Molecular profiling-selected treatment in metastatic cancer: can we change our standard of practice

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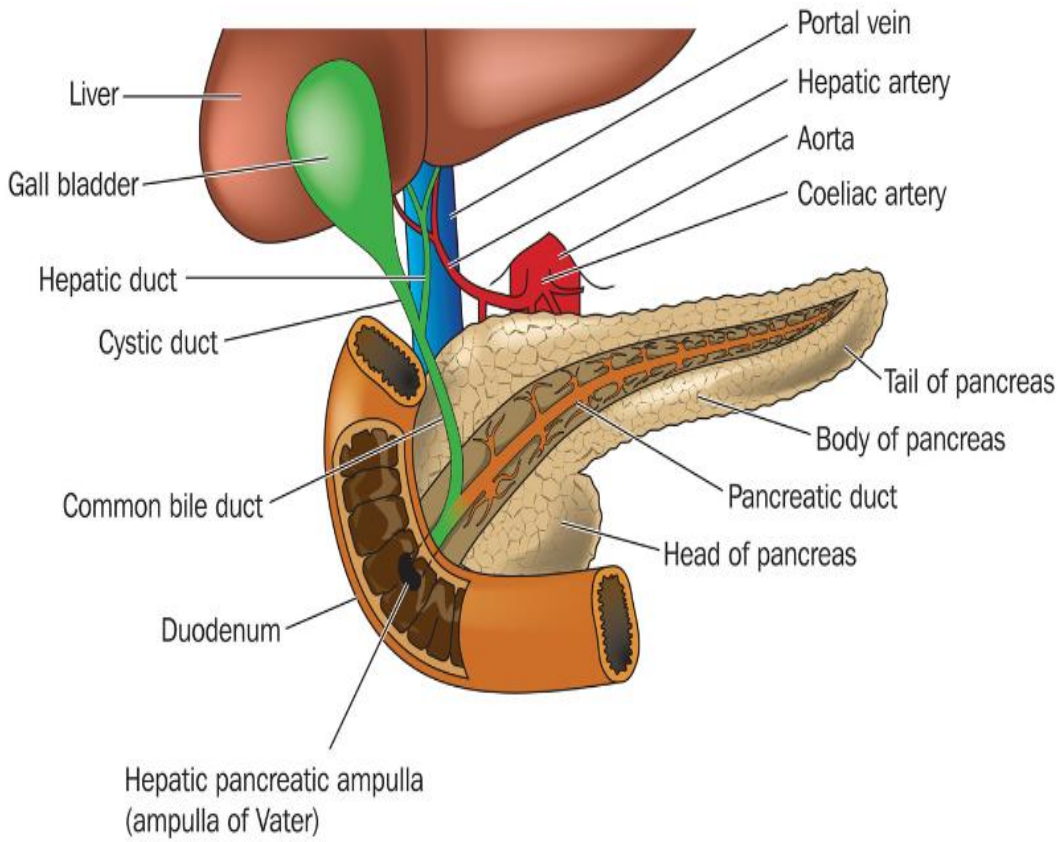
Disclosure- Caris consultant

Gastric & Esophageal cancer

- Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death worldwide.
- Esophageal cancer is the eighth most common malignancy and the sixth leading cause of cancer death worldwide. In 2012, there were approximately, 1.4 million new cases of gastric/esophageal cancers and 1.1 million deaths from these cancer types.

- At present, there is no internationally-accepted consensus regarding standard-of-care in the 1st-line metastatic setting in gastric/esophageal cancer, except for 10-25% of patients with gastric/gastroesophageal junction (GEJ) cancer whose tumors are human epidermal growth factor receptor 2 (HER2)-positive

Pancreatic Cancer: Incidence & Mortality



- Epidemiology
  - 4th most common cause of cancer death
  - In 2015, 48,960 new cases are expected in the US, with 40,560 deaths
  - Incidence much higher after 45 yrs of age

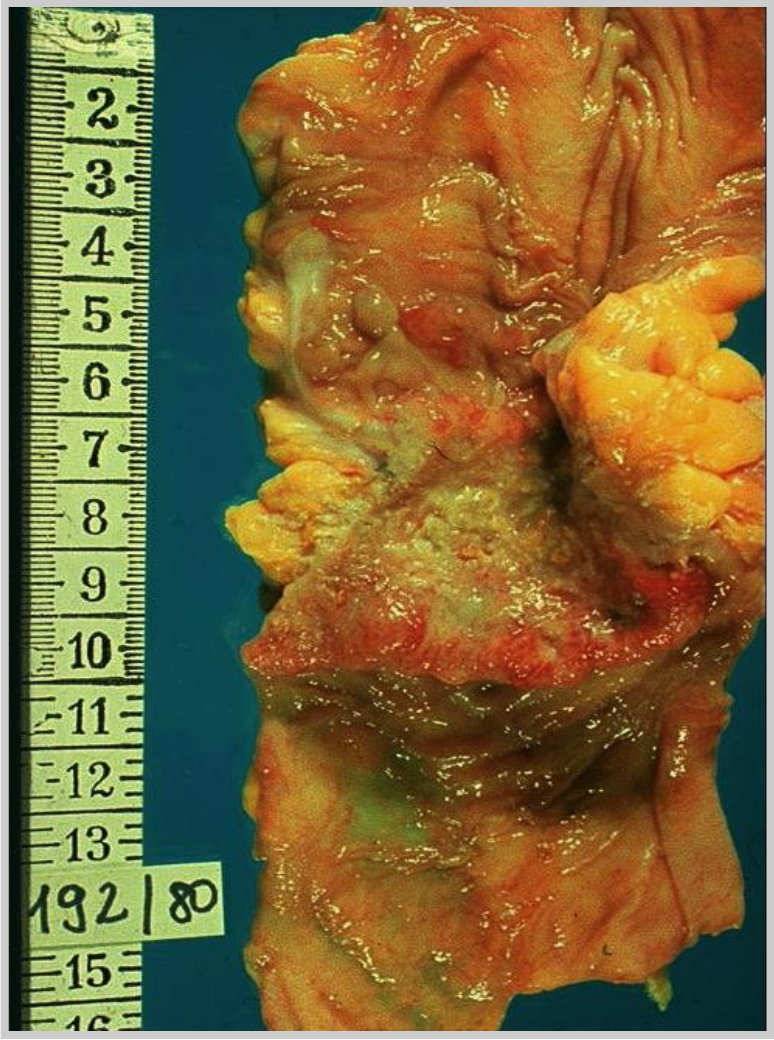
Siegel R, et al. CA Cancer J Clin. 2015;65:5-29.

FOLFIRINOX vs Gemcitabine: Efficacy

Outcome	FOLFIRINOX (n = 171)	Gemcitabine (n = 171)
ORR, %	31.6	9.4
Median PFS, mos	6.4	3.3
Median survival,* mos	11.1	6.8
1-yr survival, %	48.4	20.6

Conroy T, et al. N Engl J Med. 2011;364:1817-1825.

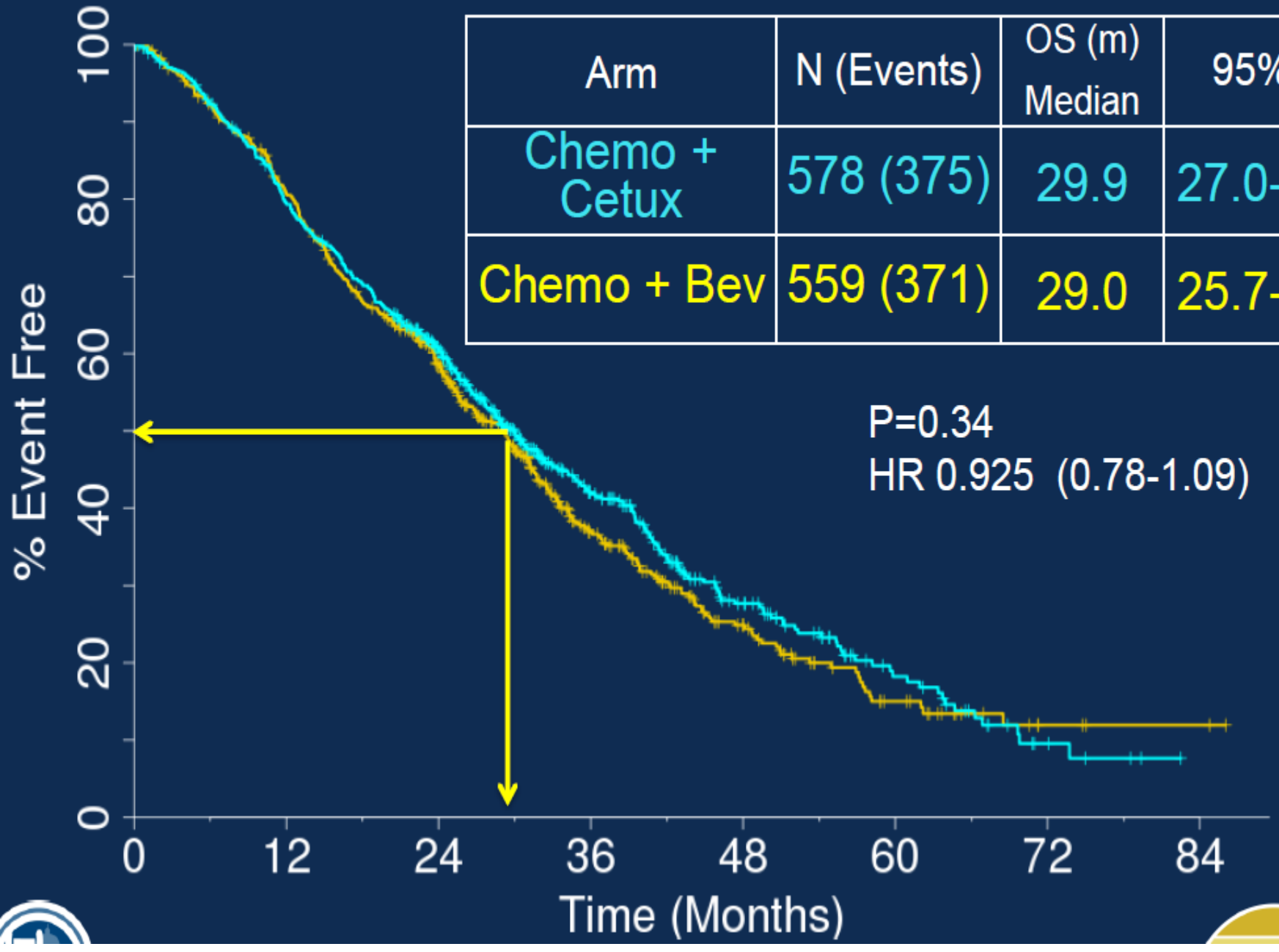
Colorectal Cancer (CRC) - Epidemiology



- Incidence worldwide 950,000 / yr
- Mortality: 500,000 / yr
- Cause of death in 2 - 2.5% of population
- Median OS with metastasis without treatment 6 months

CALGB/SWOG 80405: Overall Survival

Arm	N (Events)	OS (m) Median	95% CI
Chemo + Cetux	578 (375)	29.9	27.0-32.9
Chemo + Bev	559 (371)	29.0	25.7-31.2



CHOLANGIOCARCINOMA

- >7,000 cases annually in 2009
- 5-year survival is <15%
- Most patients present with locally advanced or metastatic disease
- Treatment commonly administered in the community, at low-volume centers.

