2021 ESMO congress

Non-immune molecular predictors of treatment response in gastric cancer (GC)

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DECLARATION OF INTERESTS

Personal financial interest of scientific consultancy for BMS, Lilly, MSD and Servier

Honorarium for speaking issues from Amgen, BMS, Lilly, MSD, Roche and Servier

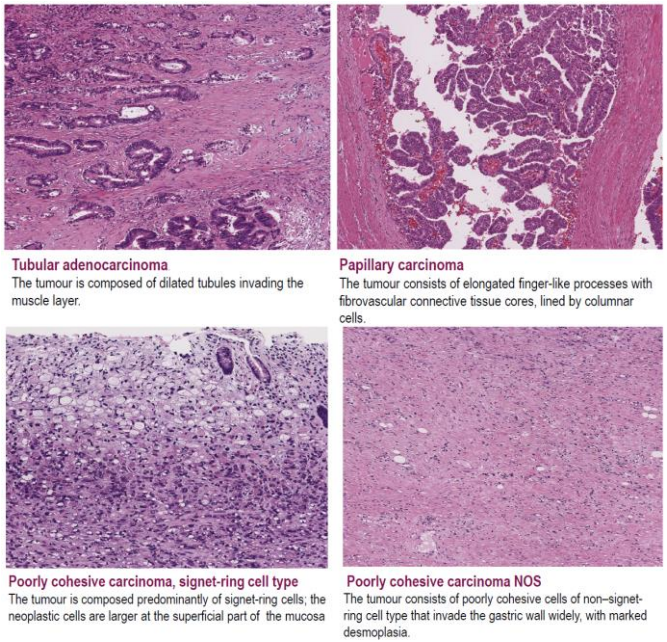
Travel expenses partially covered by Amgen, Lilly and Roche

Outline

Introduction: inter- and intra-patient heterogeneity
Main phase III trials with targeted therapies in GC
New strategies
Conclusions

Inter-patient heterogeneity of GC

Histological subtypes



Tubular adenocarcinoma
The tumour is composed of dilated tubules invading the muscle layer.

Papillary carcinoma
The tumour consists of elongated finger-like processes with fibrovascular connective tissue cores, lined by columnar cells.

Poorly cohesive carcinoma, signet-ring cell type
The tumour is composed predominantly of signet-ring cells; the neoplastic cells are larger at the superficial part of the mucosa

Poorly cohesive carcinoma NOS
The tumour consists of poorly cohesive cells of non–signet-ring cell type that invade the gastric wall widely, with marked desmoplasia.

GC is not one disease

Different histological subtypes

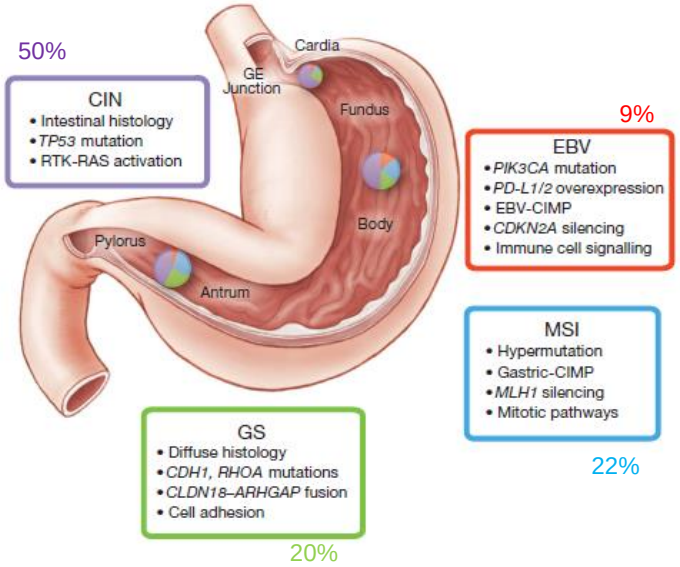
Not prognostic

Not predictive of response

WHO classification (5th Ed. 2019)

Inter-patient heterogeneity of GC

Molecular subtypes



GC is not one disease

4 different molecular subtypes

(Prognostic)

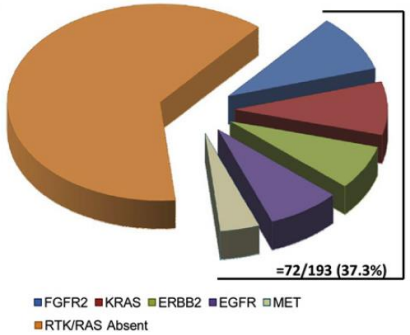
Not predictive of response (except MSI)

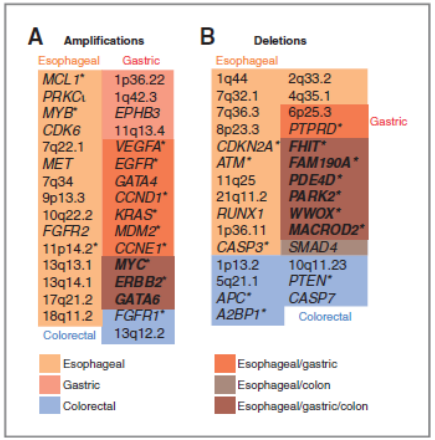
TCGA 2014

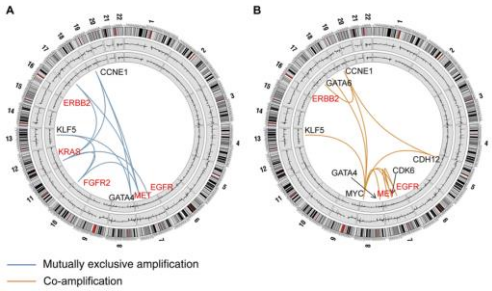
Targeted therapies

Main phase 3 trials in GC

- First molecular characterization of GC distinguish up to 40% of tumors harboring amplifications on FGFR2, KRAS, HER2, EGFR and MET (mutually exclusive)

