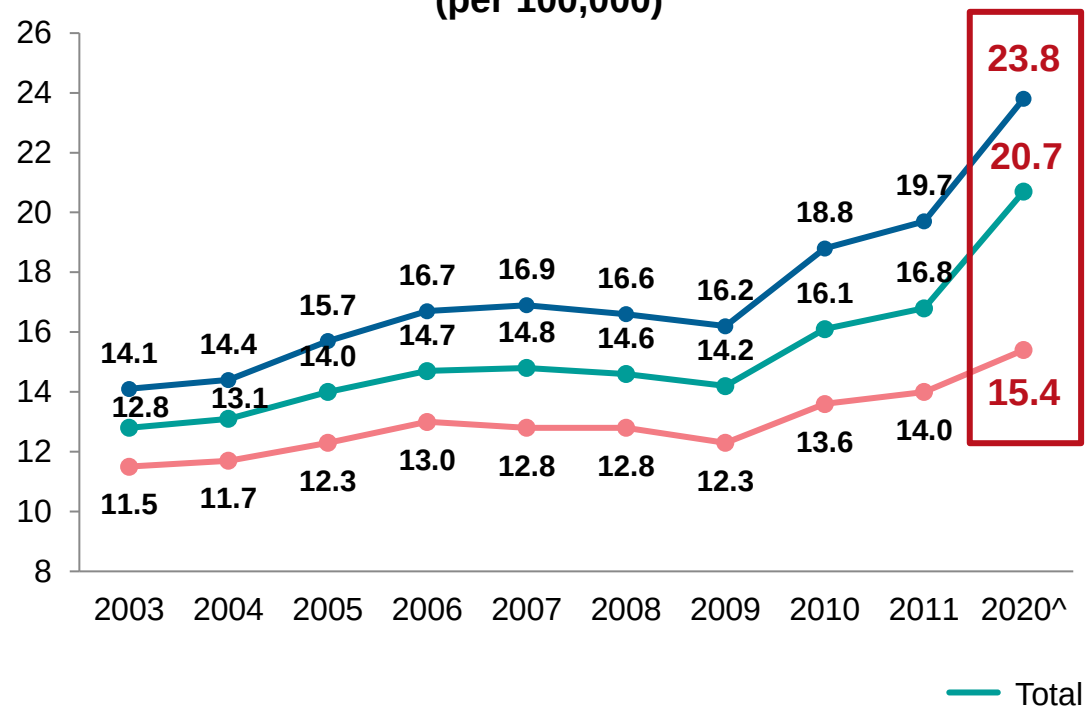
Study ID	% Weight	Hazard Ratio 95% CI
Toiyama (2011)	8.28%	2.99 (1.67, 5.35)
Catenacci (2011)	3.25%	4.70 (1.31, 16.90)
Catenacci (2011)	11.01%	1.34 (0.93, 1.92)
Lee (2012)	6.33%	2.27 (1.05, 4.93)
Li (2012)	4.88%	0.58 (0.22, 1.51)
Taniguchi (1998)	5.02%	1.90 (0.74, 4.85)
Tsugawa (1998)	4.20%	9.30 (3.18, 27.25)
Nakajima (1999)	4.00%	1.62 (0.53, 4.90)
Huang (2001)	1.50%	9.30 (1.22, 70.81)
KUBICKA (2002)	5.33%	3.77 (1.54, 9.24)
Han (2005)	2.11%	0.65 (0.05, 1.49)
DREBBER (2008)	7.79%	1.90 (1.00, 3.50)
Lee (2011)	10.58%	1.60 (1.08, 2.38)
Zhao (2011)	8.71%	1.88 (1.09, 3.24)
Graziano (2011)	8.48%	2.91 (1.65, 5.11)
Shi (2012)	8.52%	2.10 (1.20, 3.69)
Overall (I^2 = 52.4%, p = 0.007)	**100.00%**	2.11 (1.62, 2.75)