ABC-02 - Study schema

+ QoL

Eligible patients (n=400*)

Randomized 1:1

(stratified by centre, primary site, PS, prior therapy and locally advanced vs. metastatic)

Arm A

Gem *1000 mg/m²* *D1,8,15 q 28d*, 24 weeks (6 cycles)

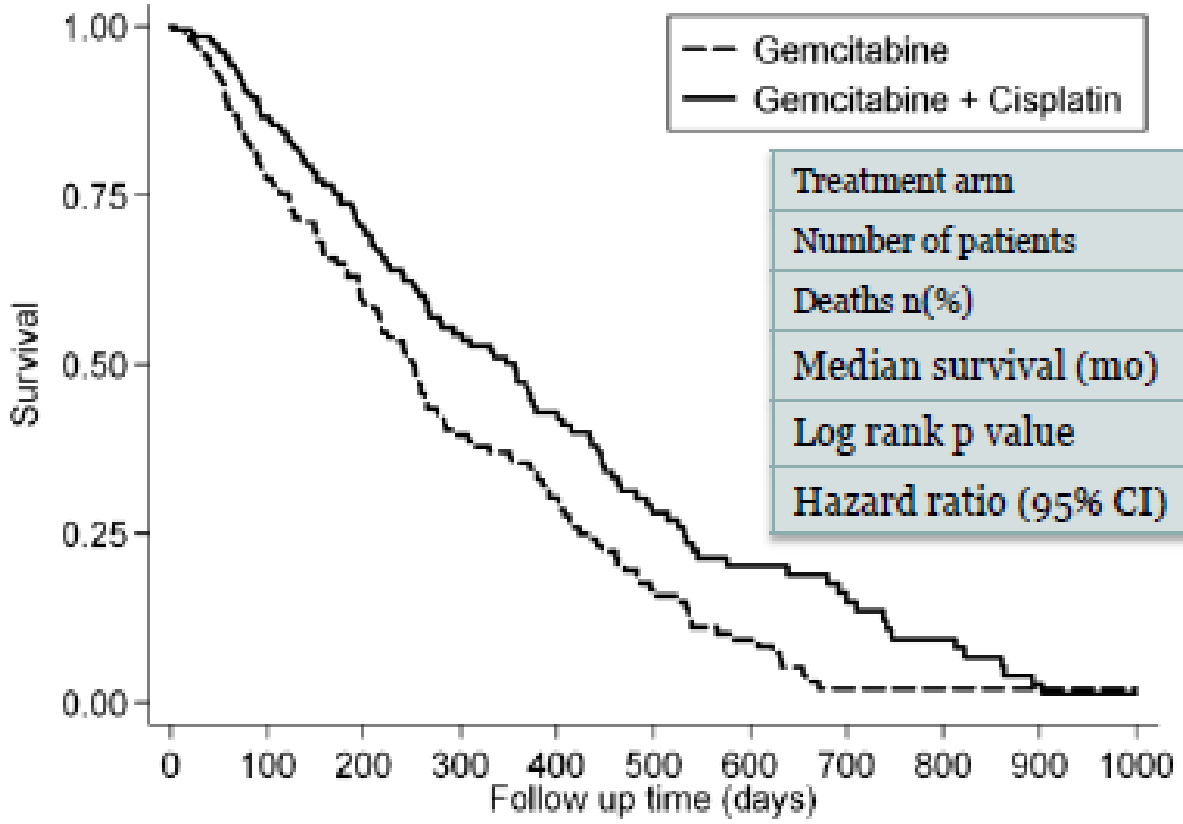
Arm B

Cisplatin *25 mg/m²*
+ **Gem *1000 mg/m²*** } *D1,8 q 21d*

24 weeks (8 cycles)

Upon disease progression, management will be on clinician's discretion (mostly best supportive care)

ABC-02 - Results: Overall Survival (ITT)



Treatment arm	Gem	Gem + Cis
Number of patients	n=206	n=204
Deaths n(%)	141 (68.5)	122 (59.8)
Median survival (mo)	8.3	11.7
Log rank p value	0.002	
Hazard ratio (95% CI)	0.70 (0.54, 0.89)	

Triple Negative Breast Cancer

- Breast cancer is the most frequent tumor worldwide; approximately 10% to 20% of these patients will be diagnosed with triple-negative breast cancers

- These group presents with a varied natural history but are collectively associated with poor prognosis with high risk of relapse and short progression-free survival (PFS) and overall survival (OS).

- As many as 50% of patients diagnosed with **early-stage triple-negative breast cancer** (stages I to III) experience disease recurrence, and 37% die in the first 5 years after surgery.

Triple Negative Breast Cancer

- **patients with metastatic triple-negative breast cancer** have short PFS after failure of first-line chemotherapy :median PFS, 3 to 4 months.

- Current guidelines support that triple-negative breast cancer should be treated with conventional strategies primarily driven by the patient's characteristics and the toxicity profile of the treatment to be chosen.

- **At present, approved targeted therapy exists and the standard remains cytotoxic chemotherapy.**

Transitional cell carcinoma(TCC)

- advanced or metastatic TCC
  - First-line chemotherapy regimens for advanced or metastatic TCC consists of gemcitabine and cisplatin) (GC) or a combination of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC).
  - Taxanes or vinflunine have been used as second-line therapy (after progression on a platinum containing chemotherapy).
  - Immunotherapy such as pembrolizumab is often used as second-line therapy for metastatic urothelial carcinoma that has progressed despite treatment with GC or MVAC.

Change Clinical Practice with Caris Multiplatform Molecular Profiling

DNA

592 genes profiled with **full exon coverage** (average depth of coverage is **750x)** ✓
Point mutations, insertion/deletions ✓
Copy Number Variation in **442 genes** ✓
Total Mutational Burden ✓
MMR (NGS+PCR)/MSI ✓
Pyrosequencing (MGMT Methylation) ✓

RNA

Gene fusion panel of **over 12 genes** ✓
CISH tests where described in guidelines ✓

Protein

12 Validated **Immunohistochemistry tests** ✓
MSI/MMR(PCR+NGS) ✓
PD-L1 ✓

PD-L1
Programmed Cell Death-Ligand 1 by IHC
64,000+
TESTS PERFORMED

MSI
Microsatellite Instability by NGS
24,000+
TESTS PERFORMED

TMB
Tumor Mutational Burden by NGS
33,000+
TESTS PERFORMED

- **NEW YORK STATE ,department of health recommendation**: “Establish minimum criteria for depth and uniformity of coverage, i.e. number of reads, across all target areas. **a minimum average of 500 reads or greater is <u>strongly</u> recommended”.**

- **Profiling Guidelines - NCCN Guidelines® recommend “broad molecular profiling” (Full Exon ,not Hot Spot**).

- **Caris Type of Sequencing: 592 genes** profiled with **full exon** coverage .average **depth of coverage is 750x.**

The assay validations performed at Caris exceed CAP, CLIA, NYS and ISO 15189 regulatory standards.

CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS
CERTIFICATE OF ACCREDITATION

LABORATORY NAME AND ADDRESS
CARIS MPI, INC
DBA CARIS LIFE SCIENCES
4610 SOUTH 44TH PLACE STE 100
PHOENIX, AZ 85040

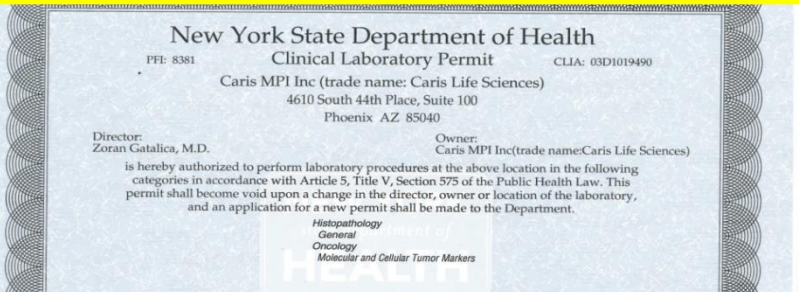
CLIA ID NUMBER
03D1019490
EFFECTIVE DATE
05/21/2014
EXPIRATION DATE
05/20/2016

LABORATORY DIRECTOR
ZORAN GATALICA M.D.

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown hereon (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

Judith A. Yost, Director



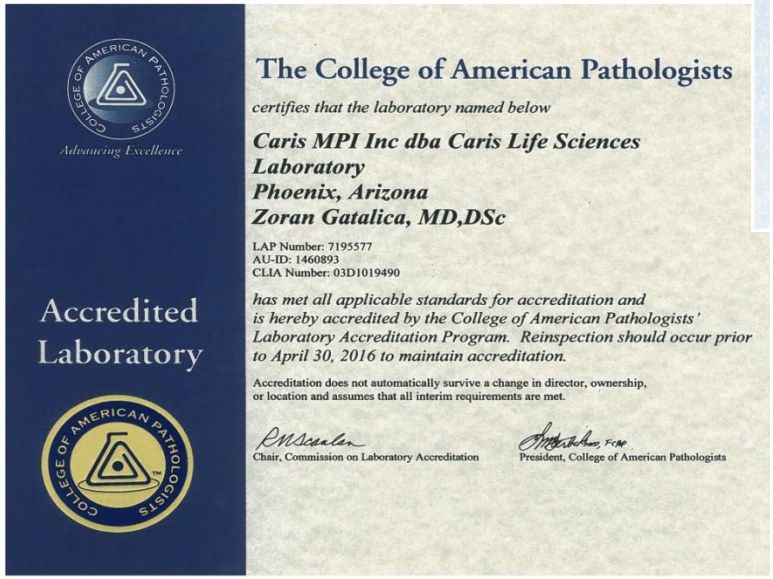
New York State Department of Health
PFI: 8381 Clinical Laboratory Permit CLIA: 03D1019490
Caris MPI Inc (trade name: Caris Life Sciences)
4610 South 44th Place, Suite 100
Phoenix AZ 85040

Director:
Zoran Gatalica, M.D.

Owner:
Caris MPI Inc(trade name:Caris Life Sciences)

is hereby authorized to perform laboratory procedures at the above location in the following categories in accordance with Article 5, Title V, Section 575 of the Public Health Law. This permit shall become void upon a change in the director, owner or location of the laboratory, and an application for a new permit shall be made to the Department.

