

Caris Life Sciences

Fulfilling the promise of precision medicine

Leading biosciences company focused on improvement of cancer care through delivering innovative diagnostic and theranostic services

- Founded 2008 in US, located in Dallas and Phoenix
- Since 2012 offering services throughout Europe and many international markets



Fielding a powerful team of professionals

managing laboratory performance and evidence processes, including

- medical oncologists
- pathologists
- molecular geneticists
- research scientists



Unmatched Laboratory Quality

6,000 square meter, Phoenix-based laboratory

- Licensed and validated according to ISO 15189:2012, CLIA and CAP standards, CE mark validation
- every patient's results are personally reviewed by a qualified molecular pathologist and geneticist before being released.



Caris Molecular Intelligence™ provides actionable treatment options – supported by the strongest clinical evidence

Thorough and Accurate Biomarker Analysis of a Patient's Tumour

Correlates Biomarker Targets to Therapeutic Agents

Extensive Clinical Literature Assessment

Informs Treatment Decisions Through an Actionable Report

Actionable Biomarkers Found in 95% of Cases

Average of 25 Clinically Relevant Results Reported per Patient

MI PROFILE
MOLECULAR INTELLIGENCE TUMOUR REPORT

PATIENT	SPECIMEN INFORMATION	ORDERED BY
Patient Name: Case Number: 7022-111111 Date of Birth: 00/00/1960 Sex: Female	Primary Tumor Site: Pancreas, NEC Specimen Site: Pancreas Specimens Collected: 09/09/2014 Specimens Received: 09/09/2014 Initiation of Testing: 02/20/2014 Completion of Testing: 02/20/2014 Specimen ID: P12-12	Ordering Physician Name: The Cancer Centre 1234 Main Street Dallas, TX 12345 P:204-456-7890

Caris Molecular Intelligence Summary

Agents Associated with Potential BENEFIT	Target Agents in CLINICAL TRIALS, Associated by Biomarker Expression	Agents Associated with Potential LACK OF BENEFIT
ON-SCREEN COMPOUNDS* abiraterone docetaxel paclitaxel nab-paclitaxel OFF-SCREEN COMPOUNDS* paclitaxel gemtuzumab	Target Agents in CLINICAL TRIALS, Associated by Biomarker Expression MET targeted therapy ERK inhibitors mTOR inhibitors Cell cycle inhibitors CDK4 inhibitors Taxanes Multikinase inhibitors	gemtuzumab temozolomide, dacarbazine irinotecan, etoposide, abiraterone, enzalutamide taxanes, temozolomide, irinotecan, leucovorin, capecitabine, oxycodone, tramadol, morphine, acetate gemtuzumab, irinotecan, temozolomide, dacarbazine, paclitaxel, nab-paclitaxel, docetaxel, enzalutamide

Caris Molecular Intelligence May Be Clinically Helpful For



Metastatic cancers refractory to standard treatments, e.g.

- Breast cancer
- Lung cancer
- Ovarian cancer
- Colorectal cancer



Aggressive cancers with few standard treatment options, e.g.

- Melanoma
- Pancreatic cancer



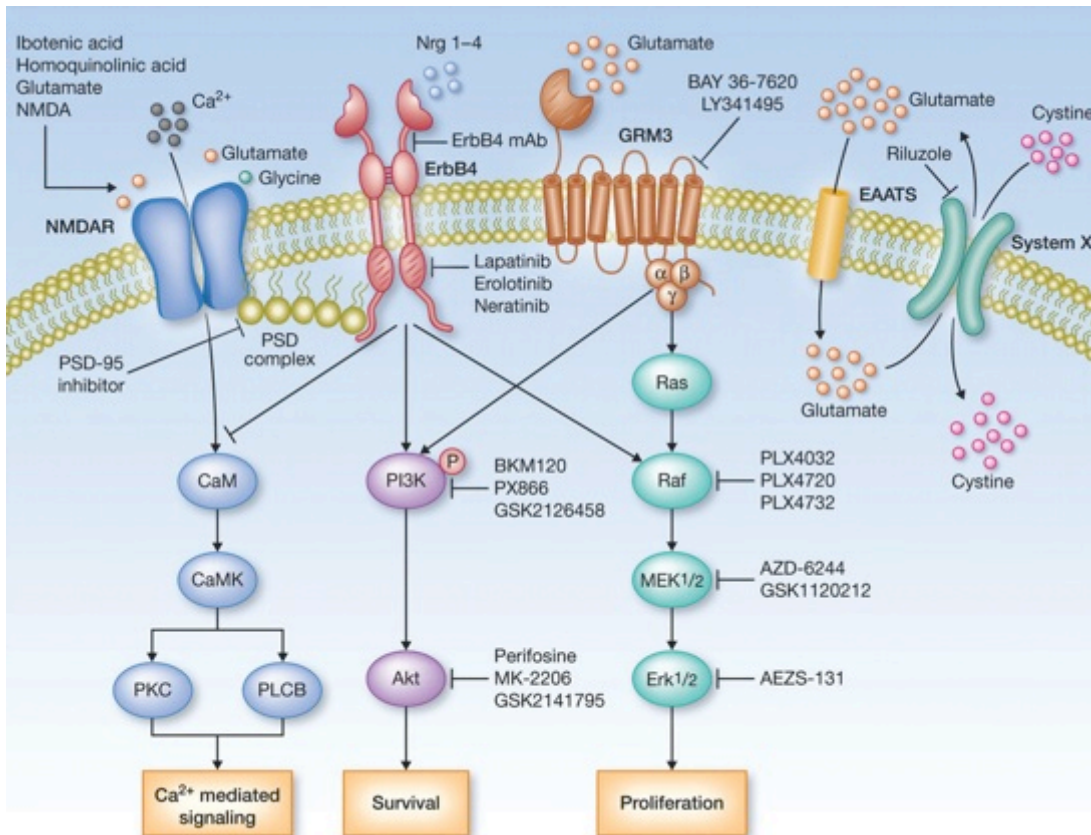
Rare and less common cancers with limited standard of care options, e.g.