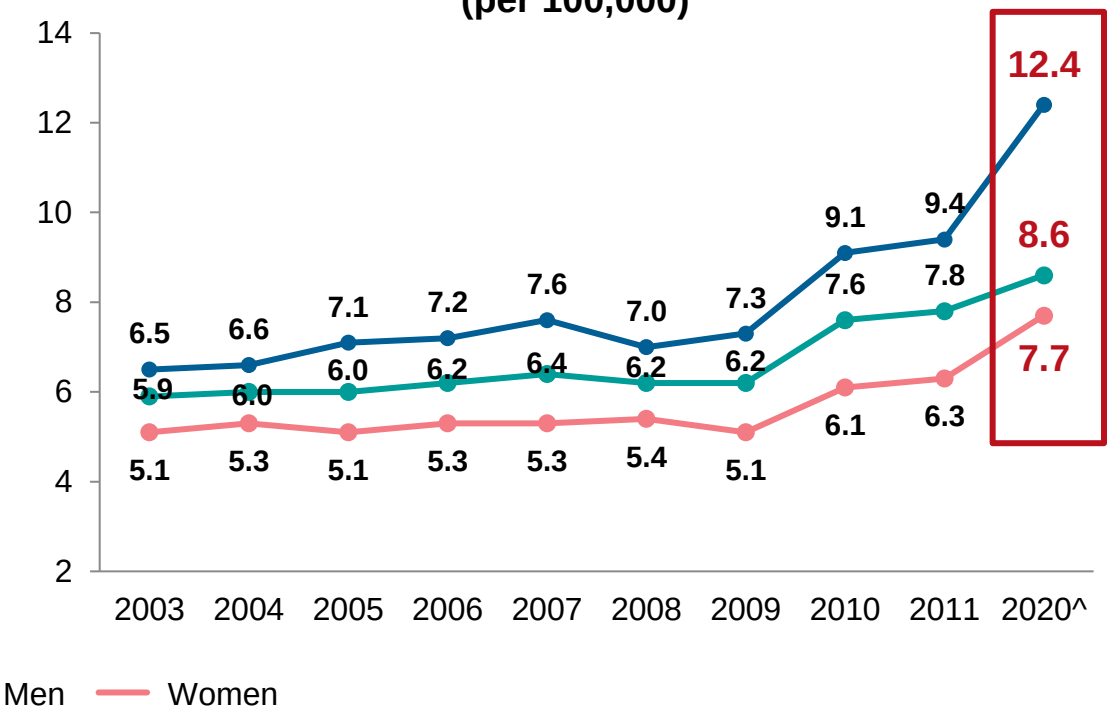
Note: Weights are from random effects analysis.
Source: Shan Yu, et al. PLoS One. 2013.

Colorectal Cancer (CRC)
Increasing Incidence and Mortality in China

China CRC Incidence (2003–2020)



China CRC Mortality Rate (2003–2020)



Total Men Women

While age is major factor in incidence of CRC, risk factors may also include dietary habits (low-fiber diets, diets rich in red and processed meat, excessive alcohol intake), smoking, less physical activity, and hereditary factors

Source: Jinzhou Zhu, et al. Dig Dis Sci 2017; Yong Yang, et al. Chin J Cancer Res 2020.

Limited Effective Therapies Available for Metastatic CRC in China

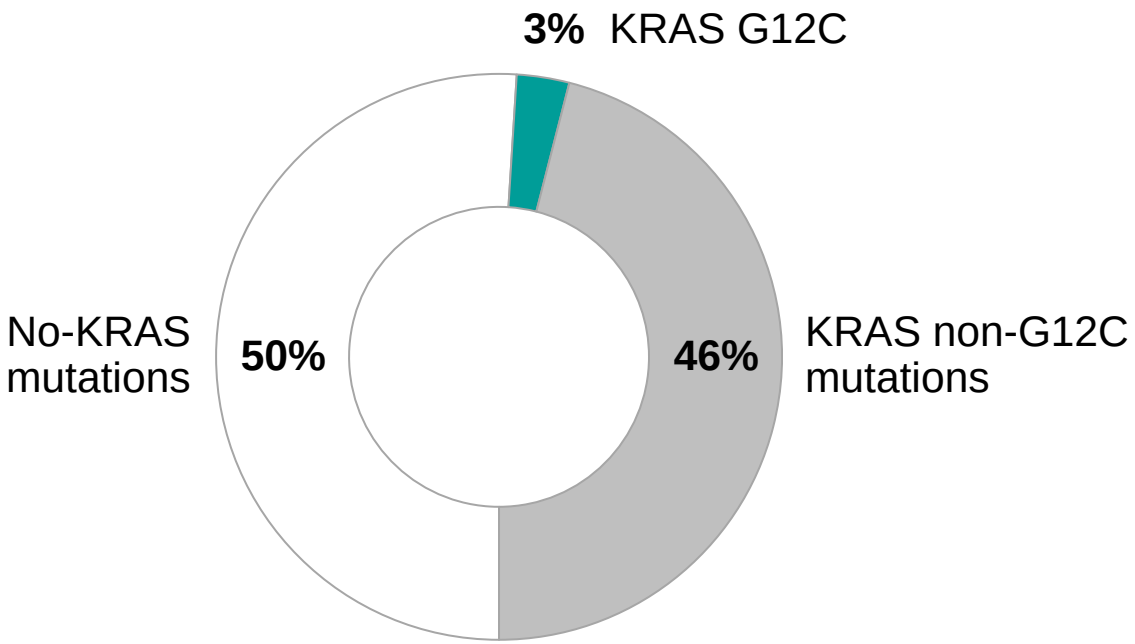
Targeted Therapies Available for Metastatic CRC in US and China