Histopathology
General
Oncology
Molecular and Cellular Tumor Markers



Advancing Excellence

Accredited Laboratory

The College of American Pathologists

certifies that the laboratory named below

Caris MPI Inc dba Caris Life Sciences Laboratory
Phoenix, Arizona
Zoran Gatalica, MD,DSc

LAP Number: 7195577
AU-ID: 1460893
CLIA Number: 03D1019490

has met all applicable standards for accreditation and is hereby accredited by the College of American Pathologists' Laboratory Accreditation Program. Reinspection should occur prior to April 30, 2016 to maintain accreditation.

Accreditation does not automatically survive a change in director, ownership, or location and assumes that all interim requirements are met.

Chair, Commission on Laboratory Accreditation

President, College of American Pathologists

ilac-MRA

American Association for Laboratory Accreditation

Accredited Laboratory
A2LA has accredited
CARIS MPI, INC. (D/B/A CARIS LIFE SCIENCES)
Phoenix, AZ
for technical competence in the field of
Clinical Testing

This laboratory is accredited in accordance with the recognized International Standard ISO 15189:2012 *Medical laboratories - Requirements for quality and competence*. This accreditation demonstrates technical competence for a defined scope and the operation of a laboratory quality management system (*refer to joint ISO-ILAC-IAF Communiqué dated September 2009*).

Presented this 22nd day of November 2013.

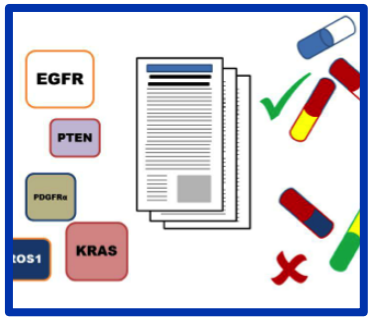
President & CEO
For the Accreditation Council
Certificate Number 3531.01
Valid to January 31, 2016
Revised: July 15, 2014

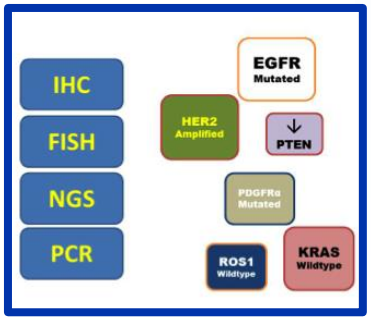
For the tests or types of tests to which this accreditation applies, please refer to the laboratory's Clinical Scope of Accreditation.

Four critical success factors for CMI

EVIDENCE

- Continuous study of the medical literature
- Board of experts defines associations
- Only clinically validated predictive biomarkers are considered





REPORT

- Easy to interpret
- Drugs associated with clinical benefit and lack of benefit
- Reference to clinical trials
- Detailed results and further reading

ANALYSIS

- Multiplatform profiling
- Precision IHC testing
- High-throughput workflows: < 12 days
- Highest Quality Standards

INTERPRETATION

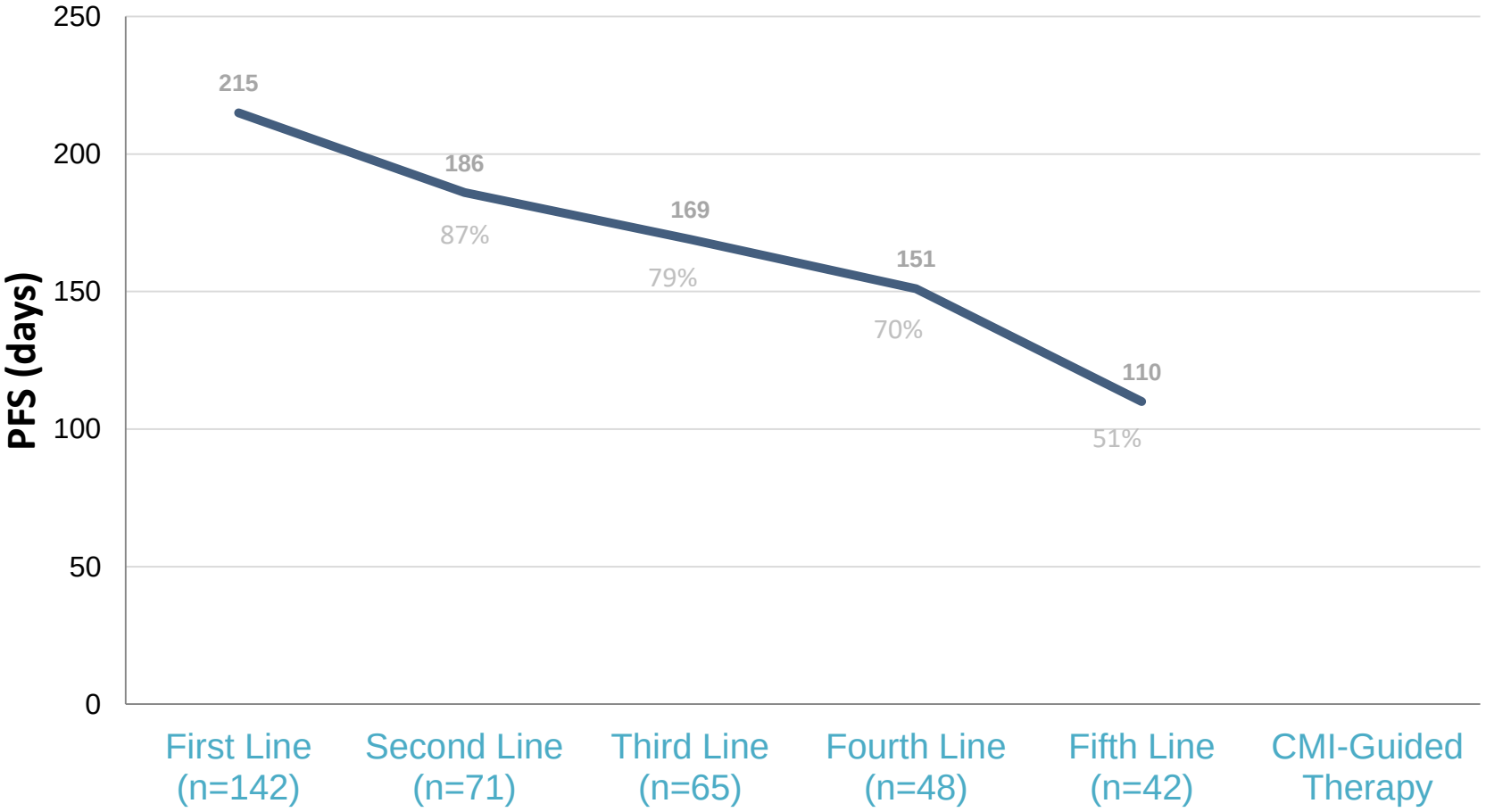
- Caris Clinical Team follows each case
- Email with executive summary
- Telephone call with Caris oncologist offered

Bisgrove study

- First successful publication of outcomes from molecular profiling
  - Dan von Hoff won the Karnofsky award in 2010
  - Cited over 70 times
- Molecular targets identified for 98% of patients
- Mostly targets for conventional agents were identified
- Treatment suggested by molecular profiling led to clinical benefit in 27% of treated patients

Progression Free Survival to assess clinical benefit:

PFS is getting shorter in subsequent lines of therapy



Adapted from Bailey et al. (2012) *Progression-free survival decreases with each subsequent therapy in patients presenting for Phase I Clinical Trials. Journal of Cancer 2012 3:7-13*

Bisgrove Study Primary Endpoint

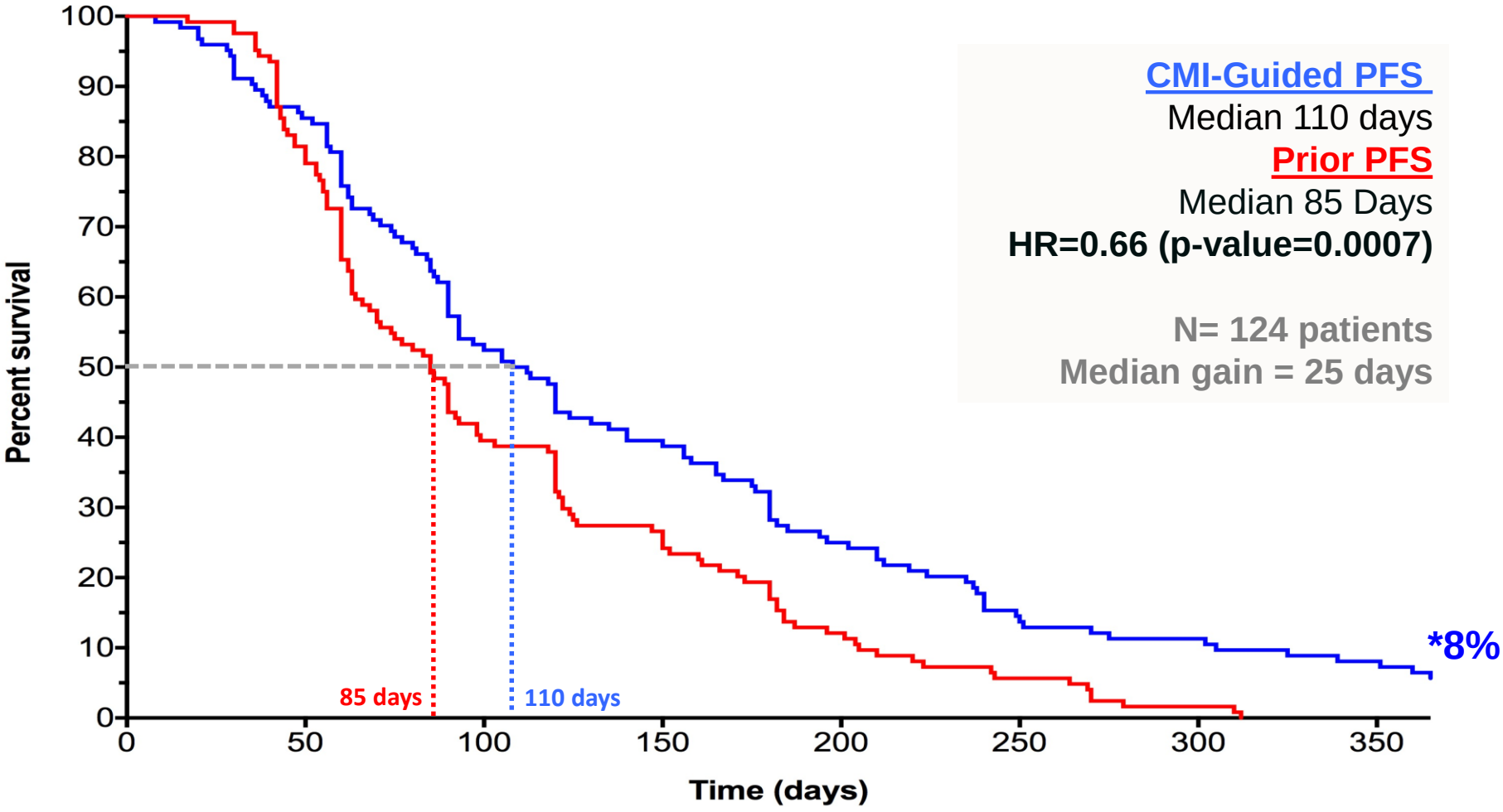
Compare progression free survival (PFS) for therapy selected by molecular profiling with PFS for the last line of therapy on which the patient progressed.