- Sarcomas
- Gliomas
- Cancer of Unknown Primary (CUP)

Relevant Biomarkers are Analysed Using and Proven Accepted Technologies

BIOLOGIC PROCESS	TECHNOLOGY	BIOMARKERS
DNA Mutations	Next Generation Sequencing	ABL1, AKT1, ALK, APC, ATM, BRCA1/2, BRAF, CDH1, cKIT, cMET, CSF1R, CTNNB1, EGFR, ERBB2 (HER2), ERBB4, FBXW7, FGFR1, FGFR2, FLT3, GNA11, GNAQ, GNAS, HNF1a, HRAS, IDH1, JAK2, JAK3, KDR (VEGFR2), KRAS, MPL, NOTCH1, NPM1, NRAS, PDGFR α , PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, STK11, TP53, VHL
	PCR	BRAF
	Sanger Sequencing	IDH2
DNA, RNA	Fragment Analysis	EGFRvIII, MSI
Gene Rearrangements Gene Copy Number Variations	FISH / CISH	ALK, cMET, EGFR, HER2, ROS1, TOP2A, 1p19q
Epigenetic Changes	Pyro-sequencing	MGMT Methylation
Protein Expression	IHC	AR, cMET, EGFR, ER, ERCC1, HER2, H3K36me3, MLH1, MSH 2,6, MGMT, PBRM1, PD-1, PD-L1, Pgp, PMS2, PR, PTEN, RRM1, SPARCm, SPARCP, TLE3, TOPO1, TOP2A, TS, TUBB3

Caris has established over 33,000 biomarker rules to help guide treatment decisions

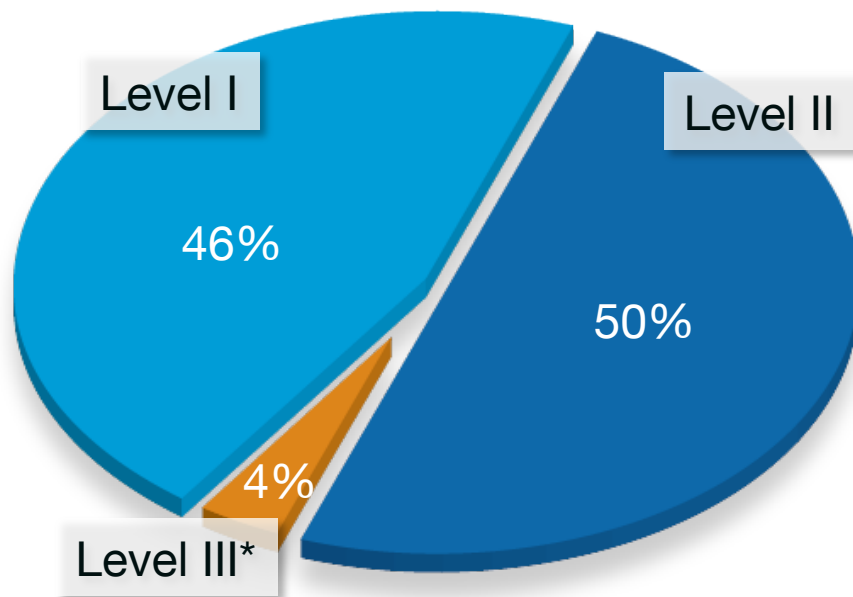


The Caris “Rules Engine” evaluates biomarker and drug associations along each molecular pathway.

The evidence team continually updates the rules to resolve competing or conflicting biomarker interactions

The Caris processes make sure we identify the drugs offering the most – and the least – potential clinical benefit for **CANCER** patients.

96% of drug / biomarker associations are based on Level I or Level II evidence



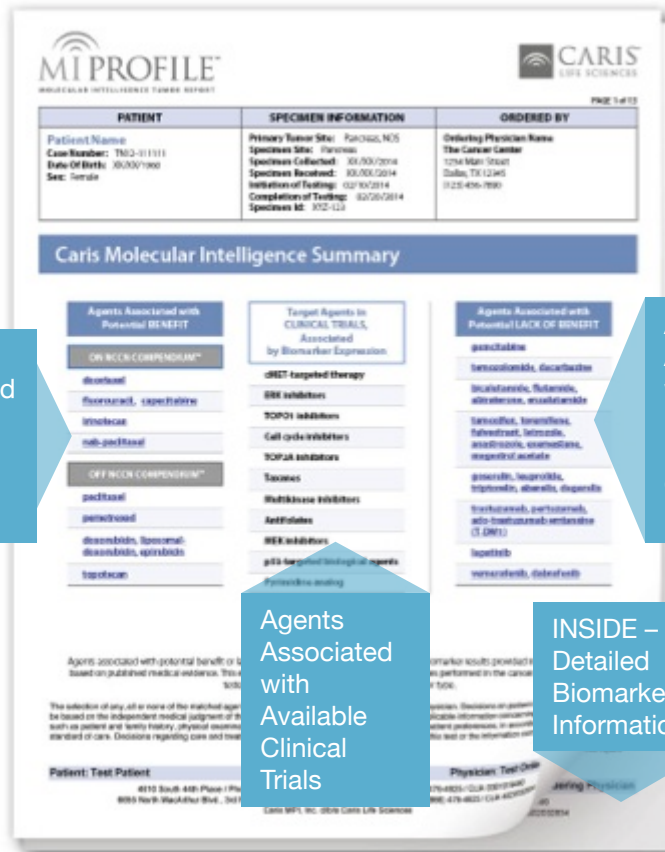
Current Methods of the U.S. Preventive Services Task Force As Applied by Caris Life Sciences

Hierarchy of Research Design

- I Evidence obtained from at least one properly randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

* Level III evidence associates ROS1 to crizotinib, which is included in the NCCN Guidelines for the treatment of NSCLC

Clinical Utility Maximised with Easy-To-Interpret Reports



Average of 25 Clinically Relevant Results Reported per Patient.*

Top page:

- Easy-to-Interpret Summary

Content:

- Detailed Biomarkers Results
- Clinical Trial Information
- References Supporting Biomarker Drug Associations

⇒ Caris Offers Consultation to Support Interpretation of the Reports

* MI Profile offering. Clinically relevant results include agents with potential benefit, agents with lack of potential benefit and clinical trials.