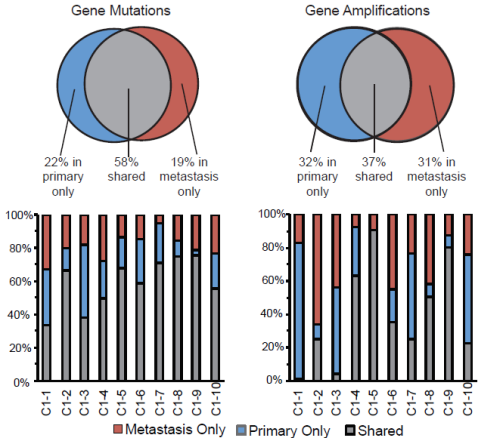


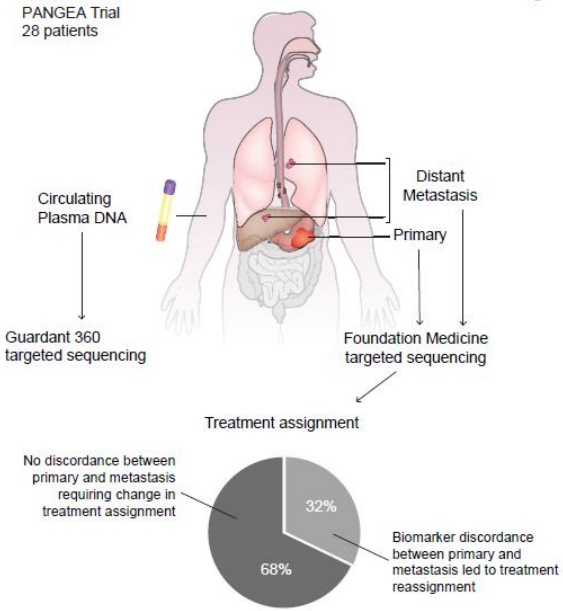




Deng Gut 2012, Dulak Can Res 2012

Intra-patient heterogeneity of GC





≈ 30% of discordance between primary and metastases (tissue)

ctDNA is more similar to metastatic tissue

… should we rely on the primary tumor for biomarker guided therapies?

Pectasides Can Discov 2017

Targeted therapies

Main phase 3 trials in GC

- Only 4 of 19 positive trials

Pathway	Trial	Line	Screening	Agent	mOS	Hazard ratio
HER2	ToGA	1st	*HER2* (FISH)	Trastuzumab	13.8 vs. 11.1 m	HR 0.74
	LOGIC	1st	*HER2* (FISH)	Lapatinib	12.2 vs. 10.5 m	HR 0.91
	JACOB	1st	HER2 3+, or HER2+&ISH+	Trastuzumab + Pertuzumab	17.5 vs. 14.2 m	HR 0.84
	TyTAN	2nd	*HER2* (FISH)	Lapatinib	11.0 vs. 8.9 m	HR 0.84
	GATSBY	2nd	HER2 3+, or HER2+&ISH+	T-DM1	7.9 vs. 8.6 m	HR 1.15
EGFR	REAL-3	1st	-	Panitumumab	8.8 vs. 11.3 m	HR 1.37
	EXPAND	1st	-	Cetuximab	9.4 vs. 10.7 m	HR 1.00
	GOG	1st	-	Gefitinib	3.73 vs. 3.67 m	HR 0.90
mTOR	GRANITE-1	2nd & 3rd	-	Everolimus	5.4 vs. 4.3 m	HR 0.90
MET	RILOMET1	1st	MET (IHC)	Rilotumumab	8.8 vs. 10.7 m	HR 1.34
	METGastric	1st	MET (IHC)	Onartuzumab	11.0 vs. 11.3 m	HR 0.82
VEGF	AVAGAST	1st	-	Bevacizumab	12.1 vs. 10.1 m	HR 0.87
	RAINFALL	1st	-	Ramucirumab	11.2 vs. 10.7 m	HR 0.96
	RAINBOW	2nd	-	Ramucirumab	9.6 vs. 7.4 m	HR 0.80
	REGARD	2nd	-	Ramucirumab	5.2 vs. 3.8 m	HR 0.77
	Li et al.	3rd	-	Apatinib	6.5 vs. 4.7 m	HR 0.70
PARP	GOLD	2nd	ATM (IHC)	Olaparib	12 vs. 10 m	HR 0.73
STAT3	BRIGHTER	2nd	-	Napabucasin	6.93 vs. 7.36 m	HR 1.01

Bang Lancet 2010, Hecht JCO 2016, Tabernero Lancet Oncol 2018, Satah JCO 2014, Thuss-Patience Lancet Oncol 2017, Waddell Lancet Oncol 2013, Lordick Lancet Oncol 2013, Dutton Lancet Oncol 2014, Othsu JCO 2013, Catenacci Lancet Oncol 2017, Shah Jama Oncol 2020, Othsu JCO 2011, Fuchs Lancet Oncol 2019, Wilke Lancet Oncol 2014, Fuchs Lancet 2014, Li JCO 2016, Bang Lancet Oncol 2017, Shah ASCO 2018

Targeted therapies

HER2

- HER2 is overexpressed in 15-25% of GC
- The ToGA trial demonstrated clinically meaningful survival results only in HER2-positive with IHC3+ or IHC2+&ISH+
- None other phase 3 clinical trial could demonstrate benefit in HER2-positive population

HER2	ToGA	1st	*HER2* (FISH)	Trastuzumab	13.8 vs. 11.1 m	HR 0.74
	ToGA	1st	HER2 3+, or HER2+&ISH+	Trastuzumab	16.0 vs. 11.8	HR 0.65
	LOGIC	1st	*HER2* (FISH)	Lapatinib	12.2 vs. 10.5 m	HR 0.91
	JACOB	1st	HER2 3+, or HER2+&ISH+	Trastuzumab + Pertuzumab	17.5 vs. 14.2 m	HR 0.84
	JACOB - final analysis	1st	HER2 3+, or HER2+&ISH+	Trastuzumab + Pertuzumab	18.1 vs. 14.2 m	HR 0.85
	TyTAN	2nd	*HER2* (FISH)	Lapatinib	11.0 vs. 8.9 m	HR 0.84
	GATSBY	2nd	HER2 3+, or HER2+&ISH+	T-DM1	7.9 vs. 8.6 m	HR 1.15

Better selection

*Clinical activity do exist: final analysis confirm a **15% reduction in the risk of death** by adding pertuzumab*

*Biomarker analysis: **lower efficacy of T-DM1 in pts with heterogeneous HER2 expression**, compared with those with more homogeneous expression (≥80%)*