If PFS_b/PFS_a ratio was $\geq$ 1.3, MP-selected therapy was defined as having benefit for patient.

PFS: length of time during and after treatment in which a patient is living with a disease that does not get worse.

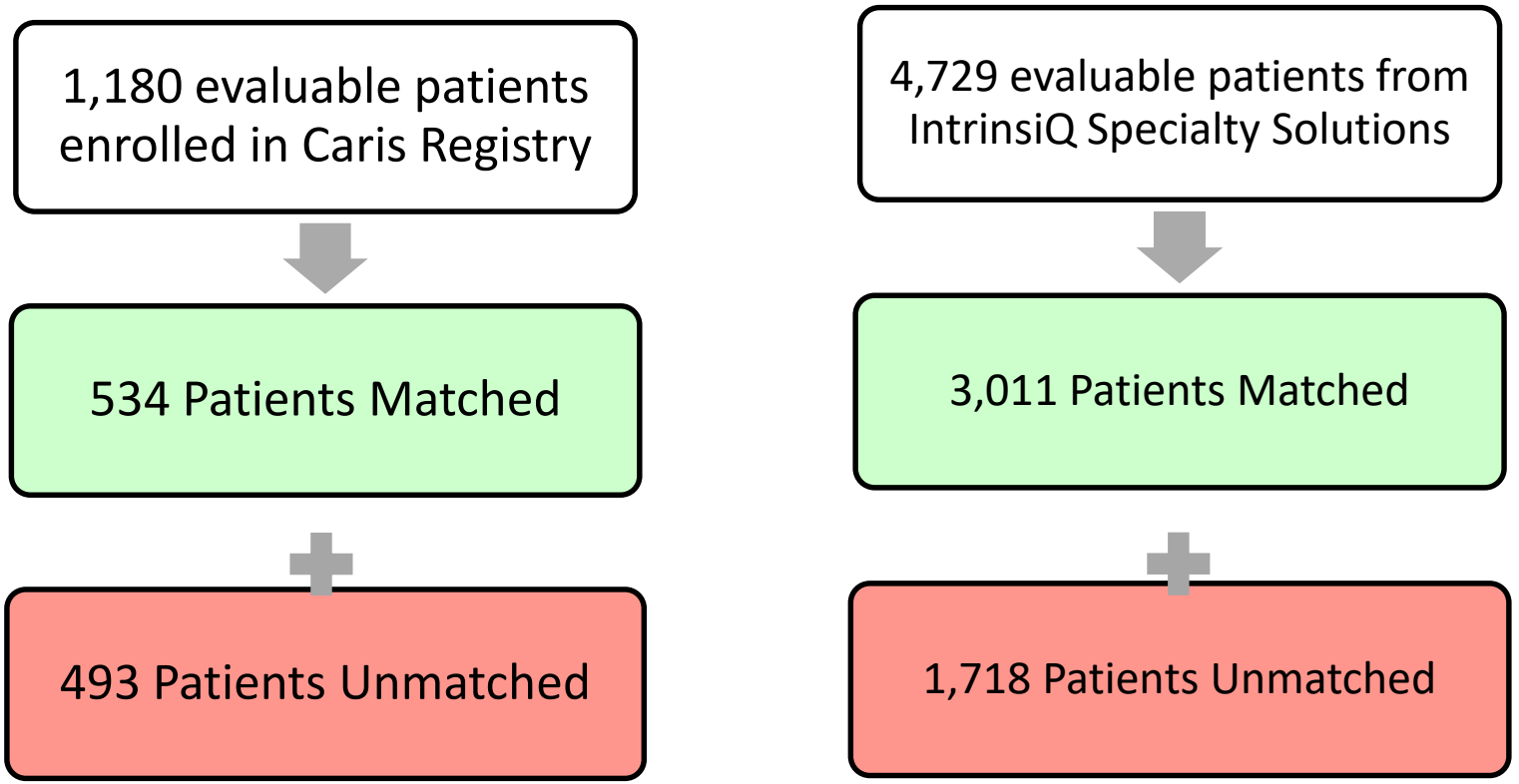
Temple, R. *Clinical Measurement in Drug Evaluation*. Ningano W. Thicker GT, eds. John Wiley and Sons Ltd: 1995; Von Hoff, D.D. 1999; Dhani et al. *Clinical Cancer Research*. 2009; 15: 118-123.

CMI-Guided treatment leads to gain of PFS



Based on analysis of raw data from Jameson et al, Dean et al, Chahine et al and Seeber et alc

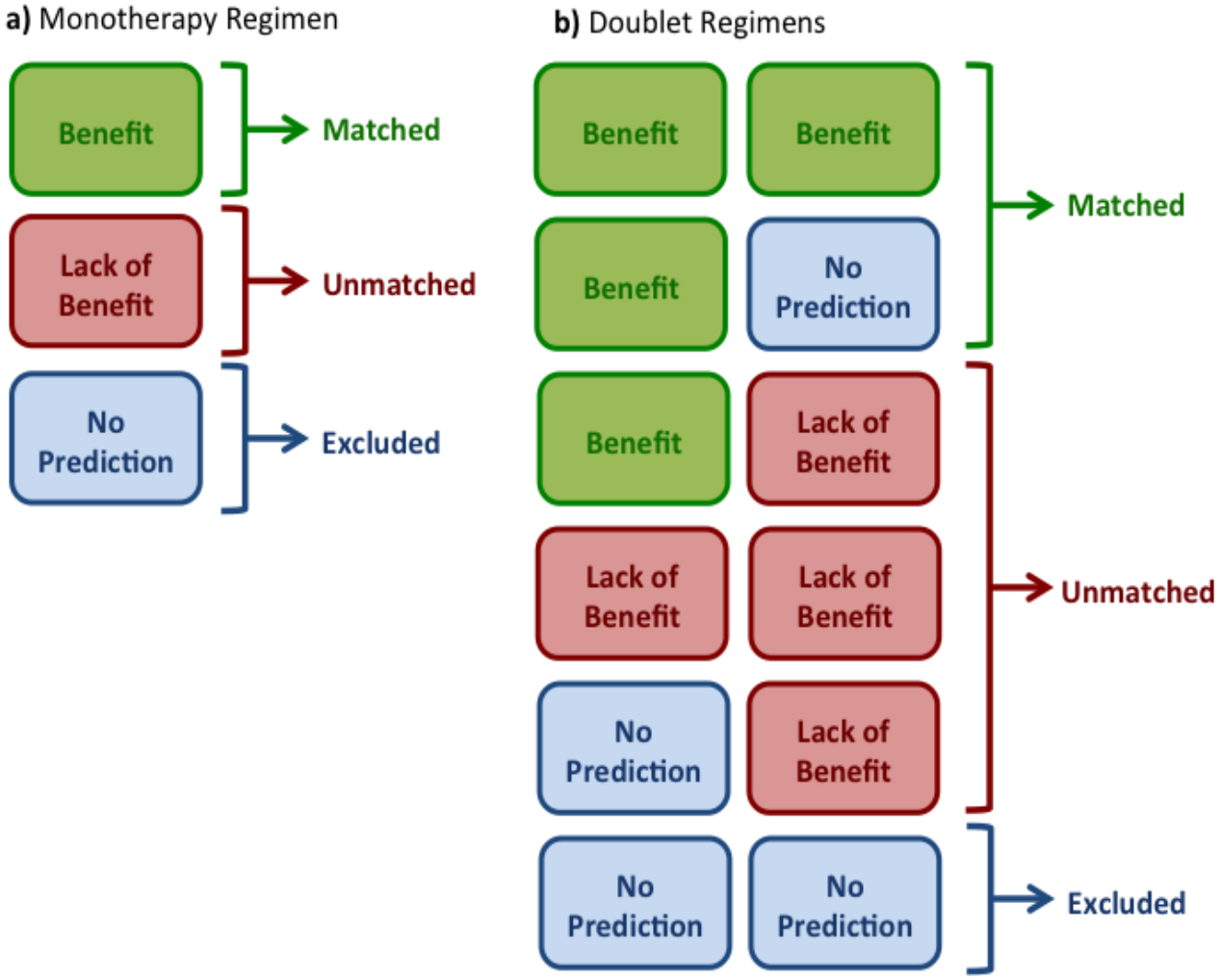
Patients Profiled using Caris Molecular Intelligence
(IHC, FISH/CISH, FA, NGS)
Performed under accreditation from CLIA, CAP and ISO5189:2012



Spetzler D et al. (2015) *Multi-platform molecular profiling of 1,180 patients increases median overall survival and influences treatment decision in 53% of cases. Presented at ECCO 2015*

Marshall et al. (2015) *Panomics validation of time to next treatment (TNT) as a surrogate outcome measure in 4729 cancer patients. J Clin Oncol 34, 2016 (suppl; abstr 11521)*

Cohort Definitions for Monotherapies and Doublet Combinations Based on Predictive Association with Biomarker Results