Connecting Patients to Relevant Clinical Trials

MI PORTAL
Caris Molecular Intelligence Physician Portal

Home | Requisitions | Messages | User Profile

Welcome [User Name] | Logout | FAQ | Help

Clinical Trials Connector™

Patient Name: **Firstname USA-Cast** DOB: **88/88/1988** Case ID: **9888-100000** Physician: **USA Physician Test**

Primary Tumor Site: **Appendix**

Biomarker: Drug: Phase: Title: Search Reset

Sponsor: State:

[View Trial](#) [Compare Trials](#) [Export to Excel](#) [Print Selection](#)

NCT ID	Title	Biomarker	Drug	Phase	Sponsor	State
NCT00133899	Lapatinib and FOLFIRI in Treating Patients With Advanced Solid Tumors	Her2/neu	lapatinib	Phase 1	University of California, San Francisco	California
NCT00488213	Pyridoxine in Preventing Hand-Foot Syndrome Caused by Capecitabine in Patients With Cancer	TS	capecitabine	Phase 2	National Cancer Centre, Singapore	
NCT00610940	Everolimus, Fluorouracil, Levamisole, Paclitaxel, and Oxaliplatin in Treating Patients With Solid Tumors That Did Not Respond to Treatment	TS	fluorouracil	Phase 1	UNC Lineberger Comprehensive Cancer Center	North Carolina
NCT00731276	Irinotecan in Treating Asian Patients With Solid Tumors	TS	capecitabine	Phase 1	National Cancer Centre, Singapore	
NCT00740805	Vedotinib, Cyclophosphamide, and Doxorubicin Hydrochloride in Treating Patients With Metastatic or Unresectable Solid Tumors or Non-Hodgkin Lymphoma	TOP2A	doxorubicin	Phase 1	National Cancer Institute (NCI)	New Jersey
NCT00790816	Continuation Study of Lapatinib Monotherapy or Lapatinib in Combination with Other Anti-cancer Agents	Her2/neu	lapatinib	Phase 1	GlaxoSmithKline	South Carolina, Quebec, Alberta, Florida, California, New Hampshire, District of Columbia, New York, Arizona, North Carolina, Tennessee, Utah, Georgia, Michigan, Ohio
NCT00809133	The Efficacy of Afatinib (BB2793) + FOLFIRI (Part A), Afatinib + Paclitaxel + Bevacizumab (Part B), Afatinib + Carboplatin (Part C), and Afatinib + Paclitaxel + Carboplatin (Part D) in Patients With Advanced Solid Tumors	Her2/neu	afatinib	Phase 1	Boehringer Ingelheim	
NCT00908296	Phase I Dose Escalation Study of Concurrent BIP 1120 and BB2793 in Patients With Advanced Solid Tumors	Her2/neu	afatinib	Phase 1	Boehringer Ingelheim	
NCT01003382	Capecitabine, Capecitabine, and Gemcitabine Hydrochloride in Treating Patients With Advanced Solid Tumors That Cannot Be Removed by Surgery	BB21	gemcitabine	Phase 1	Roanoke Park Cancer Institute	New York, Virginia

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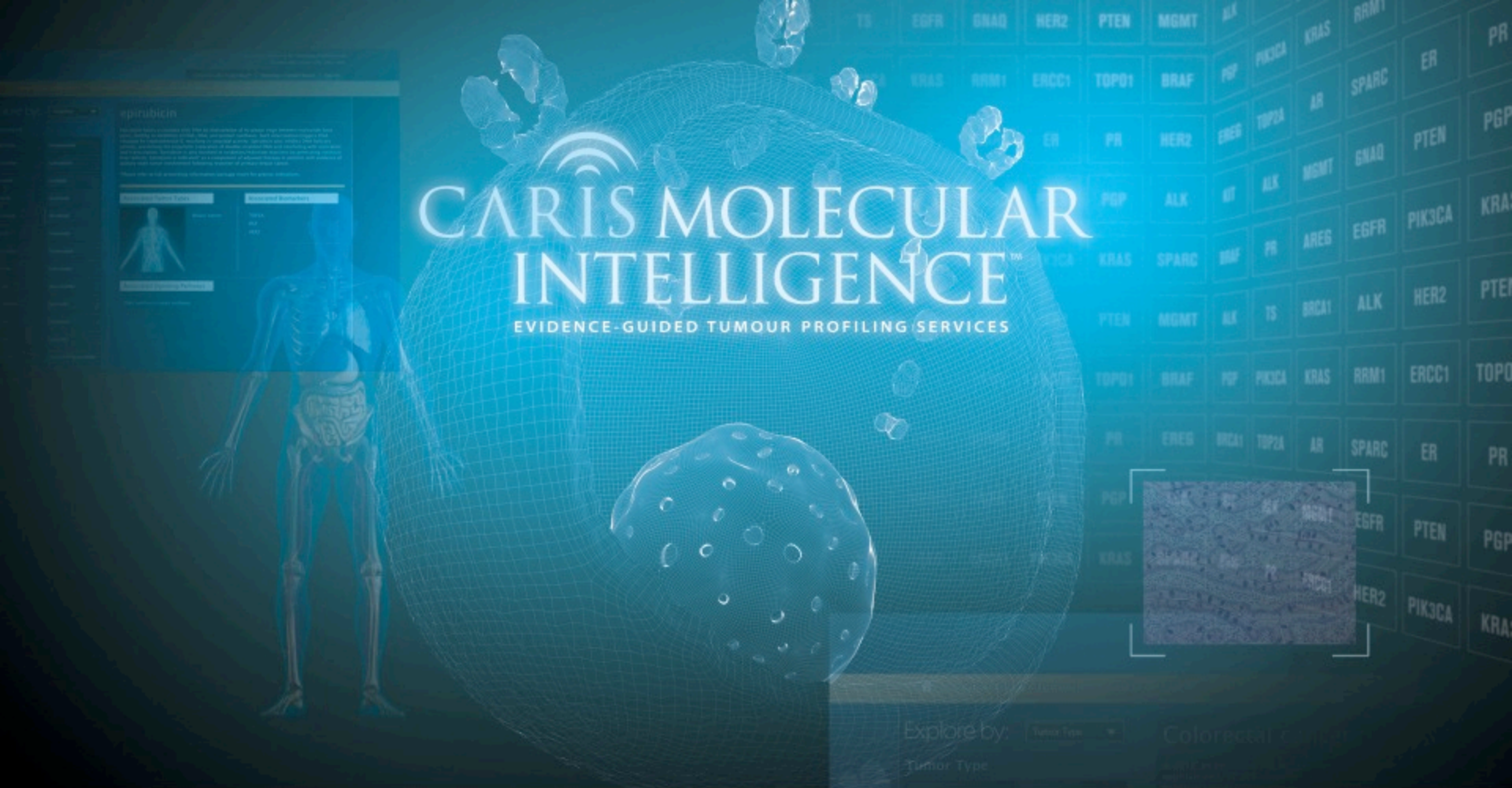
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The **Clinical Trials Connector** examines thousands of open and enrolling clinical trials