Bang Lancet 2010, Hecht JCO 2016, Tabernero Lancet Oncol 2018, Tabernero ESMO02021, Satah JCO 2014, Thuss-Patience Lancet Oncol 2017, Shah Gastric Cancer 2019

HER2 expression

- Definition of the HER2 positivity
  - IHC 3+ or IHC 2+ (ISH positive)
- Intra-tumoral heterogeneity
  - High *HER2* amplification levels have been associated with a superior benefit of trastuzumab
  - HER2 protein levels have been associated with a superior benefit of trastuzumab
  - Quantification of the HER2 protein levels may identify the true HER2 positive patients
- Up front and secondary resistance
  - Up to 55% had other genomic events (cell cycle, PI3K, RTK)
- Loss of HER2
  - Described in 30-70% of the patients, after trastuzumab therapy

Gomez-Martin J Clin Oncol 2013, An Ann Oncol 2017; Alsina Ann Oncol 2017; Pietrantonio Int J Cancer 2016; Seo Gastric Cancer 2018; Janjigian Cancer Discovery 2017; Kim J Clin Invest 2014

Targeted therapies

EGFR

- 5-10% of GC have *EGFR* amp or EGFR overexpression
- None of the phase 3 clinical trial could demonstrate benefit in unselected GC population

EGFR	REAL-3	1st	-	Panitumumab	8.8 vs. 11.3 m	HR 1.37
	EXPAND	1st	-	Cetuximab	9.4 vs. 10.7 m	HR 1.00
	GOG	1st	-	Gefitinib	3.73 vs. 3.67 m	HR 0.90

Post-hoc biomarker analysis suggest meaningful efficacy in pts with high levels of EGFR

Waddell Lancet Oncol 2013, Lordick Lancet Oncol 2013, Dutton Lancet Oncol 2014, Lordick ASCO 2013, Petty JCO 2017

Targeted therapies

MET

- MET overexpression found in 25-65% of GC, although not fully correlated with the pathway function
- Aberrant c-MET pathway activation could occur due to MET overexpression, *MET* amp or ↑ HGF
- Two phase 3 trials could not demonstrate enough efficacy when blocking the MET pathway

MET	RILOMET1	1st	MET (IHC)	Rilotumumab	8.8 vs. 10.7 m	HR 1.34
	METGastric	1st	MET (IHC)	Onartuzumab	11.0 vs. 11.3 m	HR 0.82

Patients with moderate (2+) and strong (3+) MET staining on ≥ 50% of tumor cells tended to live longer with onartuzumab

Catenacci Lancet Oncol 2017, Shah Jama Oncol 2020

Targeted therapies

Why did they failure?

- In part because of a non-adequate study design:
  - Inter-patient variability: GC is not a unique disease
    - Lack of a biomarker
    - Lack of an adequate biomarker
    - Difficulties in measuring the biomarker

- In part because of the intrinsic characteristics of GC:
  - Intra-patient variability: spatial and temporal heterogeneity

New strategies

Novel HER2-directed therapies

Antibody-drug conjugates

- Trastuzumab deruxtecan (T-Dxd) (DS-8201a)
- RC48-ADC: ongoing phase 2 trial (NCT03556345)

Monoclonal antibodies

- Margetuximab (+ PD-1 inhibitor)

Bispecific antibodies

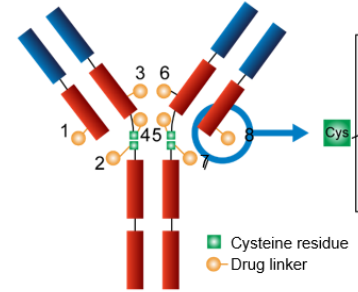
- Zanidatamab (ZW25); targets two areas on HER2 (phase 2 in combination with SOC chemo [NCT03929666], and phase 1/2 with chemo and PD-1 inhibitor [NCT04276493])

Combination with immune checkpoint inhibitors

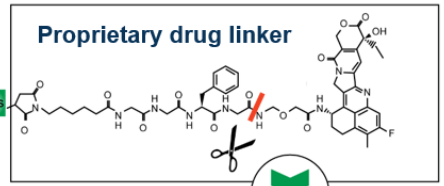
- With durvalumab, nivolumab, and pembrolizumab (phase 3 KEYNOTE-811)

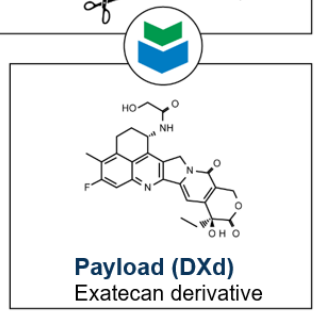
Trastuzumab Deruxtecan in Advanced HER2+ GC

Phase 2 DESTINY-Gastric01 Trial



Conjugation chemistry
The linker is connected to cysteine residue of the antibody





Payload (DXd)
Exatecan derivative

- Payload with a different MOA
- High potency of payload
- Payload with short systemic half-life
- Bystander effect
- Stable linker-payload
- Tumor-selective cleavable linker
- High drug-to-antibody ratio

Trastuzumab deruxtecan designed with goal of improving critical attributes of an ADC

Iwata H et al. ASCO 2018 (Abstract 2501)

Trastuzumab Deruxtecan in Advanced HER2+ GC

Phase 2 DESTINY-Gastric01 Trial

	Primary Cohort[1]		Exploratory Cohorts	
	T-DXd (n = 119)	PC Overall (n = 56)	Cohort 1 IHC 2+/ISH− (n = 19)	Cohort 2 IHC 1+ (n = 21)
ORR by ICR (CR + PR)	**51.3% (n = 61)** 95% CI, 41.9-60.5; *P* < .0001[a]	**14.3% (n = 8)** 95% CI, 6.4-26.2	**36.8% (n = 7)** 95% CI, 16.3%-61.6%	**19.0% (n = 4)** 95% CI, 5.4%-41.9%
Confirmed ORR by ICR (CR + PR)	**42.9% (n = 51)** 95% CI, 33.8-52.3	**12.5% (n = 7)** 95% CI, 5.2-24.1	**26.3% (n = 5)** 95% CI, 9.1%-51.2%	**9.5% (n = 2)** 95% CI, 1.2%-30.4%
CR	8.4% (n = 10)	0	0	0
PR	34.5% (n = 41)	12.5% (n = 7)	26.3% (n = 5)	9.5% (n = 2)
SD	42.9% (n = 51)	50.0% (n = 28)	63.2% (n = 12)	61.9% (n = 13)
PD	11.8% (n = 14)	30.4% (n = 17)	10.5% (n = 2)	28.6% (n = 6)
NE	2.5% (n = 3)	7.1% (n = 4)	0	0
Confirmed DCR (CR + PR + SD)	85.7% (n = 102) 95% CI, 78.1-91.5	62.5% (n = 35) 95% CI, 48.5-75.1	89.5% (n = 17) 95% CI, 66.9%-98.7%	71.4% (n = 15) 95% CI, 47.8%-88.7%
Median confirmed DOR	11.3 months 95% CI, 5.6 months-NE	3.9 months 95% CI, 3.0-4.9 months	7.6 months 95% CI, 4.1 months-NE	12.5 months 95% CI, NE-NE