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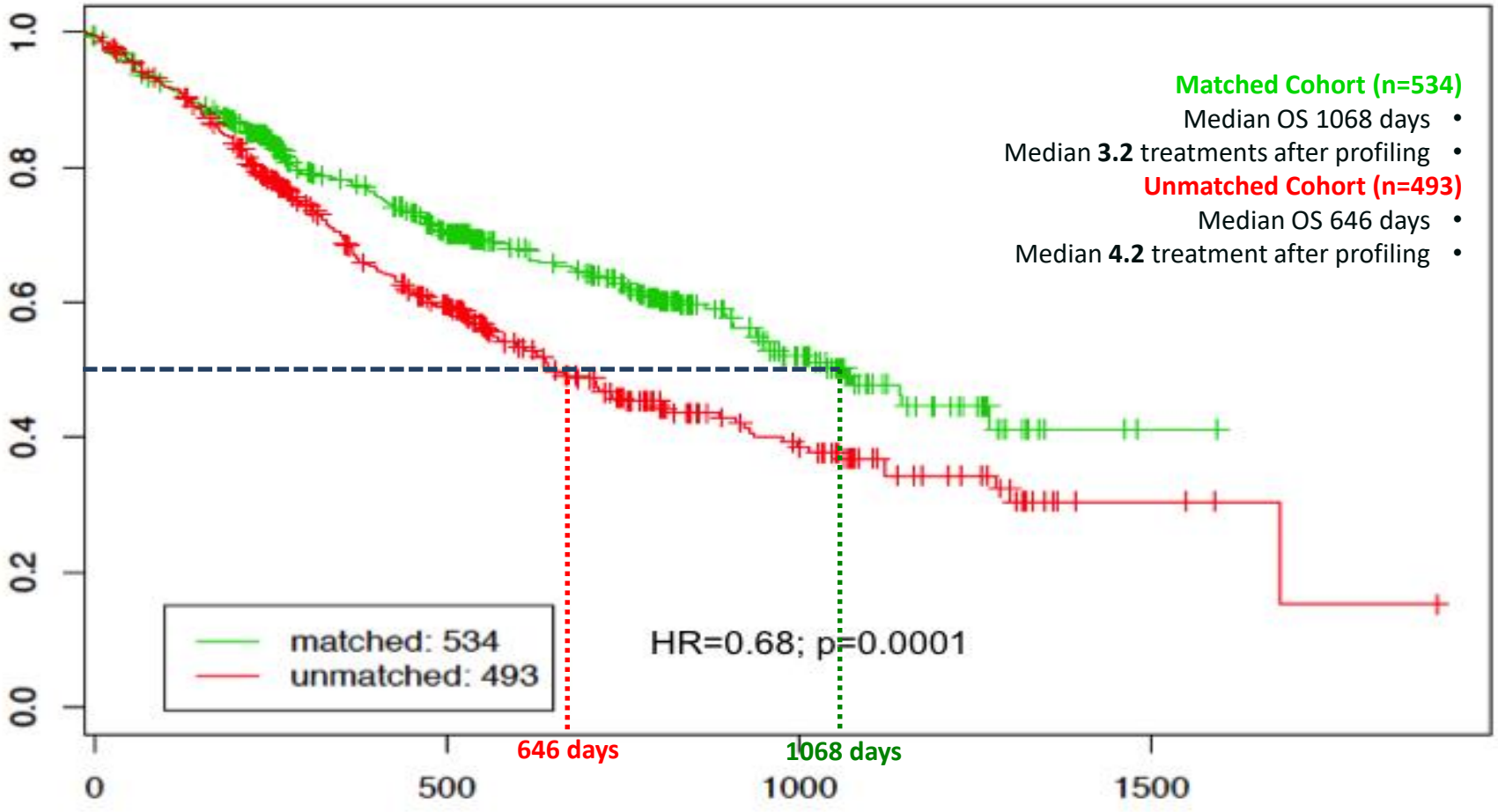
Overall Survival is higher in Matched Cohort



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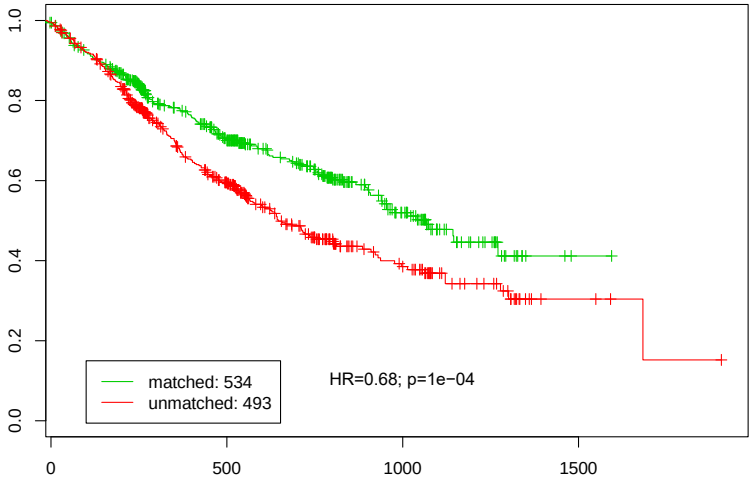
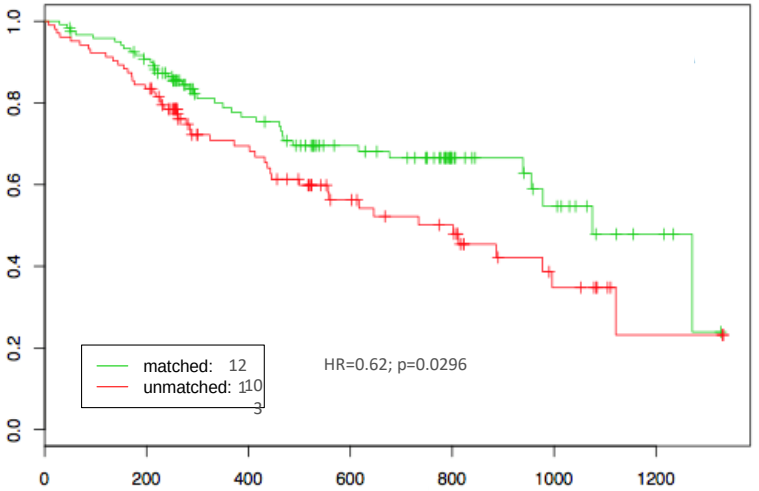
CMI Registry: Clinical Utility Across Various Indications

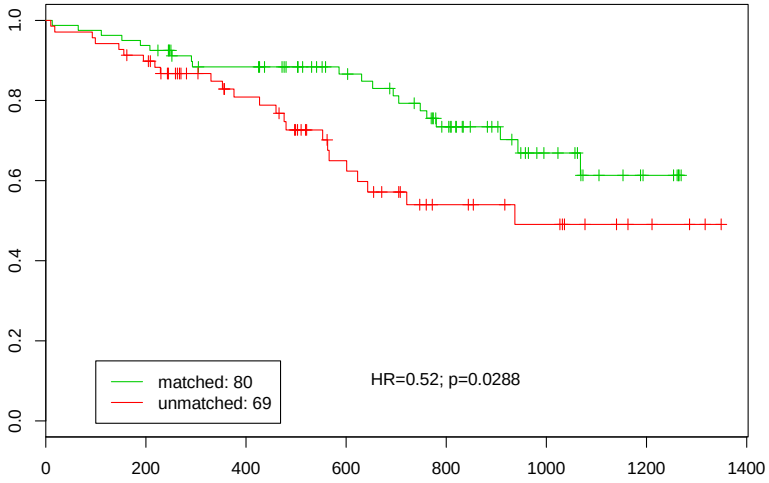
All Lineages



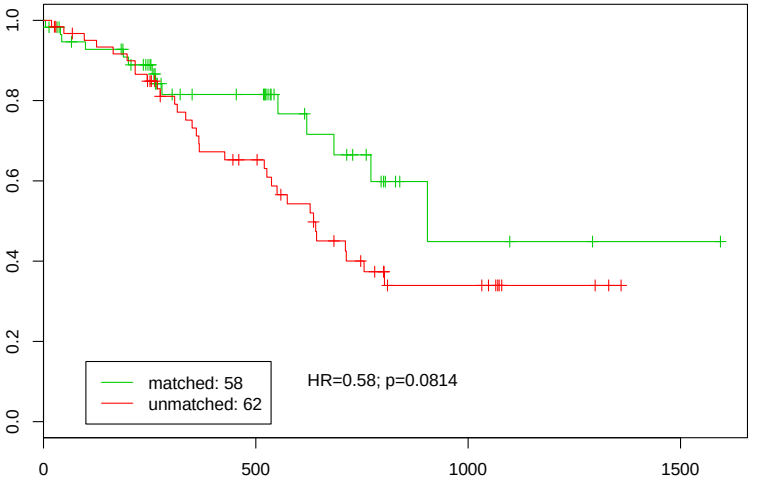
Ovarian Cancer



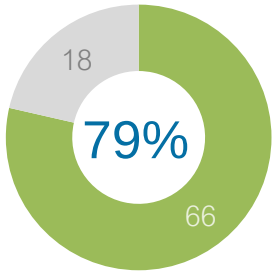
Breast Cancer



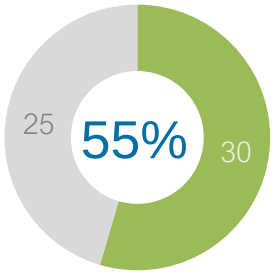
Colorectal Cancer



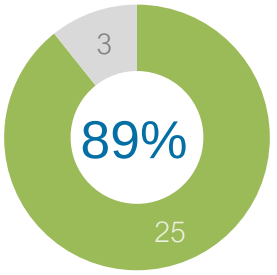
78% of Profiled Patients Are Treated In Line with CMI Report



Refractory Solid Cancers
[2]Von Hoff et al.



Refractory Pancreatic Cancers
[5]Epelbaum et al.



Refractory Breast Cancers
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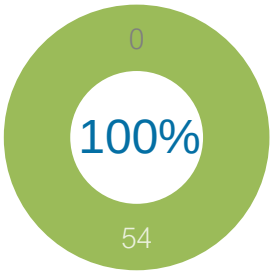
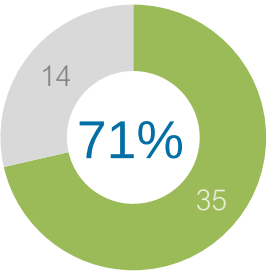


Refractory Solid Cancers
[8]Dean et al.



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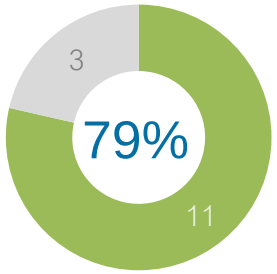
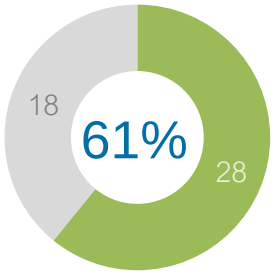
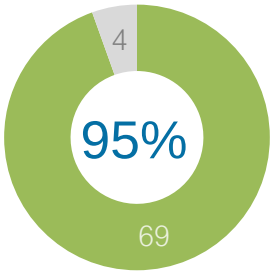


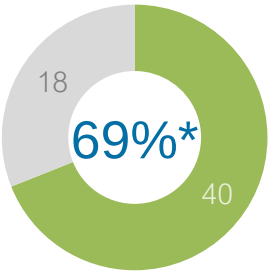
Metastatic Adenoid Cystic Carcinoma
[9]Popovtzer et al.



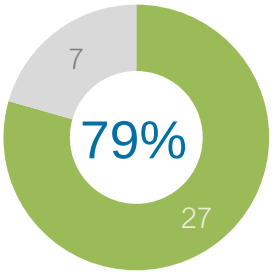
Refractory Gastric Cancers
[10]Purim et al.



Refractory Solid Cancers
[14]El Ahmadie et al.