Matches clinical trials based on:

- Biomarker profile
- Tumour type
- Gender
- Age (date-of-birth)

The Clinical Trials Connector™ simplifies the process of finding the right trial for cancer patients

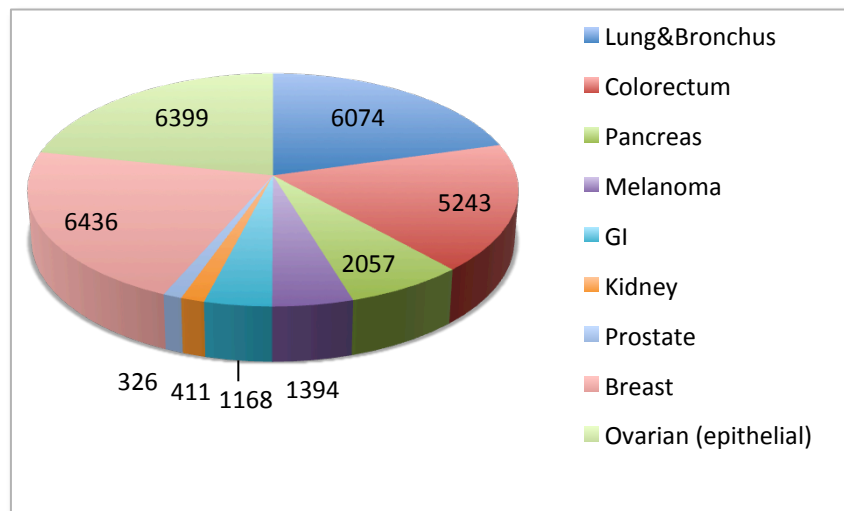


**Summary of Published and Presented Evidence,
Evaluating the Clinical Utility of CMI,
in Clinical Studies and Clinical Practice
(updated May 2014)**

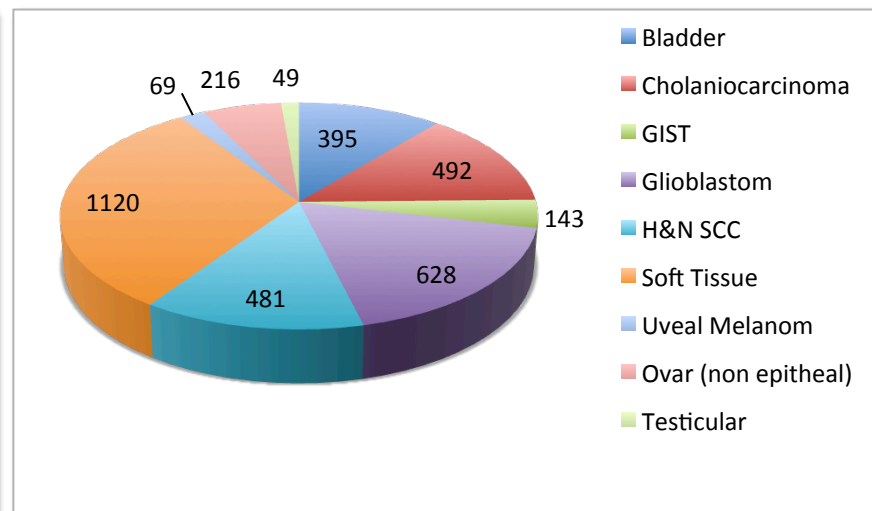


Caris has profiled more than 60,000 patients worldwide¹

Most Common Cancers^{2,3}



Less Common Cancers^{2,3}



The complete Caris database covers biomarker profiles of over 150 histological cancer subtypes.

Caris Molecular Intelligence is most suitable for

- ⇒ **Metastatic cancers** refractory to standard treatment e.g. Breast, Lung, Colorectal, Ovarian cancer
- ⇒ **Rare and less common cancers** with limited standard options e.g. Sarcoma, Glioma, CUP
- ⇒ **Aggressive cancers** with few standard options e.g. Melanoma, Pancreatic cancer

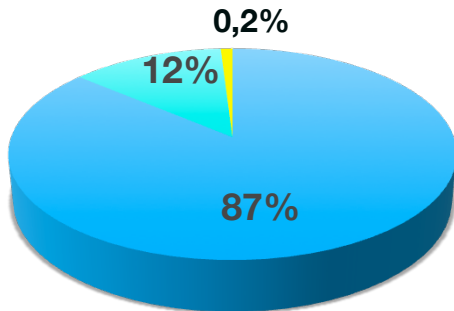
Identifies druggable targets in 90-100% of patients profiled using a multi-technology platform

Biomarker-drug associations identified in 12.265 patients profiled¹⁶:

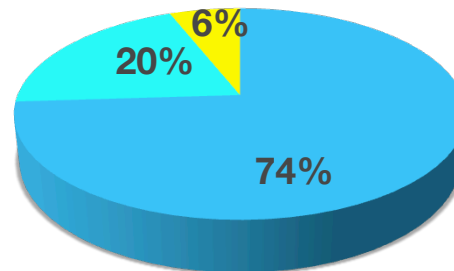
Drugs with potential benefit	Drugs with potential lack of benefit
in 93% of reports	in 97% of reports

Utilising a multi-technology platform is crucial for delivering this rate of biomarker–drug associations (displayed as percent of reports):