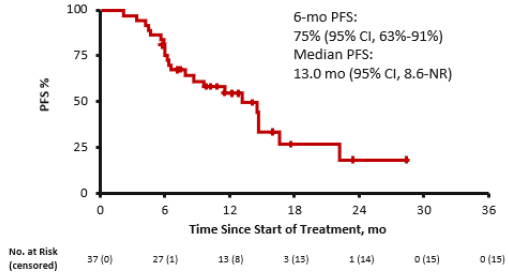
Primary cohort: HER2+ and progressed on trastuzumab-containing regimen

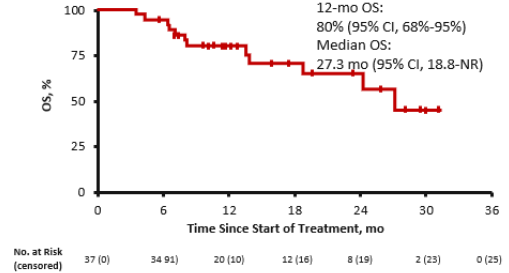
Exploratory: in ≤20 patients with naive HER2-low disease (IHC 2+/ISH- and IHC 1+)

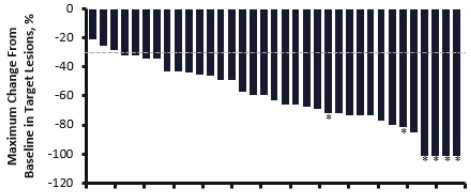
Shitara NEJM 2020; Yamaguchi ESMO 2020

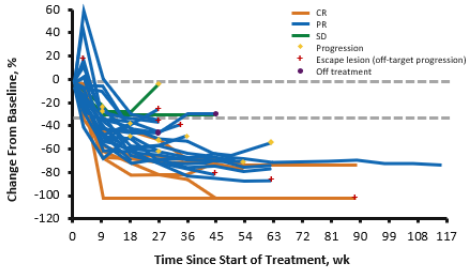
Combinations with immune checkpoints inhibitors

Pembrolizumab + trastuzumab + platin + fluoropyrimidine









N = 37 patients; most received cape/ox

- 6-mo PFS: 75%; median: 13 mo
- Median OS: 27.3 mo
- RR: 83%

Ongoing phase 3 KEYNOTE-811 (NCT03615326)

Janjigian Lancet Oncol 2020

New strategies

FGFR2

Ph II SHINE Study (AZD4547)

- 2nd line: paclitaxel vs AZD4547
- Patients selected based on *FGFR2* gene amplification or *FGFR2* polysomy

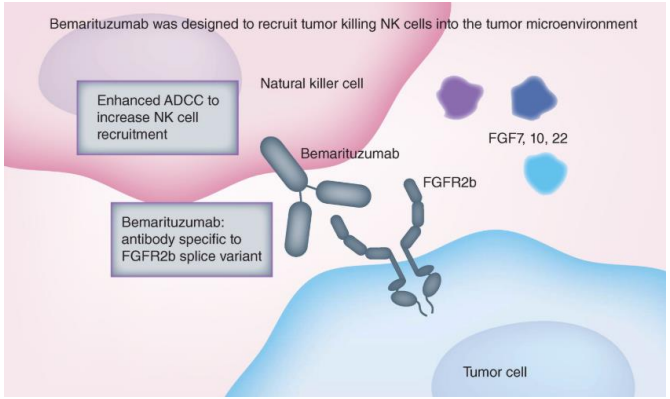
Negative

- *FGFR2* gene amplification showed high intratumor heterogeneity
- *FGFR2* CNV (in tumor and in plasma) predicted response to AZD4547
- Homogeneity of *FGFR2* amplification required to respond to AZD4547

Van Cutsem Ann Oncol 2017; Smyth ESMO Asia 2015; Pearson Cancer Discov 2016

New strategies

FGFR2: Bemarituzumab Phase 2 study



Key Eligibility Criteria

- No prior therapy for unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or *FGFR2* gene amplification by ctDNA[1]
- ECOG 0/1
- HER2 not positive
- May receive 1 dose of mFOLFOX6

Stratification Factors

- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neo-adjuvant chemotherapy

R 1:1

Double blind, placebo controlled

Bema + mFOLFOX6 (n = 77)

VS

Placebo + mFOLFOX6 (n = 78)

Treatment Q2W[2]

Primary endpoint

- Investigator-Assessed Progression-Free Survival

Secondary endpoints

- Overall Survival
- Response Rate

Statistical Plan

Trial initially designed as registrational Phase 3 (n=548) with 2-sided α 0.05
Amended after enrolling n = 155 to a proof-of-concept Phase 2 with pre-specified statistical assumptions of:

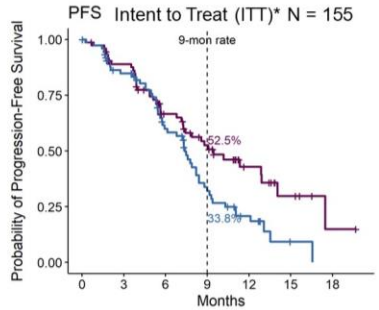
- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR≤0.76 for PFS at 2-sided α of 0.2

1 Central testing: Immunohistochemical stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X
2 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day 8[2]