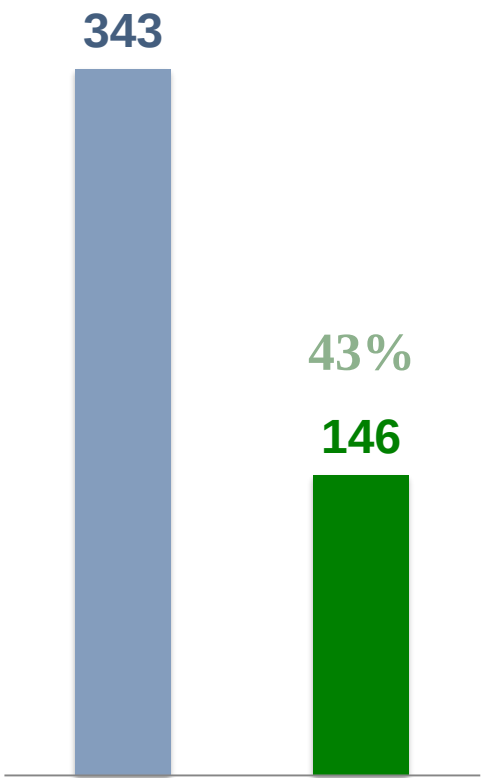
Refractory Solid Cancers
[13]Seeber et al.

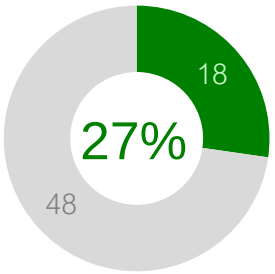


Refractory Solid Cancers
[16]Chahine et al.

* Still enrolling

43% of CMI-Guided Treatments result in Clinical Benefit





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PFS Ratio ≥ 1.3
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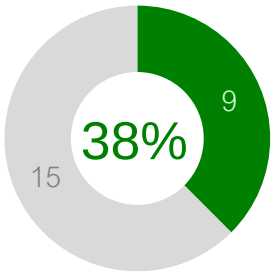

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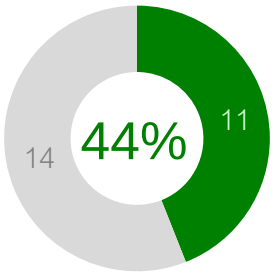

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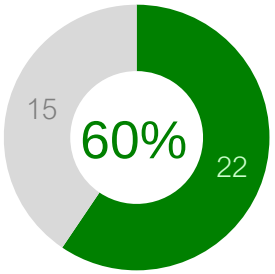

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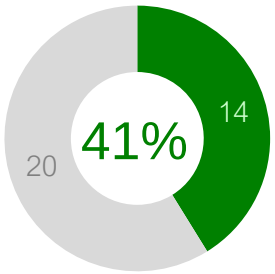
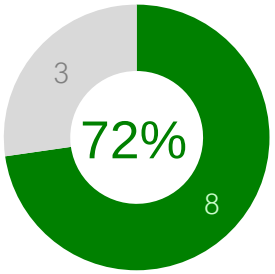
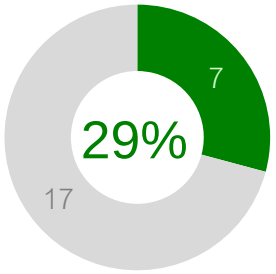


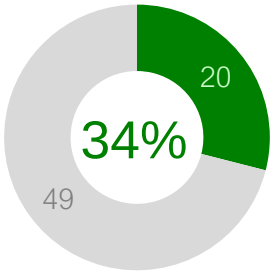
Refractory Pancreatic Cancers
OS > 6 months
[6]Ramanathan et al.



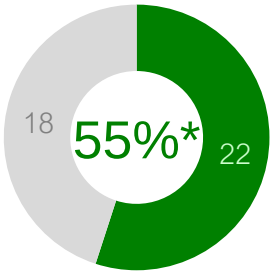
Metastatic Adenoid Cystic Carcinoma
CR/PR/SD>6 months
[9]Popovtzer et al.



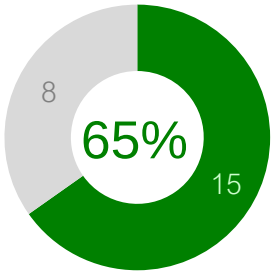
Refractory Gastric Cancers
PFS Ratio ≥ 1.3
[10]Purim et al.



Refractory Solid Cancers
RECIST Response
[14]El Ahmadie et al.



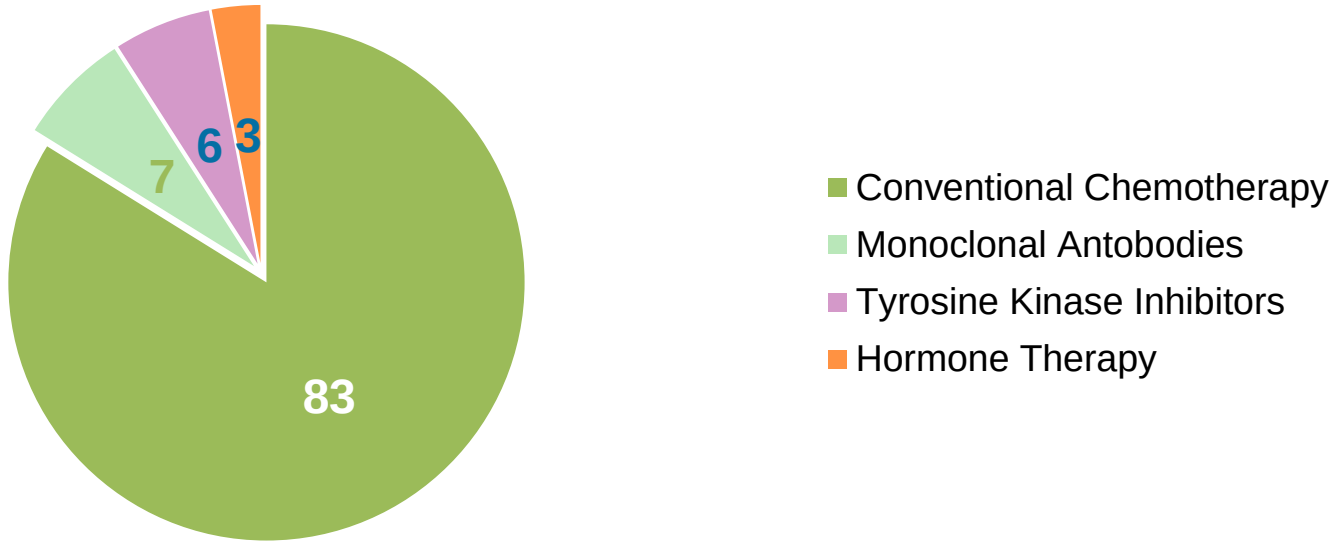
Refractory Solid Cancers
PFS Ratio ≥ 1.3
[13]Seeber et al.



Refractory Solid Cancers
PFS Ratio ≥ 1
[16]Chahine et al.

* Still enrolling

In 10 physician-led studies, 364 patients were treated in line with the findings of the CMI report (75% of those profiled)



The high utility is driven by accessibility of cheaper, cytotoxic chemotherapy options

which are not otherwise considered

MULTIOMIC PROFILING OF METASTATIC LESIONS TO GUIDE TREATMENT SELECTION: THE SIDE OUT 2 TRIAL EXPERIENCE

Study Primary Objective

The aim of this prospective pilot study was to explore if treatment selection based on Multi-omic Profiling (MoP) provides clinical benefits superior to empiric treatment selection in progressive metastatic breast cancers (MBC).

Conclusions

- ✓ This study confirmed the unique role of MoP in selecting effective treatments for MBC.
- ✓ This approach provided clinical benefits for 56% of previously treated MBC patients, which met the primary objective of the study.
- ✓ This study also suggests that irinotecan may be an under-developed drug for MBC patients.
- ✓ As such, this approach merits further investigation.

Trial design: The Side Out 2 trial (clinicaltrials.gov ID NCT01919749) was an open-label, multicenter pilot study which used the molecular profile of target lesions to guide treatment selection. Therapeutic regimens were selected only from FDA approved compounds.

Patient Population: Between 2014 and 2016, four US sites enrolled 32 previously treated MBC patients.

Key Eligibility Criteria:

- ✓ Age ≥18 years;
- ✓ ECOG of 0-1;
- ✓ Absence of symptomatic CNS metastasis;
- ✓ Adequate organ and bone marrow function;
- ✓ Documented diagnosis of metastatic breast cancer with measurable disease accessible to biopsy;
- ✓ Progression of disease on ≥ 1 prior chemotherapeutic and/or hormonal regimen(s) for advanced disease within 6 months of treatment initiation.

Response Rate Criteria: Growth Modulation Index (GMI) was used to assess patients' response to treatment based on tumor response by RECIST 1.1.

PFS_B/PFS_A ratio ≥ 1.3 = benefit for patient.

To meet the primary objective, ≥ 30% of patients must reach a GMI score ≥ 1.3 (PMID:25209003).

Study workflow

Consenting/Screening/Enrollment:
MBC patient with disease progression, clear documentation of time between treatments, and documented progression on the most recent treatment.

Tissue Collection and Multi-Omic Analysis:
Multi-omic analysis of the metastatic lesion;
- RNA-Seq & Exome Sequencing;
- Immunohistochemistry of 7 predictive markers*;
- LCM-RPPA based protein singling network analysis of 12 FDA approved drug targets and downstream substrates**.

Target(s) Found

Yes

Patient receives treatment based on identified target(s).

No

Patient receives treatment based on physician choice.

Disease Assessment Using RECIST Criteria:
Patients are assessed every 7 ± 1 weeks during the GMI monitoring window until disease progression or treatment discontinuation.

If progression is not observed at the end of therapy, patients are assessed every 3 months until progression.

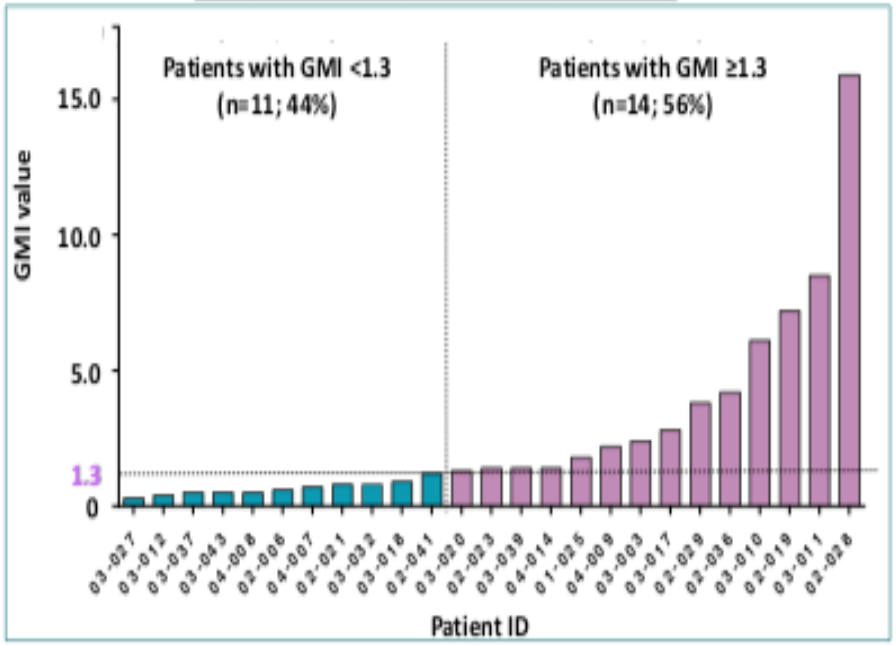
At disease progression an optional second biopsy may be performed.