Agents associated with potential benefit



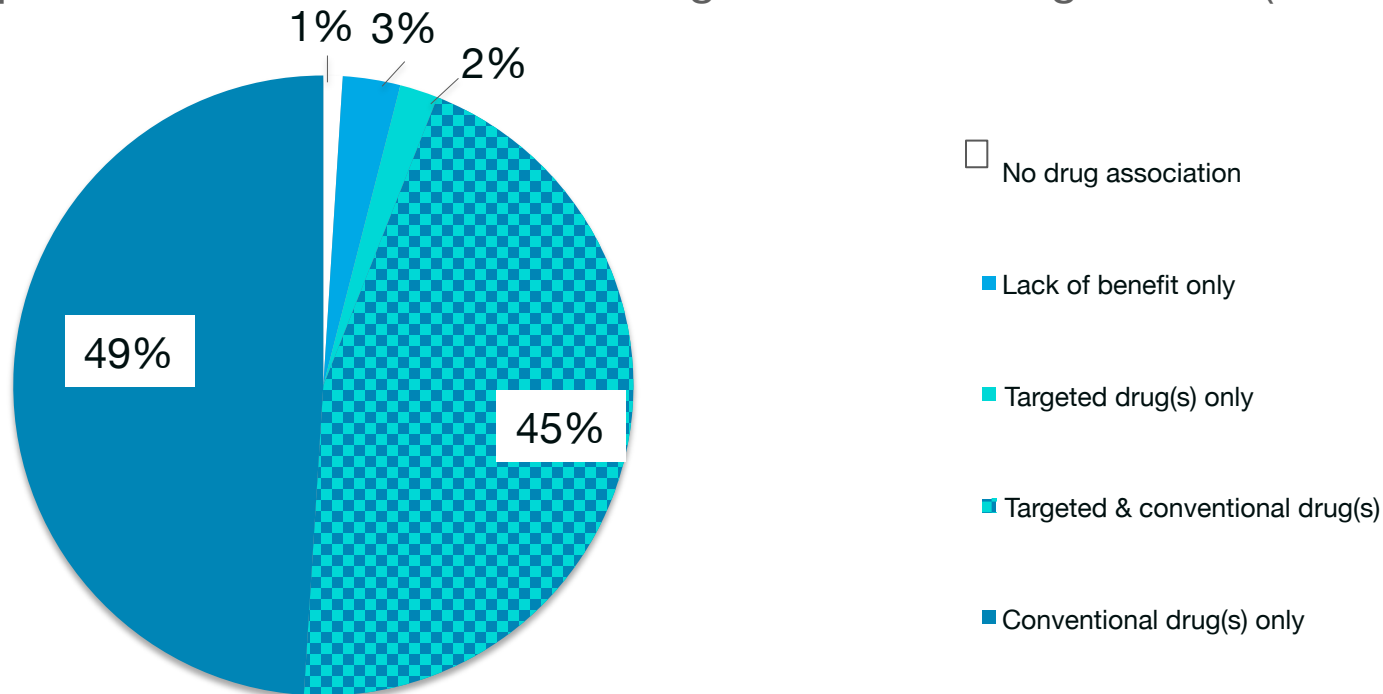
Agents associated with potential lack of benefit



- ICH/ISH
- ICH/ISH/NGS
- NGS only

Reports associations to conventional and targeted therapies

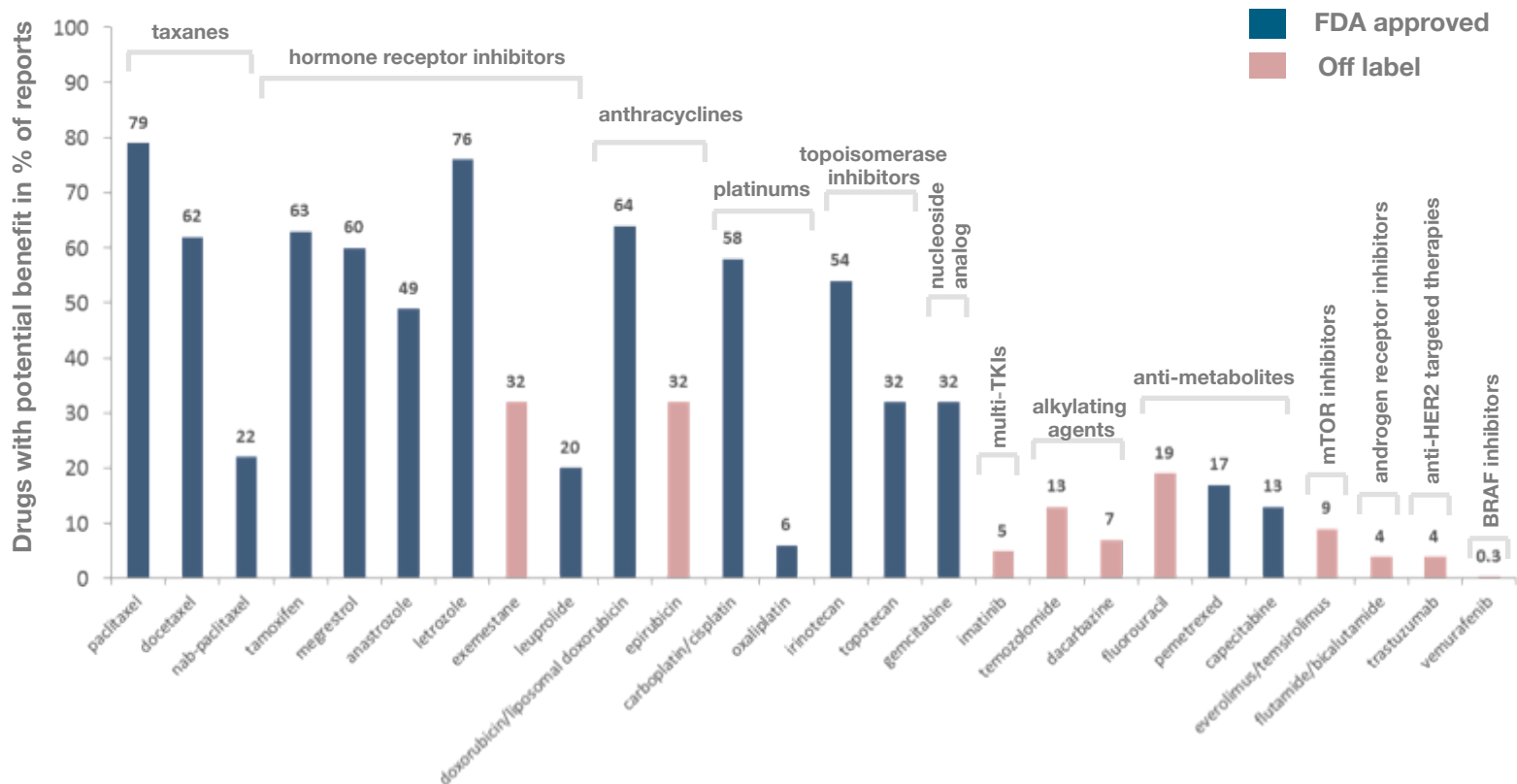
Example: Treatment Associations using Tumour Profiling of CUP (n=1'459)^{5, 8b}