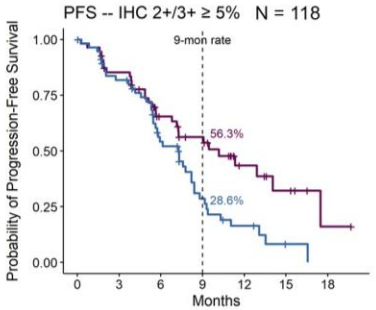
New strategies

FGFR2: Bemarituzumab Phase 2 study

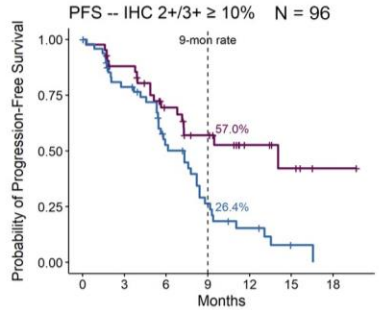
Progression-Free Survival Benefit Increased with Higher Levels of FGFR2b Overexpression



	Bema N = 77	Placebo N = 78
mPFS, mo (95% CI)	9.5 (7.3, 12.9)	7.4 (5.8, 8.4)
	P=0.0727	
HR (95% CI)	0.68 (0.44, 1.04)	



	Bema N = 58	Placebo N = 60
mPFS, mo (95% CI)	10.2 (6.8, 14.1)	7.3 (5.5, 8.2)
HR (95% CI)	0.54 (0.33, 0.87)	

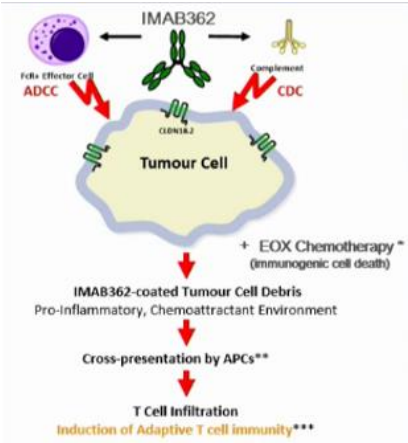


	Bema N = 44	Placebo N = 52
mPFS, mo (95% CI)	14.1 (6.8, NR)	7.3 (5.4, 8.2)
HR (95% CI)	0.44 (0.25, 0.77)	

*ITT = 149 with IHC 2+/3+ and 6 pts with IHC <2+ or not available who were enrolled based on ctDNA alone

New strategies

Claudine 18.2



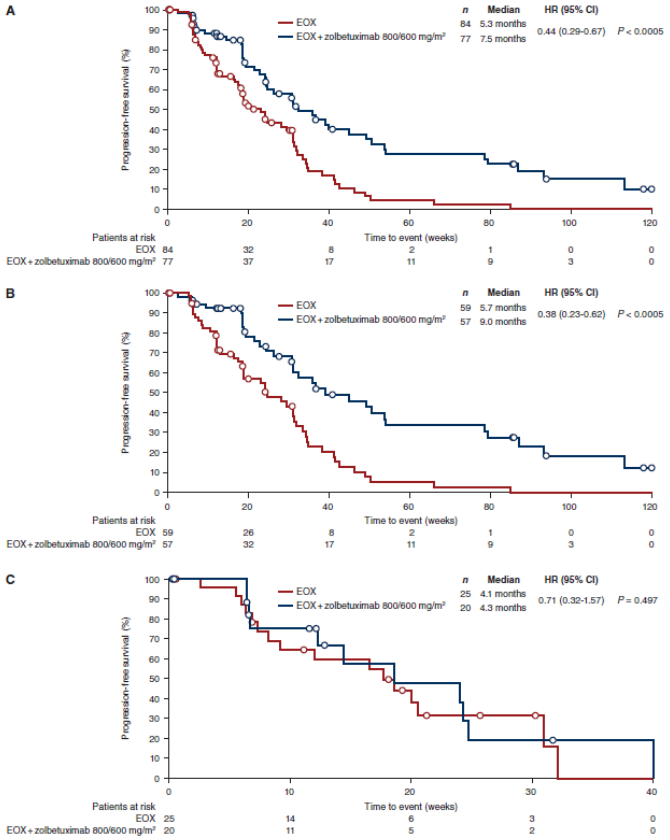
- Claudine 18.2 is a major structural component of tight junctions
  - Broadly expressed in GC, not in healthy tissues except in the stomach mucosa

- Zolbetuximab (IMAB362) is a chimeric IgG1 specific for CLDN18.2
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Complement-dependent cytotoxicity (CDC)
  - In combination with chemo, enhances T-cell infiltration and induces pro-inflammatory cytokines

New strategies

Claudine 18.2: Phase II FAST Trial

- Randomized Ph II Trial, 1st Line GC
- CLN18.2 positive patients (2+/3+ IHC staining in ≥ 40% of tumor cells)
  - Positive trial (PFS)
  - Subgroup analysis: better PFS in moderate to strong CLDN18.2 expression in **≥ 70% of tumor cells**



Overall population

≥ 70% of tumor cells positive for CLDN18.2

40-69% of tumor cells positive for CLDN18.2

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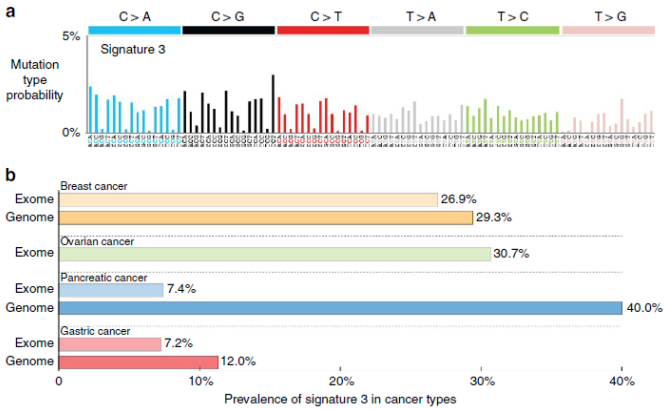
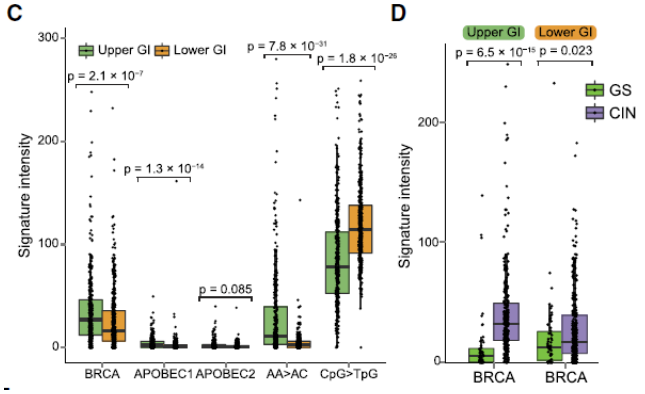
Sahin Ann Oncol 2021