*IHC markers: Androgen (AR), Estrogen (ER), and Progesterone (PR) Receptor; SPARC; TOP2A; TOPO1, and Thymidylate Synthase (TS).
**LCM-RPPA markers: ALK; pAKT S473; pc-Abl Y735; pEGFR Y1068; pERB2 Y1248; pERB3 Y1289; pERK 1/2 T202/Y204; pp70S6K T389; pPDGFR Y751; PTEN; pRet Y905; pSrc Y527.

Enrollment overview

Patient Summary	Number of Patients
Enrolled	32
Treated based on MoP	29
Treated with standard of care	3
Evaluable for GMI window	25

Patient outcome based on GMI score



- ✓ Of the 25 patients, 14 (56%) met or exceeded a GMI of 1.3.
- ✓ The most frequently selected treatments were: Irinotecan based on TOPO1 expression (n = 12; single agent n = 5) and Capecitabine based on TS expression (n = 10; single agent n = 3).
- ✓ Seven patients received endocrine therapy, 3 of whom were treated with Everolimus and Exemestane.
- ✓ Based on HER2 amplification/pathway activation, HER2 targeted agents were given to 5 patients.

Molecular characteristics of metastatic lesions and treatment

Subject ID	GMI	Receptor Status	Metastatic site	Targets	Treatment
02-03-027	0.3	ER+;PR-;HER2-	Omentum	AR; ER; TOPO1	Irinotecan; Megestrol Acetate
02-03-012	0.4	ER+;PR+;HER2-	Liver	AR; ER; TOPO1; TS	Capecitabine; Irinotecan; Megestrol Acetate
02-03-037	0.5	ER+;PR+;HER2-	Liver	TOPO1	Irinotecan
02-03-043	0.5	ER+;PR-;HER2-	Liver	TUBB3	Eribulin
02-04-008	0.5	ER+;PR+;HER2-	Chest wall/Skin	ER; p-p70S6K	Everolimus; Exemestane
02-02-006	0.6	ER+;PR-;HER2-	Lymph node	p-AKT; p-ERB2; p-ERB3; p-ERK; TS	Capecitabine; Lapatinib
02-04-007**	0.7	ER+;PR-;HER2-	Chest wall/Skin	ER; p-ERB2; p-ERK; TOPO1; TUBB3	Eribulin; Irinotecan; Lapatinib; Letrozole
02-02-021	0.8	ER+;PR-;HER2-	Omentum	ER; p-p70S6K	Everolimus; Exemestane
02-03-032	0.8	ER-;PR-;HER2-	Chest wall/Skin	TUBB3	Eribulin
02-03-018	0.9	ER+;PR-;HER2-	Liver	Thymidine Phosphorylase (TYMP)	Capecitabine
02-02-041	1.2	ER-;PR-;HER2-	Chest wall/Skin	TOPO1	Irinotecan
02-03-020	1.3	ER+;PR-;HER2-	Liver	ER; p-p70S6K	Everolimus; Exemestane
02-02-023	1.4	ER-;PR-;HER2-	Liver & Lymph node*	EZH2*; Survivin*; TOPO1; TS; TUBB3*	Capecitabine; Irinotecan; Paclitaxel
02-03-039	1.4	ER-;PR-;HER2+	Lung	TOPO1; HER2; p-ERB2; p-ERK	Irinotecan; Trastuzumab
02-04-014	1.4	ER+;PR-;HER2-	Lung	TOPO1	Irinotecan
02-01-025	1.8	ER+;PR-;HER2-	Lymph node	TS	Capecitabine
02-04-009	2.2	ER+;PR+;HER2-	Abdominal mass	AR; ER; TS; AR; TUBB3	Capecitabine; Megestrol Acetate; Vinorelbine
02-03-003	2.4	ER+;PR-;HER2-	Liver	SPARC	Paclitaxel
02-03-017	2.8	ER+;PR-;HER2-	Liver	TS; p-EGFR; p-ERB2; p-ERB3; p-ERK	Capecitabine; Lapatinib
02-02-029	3.8	ER-;PR-;HER2-***	Chest wall/Skin	TOPO1	Irinotecan
02-02-036	4.2	ER+;PR-;HER2-	Liver	TOPO1; TS	Capecitabine; Irinotecan
02-03-010	6.1	ER+;PR+;HER2-	Liver	TOPO1	Irinotecan
02-02-019	7.2	ER-;PR-;HER2+	Chest wall/Skin	p-EGFR; p-ERB2; p-ERB3/ERBB3; p-ERK; HER2; TUBB3	Docetaxel; Pertuzumab; Trastuzumab
02-03-011	8.5	ER-;PR-;HER2-	Liver	TOPO1; TS	Capecitabine; Irinotecan
02-02-028	15.9	ER+;PR-;HER2-	Chest wall/Skin	TS	Capecitabine

*A second biopsy was collected from the same patient after recurrence; **Metastatic lesion from a male breast tumor; *** Data retrieved from whole exome sequencing analysis.

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ORIGINAL RESEARCH ARTICLE

Biomarker-Driven Therapy in Metastatic Gastric and Esophageal Cancer: Real-Life Clinical Experience

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Abstract

Background Precision treatment of cancer uses biomarker-driven therapy to individualize and optimize patient care.

Objective To evaluate real-life clinical experience with biomarker-driven therapy in metastatic gastric and esophageal cancer in Israel.

Patients and Methods This multicenter retrospective cohort study included patients with metastatic gastric or esophageal cancer who were treated in the participating institutions and underwent biomarker-driven therapy. Treatment was considered to have a benefit if the ratio between the longest progression-free survival (PFS) post biomarker-driven therapy and the last PFS before the biomarker-driven therapy was ≥1.3. The null hypothesis was that ≤15% of patients gain such benefit.

Results The analysis included 46 patients (61% men; median age, 58 years; 57% with poorly-differentiated tumors). At least one actionable (i.e., predictive of response to a specific therapy) biomarker was identified for each patient. Immunohistochemistry was performed on all samples and identified 1–8 (median: 3) biomarkers per patient (most commonly: low TS, high TOPO1, high TOP2A). Twenty-eight patients received therapy after the biomarker analysis (1–4 lines). In the 1st line after biomarker analysis, five patients (18%) achieved a partial response and five (18%) stable disease; the median (range) PFS was 129 (12–1155) days. Twenty-four patients were evaluable for PFS ratio analysis; in seven (29.2%), the ratio was ≥1.3. In a one-sided exact binomial test vs. the null hypothesis, $p = 0.019$; therefore, the null hypothesis was rejected.

Conclusions Our findings demonstrated that implementing biomarker-driven analysis is feasible and could provide clinical benefit for a considerable proportion (~30%) of patients with metastatic gastric or esophageal cancer.

Methods
Study design and patient population

- Study period between January 2010 and March 2014
- The study was approved by the institutional review boards of the participating institutions:
  - Rabin Medical Center
  - Sourasky Medical Center
  - Rambam Health Care Campus
  - Hadassah Hebrew University Medical Center
  - Kaplan Medical Center
  - Wolfson Medical Center

Results:
Patients characteristics

Deomgraphics

Characteristic	**N = 46**
Gender, N (%)	
Male	28 (60.9)
Female	18 (39.1)
Age at diagnosis, years	
Median (range)	58.4 (27.2-78.3)
Ethnicity, N (%)	
Jewish	37 (80.4)
Ashkenazi	*16 (34.8)*
Sephardi	*13 (28.3)*
Not available/mixed	*8 (17.4)*
Non-Jewish	9 (19.6)
Family history of cancer, N (%)	
Yes	25 (54.3)
No	21 (45.7)

Results:
Disease characteristics

Tumor site, N (%)	
Cardia	18 (39.1)
Gastroesophageal junction	11 (23.9)
Antrum	7 (15.2)
Esophagus	7 (15.2)
Not available	3 (6.5)
Grade, N (%)	
Well differentiated	1 (2.2)
Moderately differentiated	11 (23.9)
Poorly differentiated	26 (56.5)
Not available	8 (17.4)
HER2 status,[a] N (%)	
Positive	3 (7)
Negative	20 (43.5)
Equivocal	1 (2.2)
Test not performed/test failure	22 (47.8)
Metastatic at diagnosis, N (%)	
Yes	27 (58.7)
No	17 (37.0)
Not available	2 (4.3)

Results:
Treatment regimens received prior to molecular profiling

First-line treatment for metastatic disease	**n=36**
5-FU/capecitabine + cisplatin	11 (30.6)
5FU/capecitabine + cisplatin+ docetaxel	11 (30.6)
Other	14 (39)

Second-line treatment for metastatic disease	**n=20**
FOLFIRI	7 (35.0%)
Paclitaxel	4 (20.0%)
5-FU + cisplatin + docetaxel	2 (10.0%)
Other	7 (35.0%)