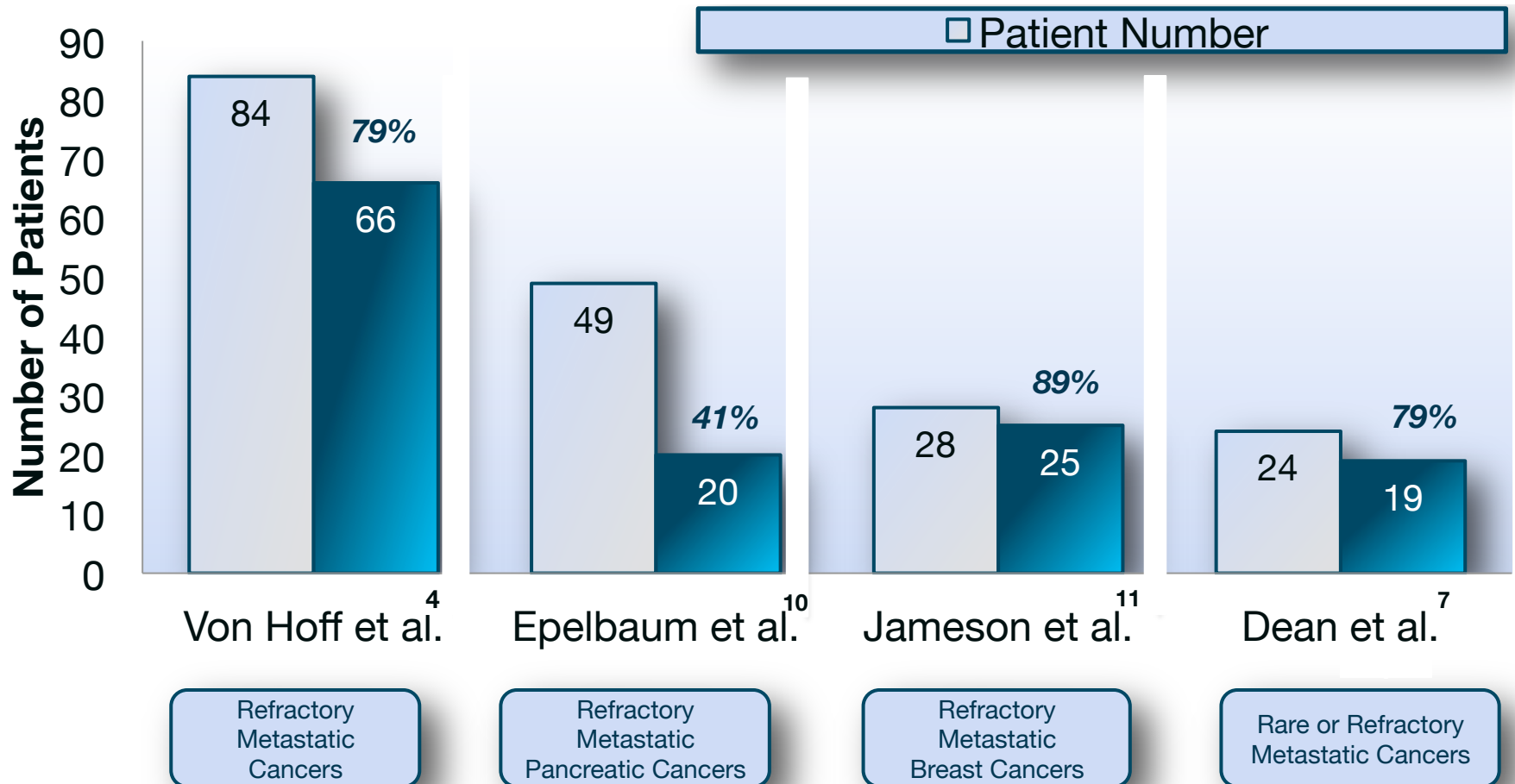
Targeted drugs include TKIs, mAbs, anti-steroidals, mTOR inhibitors
 Conventional drugs include alkylating agents, anthracyclines, camptothecans,
 pyrimidine antagonists, antimetabolites, taxanes, etc.