New strategies

DNA damaging agents





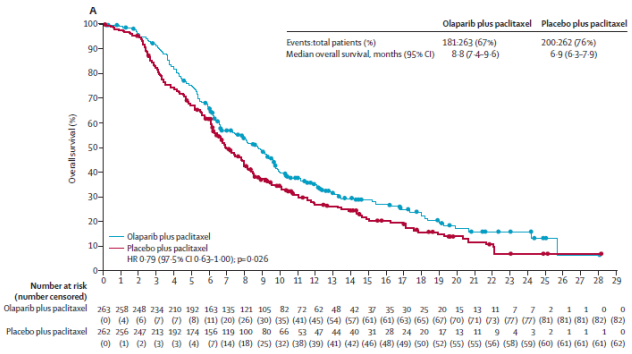
- 7-12% of GC have defective double-strand DNA break repair by homologous recombination and may benefit from either platinum therapy or PARPi

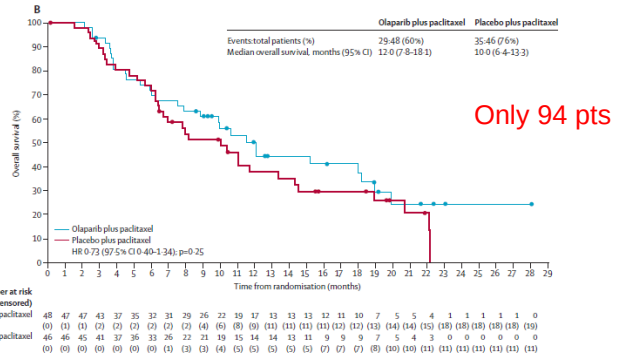
Alexandrov Nat Comm 2015; Liu Y Cancer Cell 2018

New strategies

DNA damaging agents

- Ph II with Paclitaxel + Olaparib showed improvement of OS in ATM-neg pts
- Ph III GOLD Study (2nd Line)
  - Paclitaxel + Olaparib/Placebo 100 mg BID
  - Co-primary end points: OS in All patients (525 pts) and in ATM-neg patients





Only 94 pts

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Bang J Clin Oncol 2015, Bang Lancet Oncol 2017

New strategies

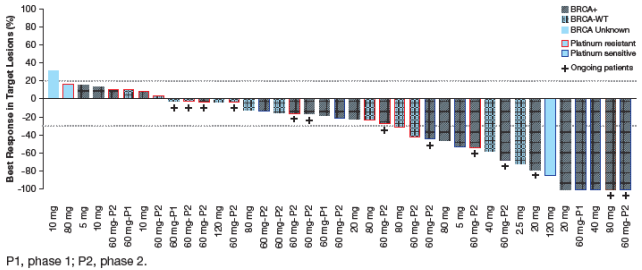
DNA damaging agents

- **Pamiparib**: a selective PARP 1/2 inhibitor that crosses the blood-brain barrier

Antitumor Activity of BGB-290 in Epithelial Ovarian Cancer and Other Solid Tumors

- A total of 39 patients were evaluable per RECIST V1.1
  - 23 patients were BRCA-mutation positive (BRCA+), 13 patients had wild-type BRCA (BRCA-WT), and 3 were of unknown BRCA status

Figure 3: Best Change from Baseline in Target Lesions in Epithelial Ovarian Cancer and Other Associated Tumors



P1, phase 1; P2, phase 2.

Ph III Trial ongoing (NCT03427814)

BeiGene, Ltd., BGB-290-303, A Phase 3, Double-blind, Randomized Study of BGB-290 versus Placebo as Maintenance Therapy in Patients with Inoperable Locally Advanced or Metastatic Gastric Cancer that Responded to Platinum-based First-line Chemotherapy.

Conclusions

- **HER2** is a well-defined target in mGC with trastuzumab already approved in the 1st line setting, and other drugs/combinations being actively validated
- **FGFR** (FGFR2b) is being revisited as a target in this setting, encouraging data with bemarituzumab.
- **Claudine 18.2** is a validated target in mGC. Zolbetuximab is being evaluated in the high-expressing population.
- **Response to a first line platinum-based therapy** may become a potential biomarker for DNA damaging. Pamiparib is being evaluated in the maintenance setting.

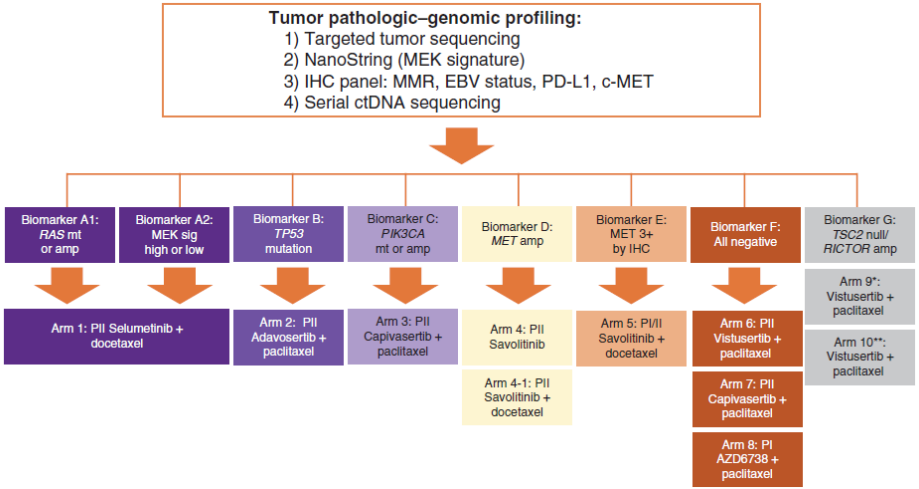
Conclusions

- While the majority of old phase 3 trials failed, due to
  - **Inexistent or poor biomarker selection**
  - High inter-patient heterogeneity: **GC is not a unique entity** (different histology, different molecular subtypes with intrinsic aberrant pathways)
  - High **intra-patient heterogeneity**: **spatial** (different tumor areas) and **temporal** (acquired resistances to targeted therapies)