Results: Actionable biomarkers

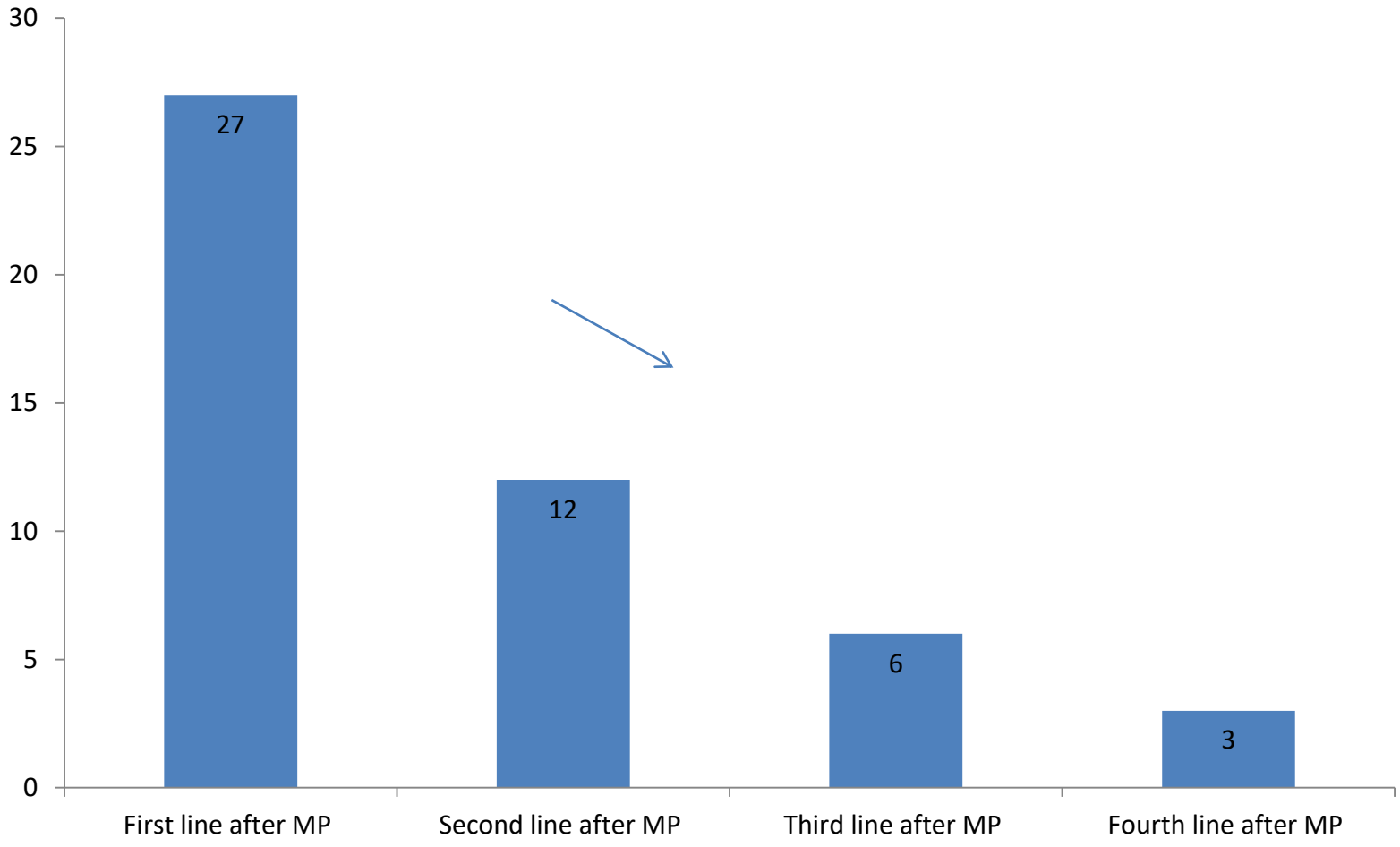
Actionable biomarker	Number of patients out of evaluable patients, N/N	Frequency, %	Drugs associated with clinical benefit
Negative/low TS	34/40	85.0	Fluoropyrimidines and other folate analogs
High TOPO1	27/40	67.5	Irinotecan
High TOP2A	27/41	65.9	Anthracyclines
Negative/low ERCC1	21/36	58.3	Platinum-based therapy
Negative/low RRM1	22/40	55.0	Gemcitabine
Negative/low MGMT	22/46	47.8	Temozolomide

Only markers that were tested in samples of at least 35 patients are included in the table.

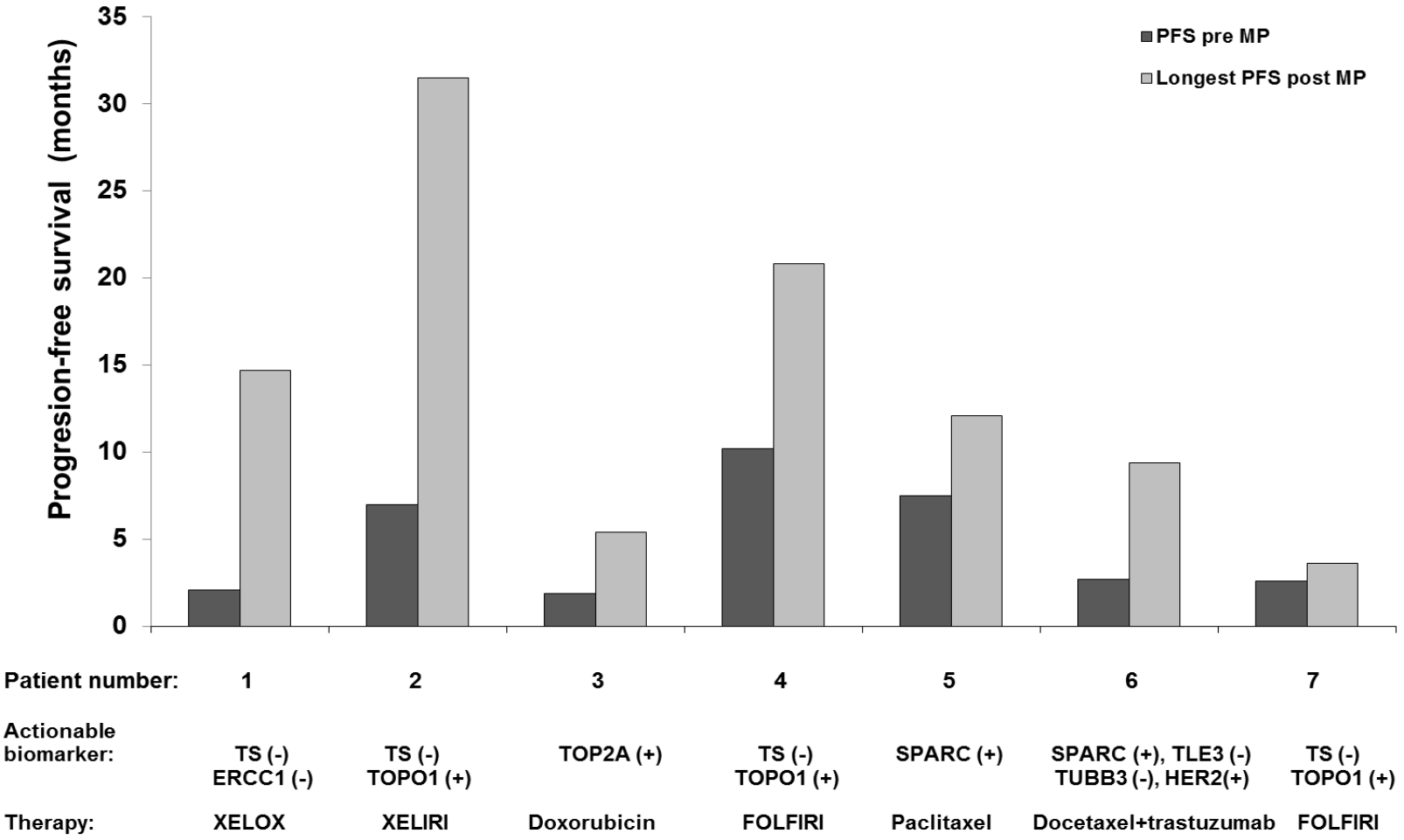
ERCC1, excision repair cross-complementation 1; MGMT, O-6-methylguanine-DNA methyltransferase; RRM1, ribonucleotide reductase M1 subunit; TOPO1, topoisomerase 1; TOP2A, topoisomerase IIA; TS, thymidylate synthase.

:Results

Patients treated according to MP



:Results
Patients achieving the PFS ratio



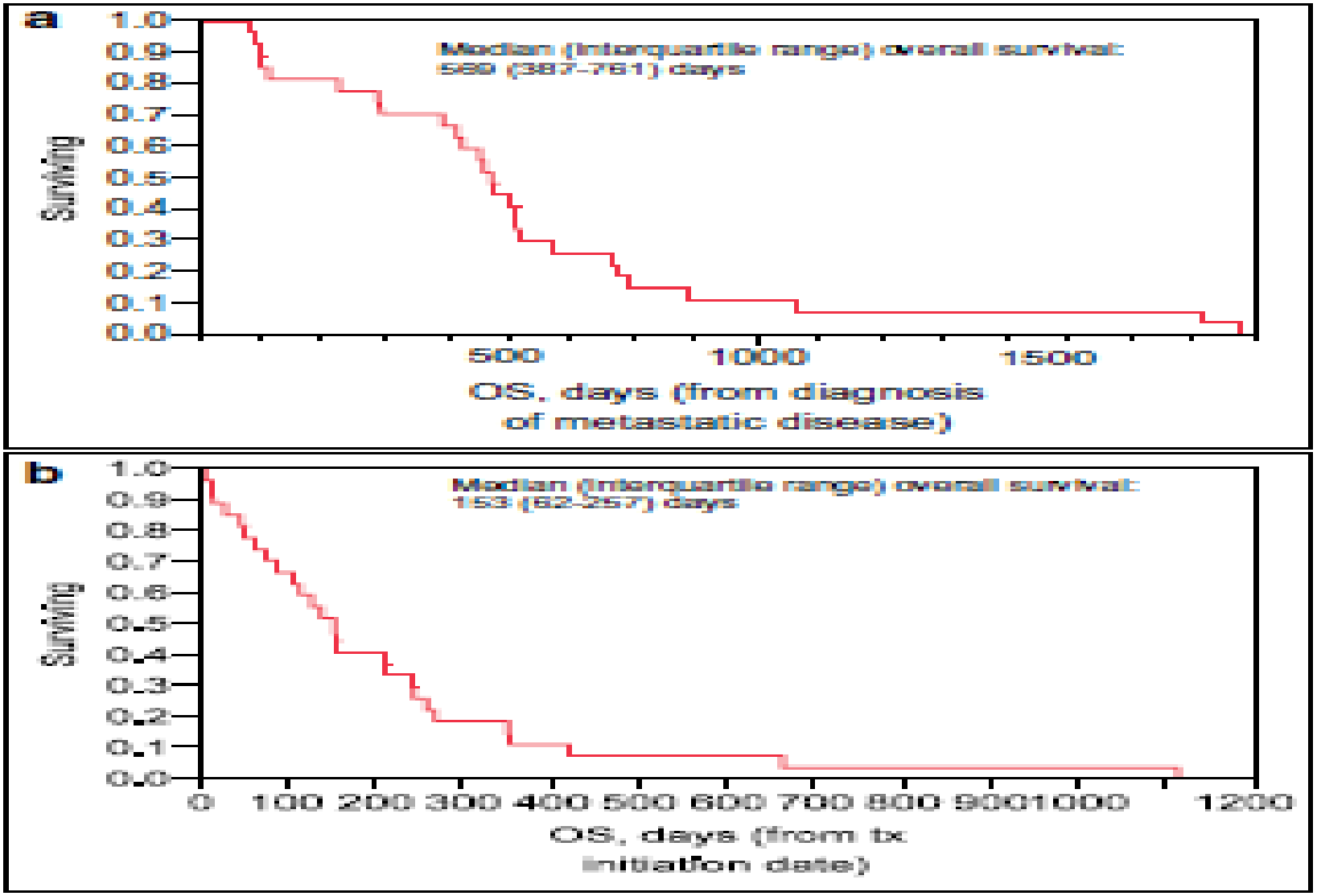


Fig. 2 Kaplan–Meier survival curve from diagnosis of metastatic disease (A) and from initiation of biomarker-driven therapy (B) for evaluable study patients who received biomarker-guided analysis (n = 27). Tick marks indicate censored observations

Conclusions

In summary, this study shows in real-life clinical practice that implementing MP is feasible and provides clinical benefit therapy (PFS ratio of ≥1.3) for a close to a third of patients with metastatic gastric/esophageal cancer. Prospective studies are warranted.

I thank the patients and
.the families
My co-authors
And Teva and Caris

THANK YOU