	Approved by FDA	Approved by NMPA
cetuximab	✓	✓
panitumumab	✓	
bevacizumab	✓	✓
regorafenib	✓	✓
fruquitinib		✓
ziv-aflibercept	✓	
pembrolizumab	✓	✓
nivolumab	✓	
ipilimumab	✓	
encorafenib	✓	

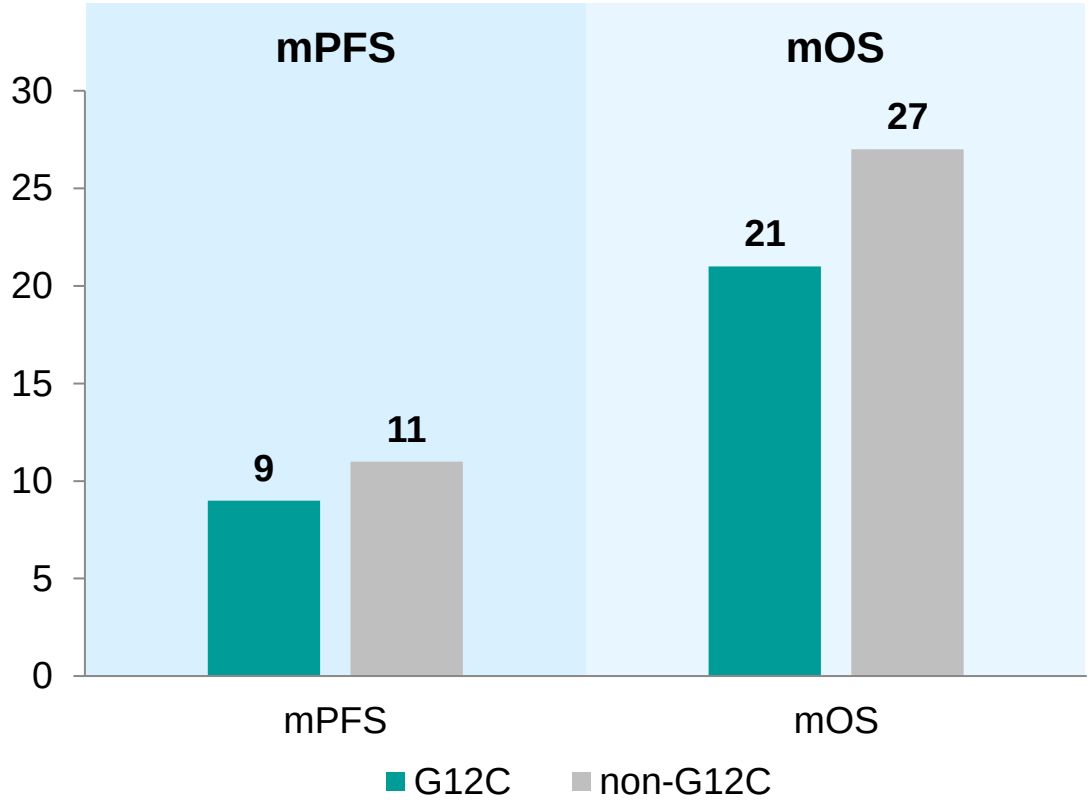
Source: Version2.2021 NCCN Colon Cancer; CSCO Guidelines (2021); Guo TA,. Int J Cancer 2019.

No Effective Treatment for KRAS-Mutant Patients
Poor Prognosis in KRAS-Mutant CRC

49% KRAS-Mutant mCRC, KRAS G12C Accounts for ~3%[1]



KRAS G12C Mutation Is Significantly Correlated with Shorter First-Line mPFS and mOS vs. Non-G12C Mutations[2]



Source: (1) Loong, H.H., et al. Transl Lung Cancer Res 2020; (2) Chida, K., et al. The Oncologist 2021.

Summary

- **China has world's highest incidence and mortality rate of GI cancers, with poor prognosis**

- For gastric cancer, 3rd largest cancer in China by incidence, **treatment options are still limited despite recent progress of PD-1s approved in first-line setting**
  - FC optimized mAb can be potential choice for HER2+ gastric cancer
  - FGFR2b accounts for 30% of HER2- patients but with poor prognosis
  - Patients with high c-MET indicate poorer OS

- The incidence and mortality of CRC is **increasing in China, with very limited treatment options**
  - KRAS G12C with poor prognosis