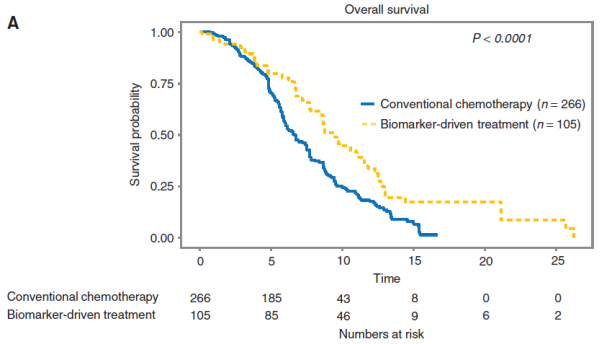
- Precision medicine needs **better designed clinical trials** with **better validated biomarkers** and **patient stratification**

The VIKTORY Trial

Targeted therapies based on patient genomic profile



- Umbrella trail
- 2nd line treatment of mGC pts based on eight biomarkers
- Prolonged PFS and OS in pts receiving a biomarker-guided therapy, compared with conventional chemotherapy



Lee Cancer Discov 2019

The PANGEA Trial

Targeted therapies based on patient genomic profile

- Personalized treatment strategy applied at 1st diagnosis and then serially over up to three ttx lines

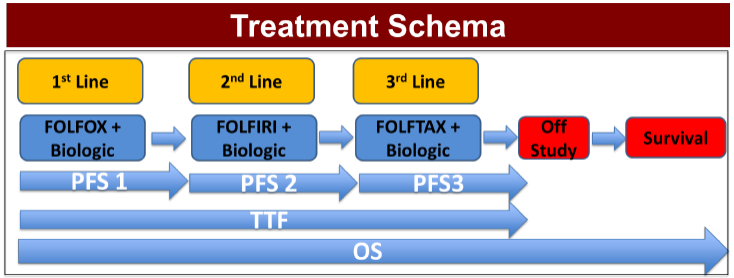


Table 2. Biomarker prioritization and treatment assignment algorithm.

Biomarker Group & Description*	Treatment Arm	Antibody Therapy
1) IO**	Anti-PD-1	nivolumab
2) *HER2* amplified***	Anti-HER2	trastuzumab
3) *EGFR* amplified***	Anti-EGFR	ABT-806
4) *FGFR2* amplified***	Anti-FGFR2	bemarituzumab^
5) *MET* amplified***	Anti-MET	none available^^
6) MAPK/PIK3CA aberrant	Anti-VEGFR2	ramucirumab
7) EGFR expressing	Anti-EGFR	ABT-806
8) All negative	Anti-VEGFR2	ramucirumab

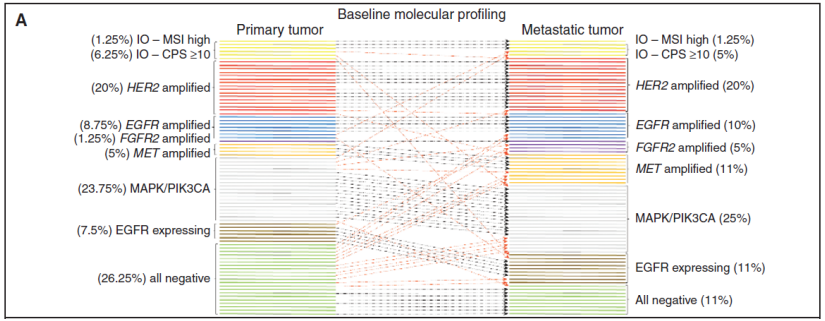
Catenacci Cancer Discov 2021

The PANGEA Trial

Targeted therapies based on patient genomic profile

Spatial and temporal heterogeneity:

- Spatial heterogeneity (primary ⟶ metastasis)
  - 28 of 80 (35%) ttx changed
- Temporal heterogeneity (1st line ⟶ 2nd line)
  - 27 of 55 (49%) patients
- Temporal heterogeneity (2nd line ⟶ 3rd line)
  - 13 of 27 (48%) patients



HER2 Baseline Spatial Heterogeneity

- 2/63 (3.2%) positive only in metastases
- 3/17 (17.6%) positive by primary tumor only

HER2 conversion

- ~45% converted to *HER2* negative over time

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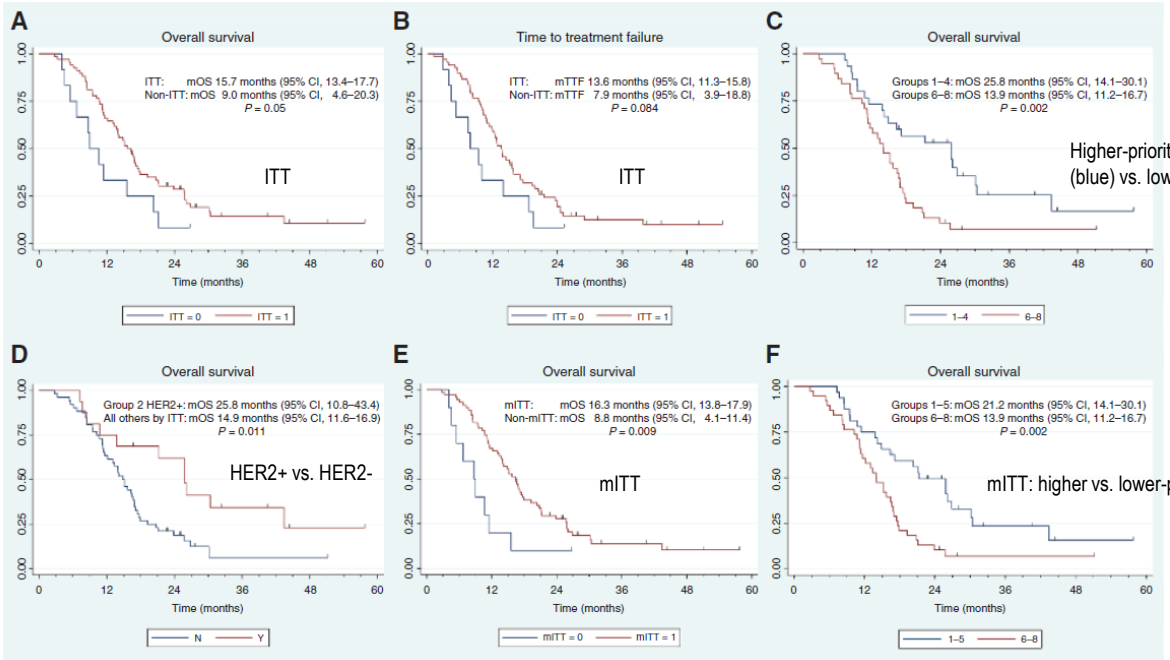
The PANGEA Trial