Reports associations to conventional and targeted therapies

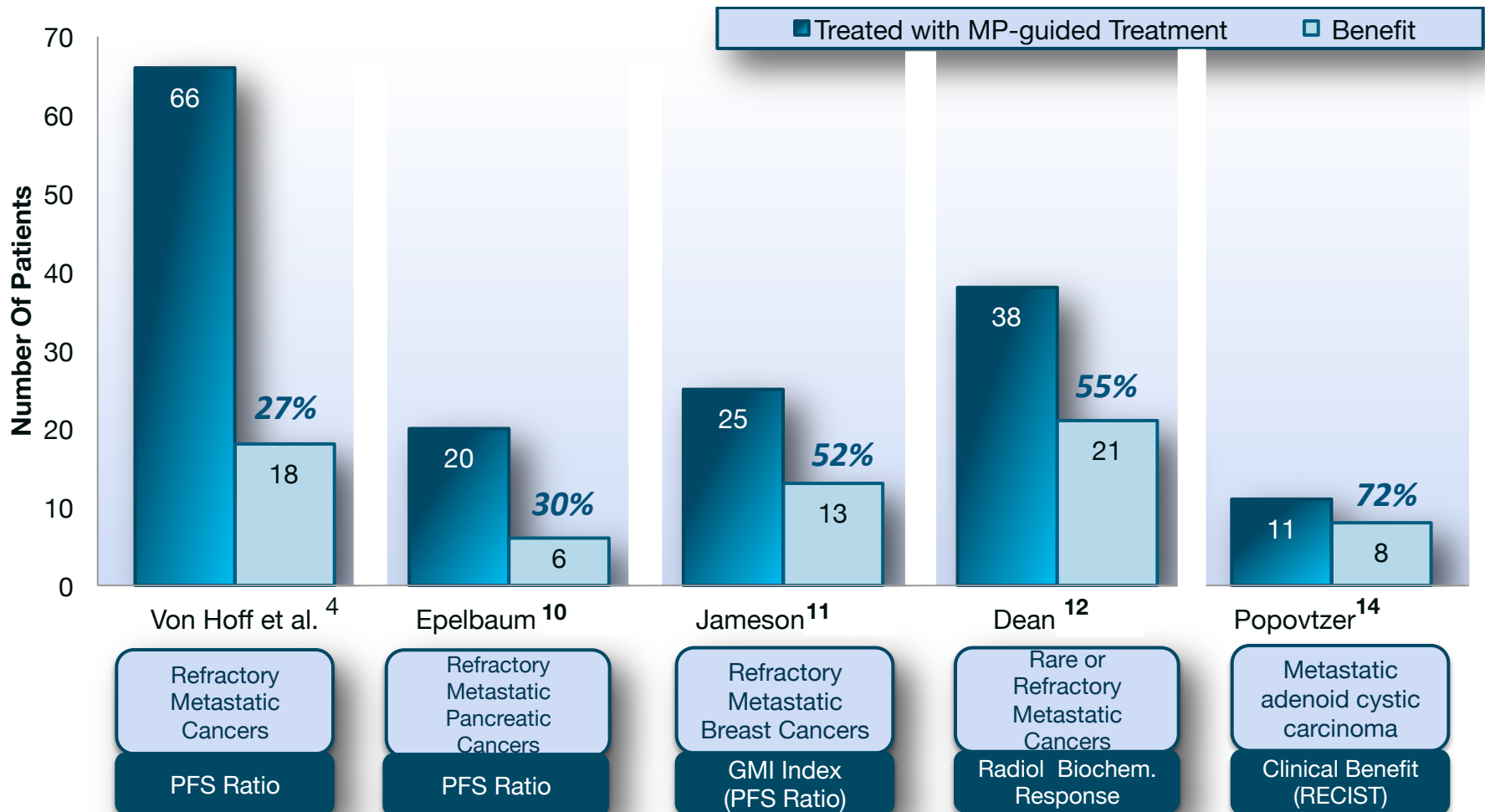
Example 2: Treatments with potential benefit, ovarian cancer registry (n= 348)¹⁷



Most Patients profiled receive a MP guided treatment in clinical practice



Many patients who receive a profiling-guided treatment experience a measurable clinical benefit



Patients are considered to benefit from profiling guided treatment with a PFS increase of $\geq 30\%$

PFS 1 last therapy prior to profiling

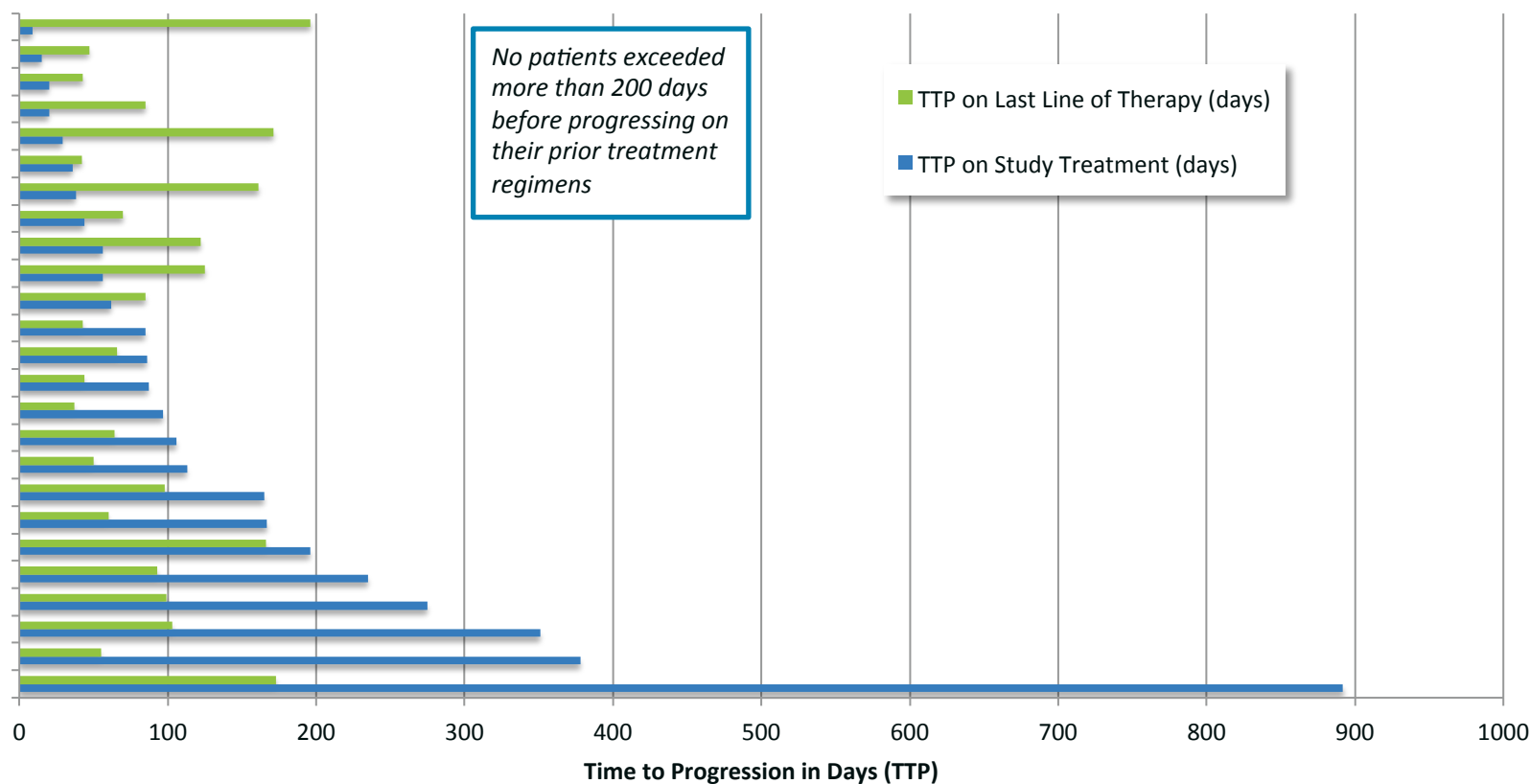
PFS 2 post-profiling guided therapy $+\geq 30\%$

If the PFS2/PFS1 ratio is ≥ 1.3 , profiling-guided therapy is defined in clinical trials as having benefit for patients^{4,11,12}.