Targeted therapies based on patient genomic profile



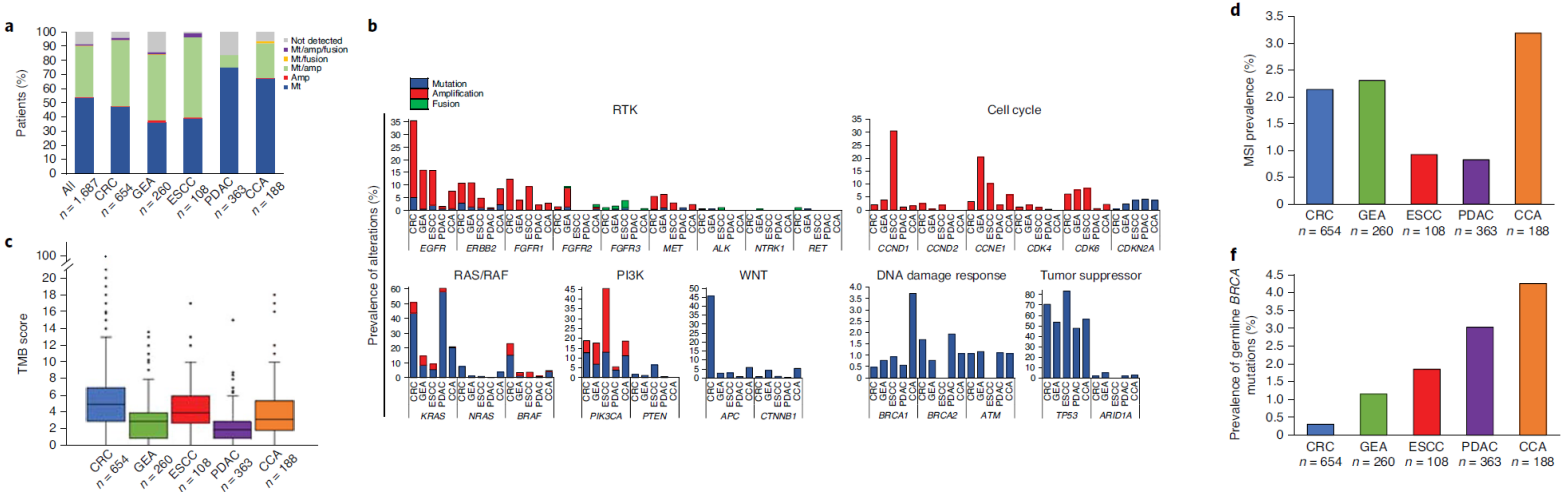
2021 ESMO congress

Catenacci Cancer Discov 2021

SCRUM-Japan GI-SCREEN and GOZILA studies

Large-scale sequencing to screen GC patients for trial eligibility

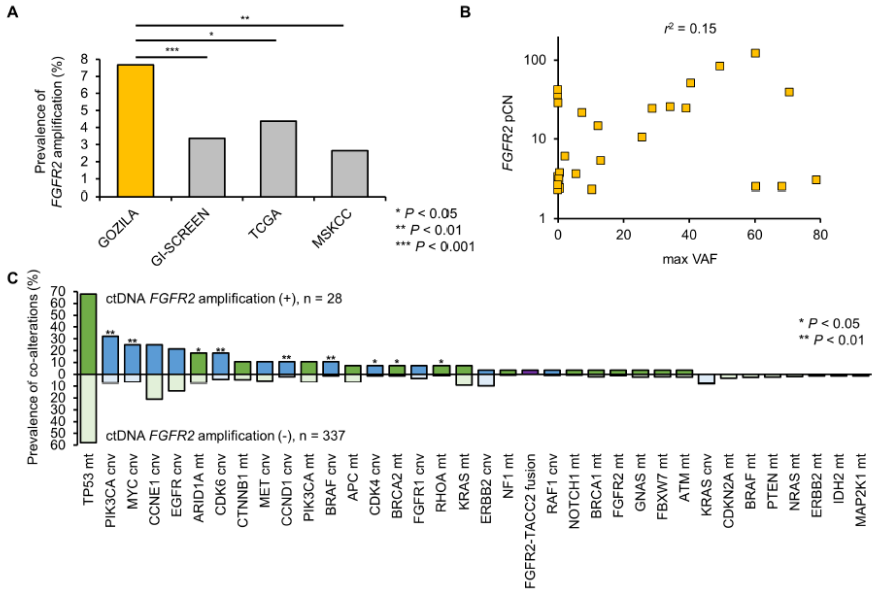
- Feasibility of large-scale sequencing for GC precision medicine
- ctDNA genotyping revealed the presence of rare molecular alterations



Nakamura Nat Med 2020

SCRUM-Japan GI-SCREEN and GOZILA studies

ctDNA detects *FGFR2* amp and concurrent genomic alterations associated with FGFR inhibitor efficacy



- *FGFR2* amp more freq in ctDNA (7.7%) than in tissue (4.4%)
- *FGFR2* amp associated with worse prognosis
- Two patients with normal *FGFR* in tissue but with amp in ctDNA after PD to 1st line ttx did respond to FGFRi
- One pt with *FGFR2* and *MET* co-amp (ctDNA) with limited benefit from FGFRi

- Large-scale sequencing of ctDNA allows to better understanding of the incidence, prognosis and predictive value of molecular alterations, as well as to identify those patients who can benefit from targeted therapies

Jogo Clin Cancer Res 2021

2021 ESMO congress

Thank you very much!

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