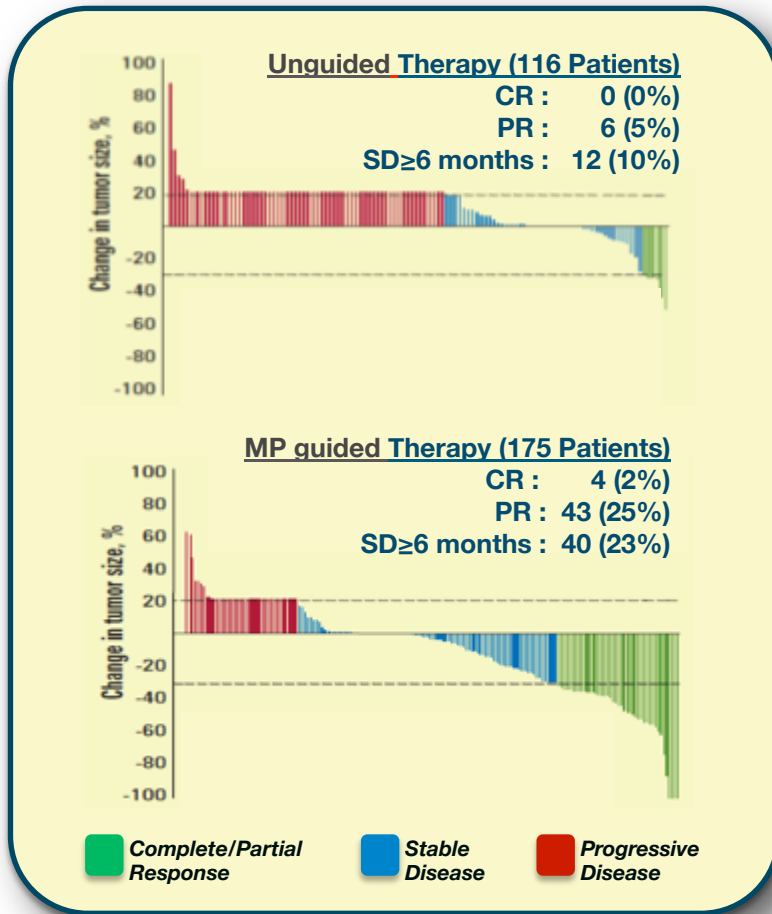
A PFS ratio of ≥ 1.3 was shown in:

- **52%** (13/25) of patients with metastatic refractory breast cancer¹²
- **37.5%** (6/16) of patients with advanced pancreatic cancer¹¹
- **27%** (18/66) of patients of a phase I population (various cancers)⁴

Comparison of PFS on profiling guided therapy vs prior therapy for patients with metastatic refractory breast cancer¹¹



Tumour profile guided therapy improves outcomes when compared to unguided therapy



The MD Anderson Experience

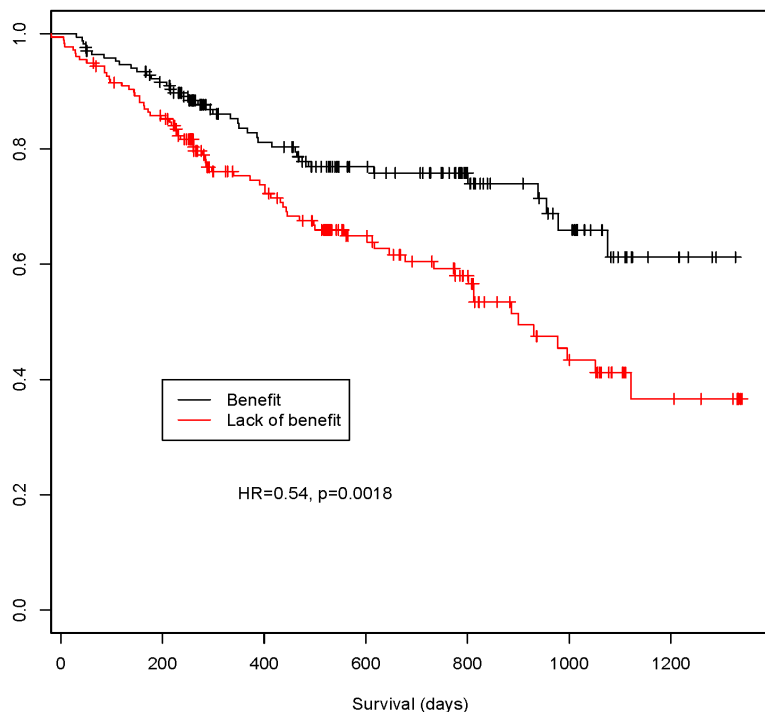
MP guided treatment was associated with a **higher overall response rate (27% vs. 5%; P < 0.0001)**, **longer time-to-treatment failure (TTF; P < 0.0001)**, and **longer survival (median, 13.4 vs. 9.0 months; P = 0.017)**.

Tsimberidou D et al. 2012¹³

Note: retrospective analysis of patient outcomes after MP guided inclusion into phase I trials (limited panel assessed: PIK3CA, BRAF, KRAS, NRAS, GNAQ, MET, EGFR, KIT, and TP53)

Treatment in line with profiling results can improve post-profiling survival

Initial report from the Caris Registry™ 15



- Patients with ovarian, fallopian tube, or primary peritoneal cancer patients were stratified based on the therapies they received:
- The “Benefit” cohort (n= 170) received at least one agent designated to be of potential benefit and no agents with potential lack of benefit while the “Lack of Benefit” cohort (n=178) received at least one agent with potential lack of benefit.
- Patients in the Benefit cohort experienced **significantly longer post-profiling survival**, as evidenced by a **46 percent reduction in the risk of death**, compared to the Lack of Benefit cohort (Hazard Ratio = 0.54, 95 percent CI 0.37-0.80; p=0.0018)¹⁵.