Molecular Profiling guided treatment in refractory solid tumors: practical impact and clinical responses: Experience of a single center.

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Translational research session

Abstract

Purpose: To describe the epidemiological characteristics and tumor responses of patients whose tumors underwent Molecular Profiling (MP) using the Caris Molecular Intelligence MI Profile ® (CMI) in a single-tertiary center: Hotel Dieu de France University Hospital affiliated to the Faculty of Medicine at Saint-Joseph University, Beirut, Lebanon.

Methods: This retrospective single-center, observational study was conducted on patients with refractory or progressing metastatic solid tumors, whose tumor biopsy samples were sent for MP between October 2013 and July 2015. Specific testing was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification (CISH or FISH), and/or RNA fragment analysis. Patient's characteristics, tumor response and duration of response were reported.

Results: 107 patients' biopsy samples were sent for MP using CMI. We identified 73 patients who met inclusion criteria. At time of data collection, 69 patients were treated according to MP and followed up for more than 2 months. The average age was 59.8 years. Women represented 52.3% of the sample. 96% had a PS of 1 or less. The majority of MP samples were obtained from a metastatic site (71%). Lung cancer was the most represented malignancy (18%). 60 patients (82% of the studied sample) were assessable at time of the last data collection. Therapy was effective in controlling the disease in 70 % of the patients. 7 patients (12%) had a complete response with partial response in a further 13 (22%). The average duration of response was 4.7 months.

Conclusion: Broad multiplatform profiling is a valuable clinical tool that is on the way of becoming a key player in everyday practice. Its use offers significant orientation in the choice of therapeutic opportunities for patients with metastatic, refractory or progressing solid tumors with good performance status. These promising results are a first step toward understanding practical translations of MP into tumor response.

Key words: Molecular Intelligence, MI Profile ®, retrospective study, refractory tumors.

Background

- Over recent years, tumor profiling has become a standard in many large university centers since its implementation helped guide recruitment of patients into clinical trials with targeted drugs. (1)
- A pilot study has shown that comprehensive molecular profiling can be used to find molecular targets in patients with refractory metastatic cancer. In 18 of 66 patients treated with a molecularly guided therapy, the approach resulted in a longer PFS on an MP-suggested regimen than on the prior regimen on which the patient had just experienced progression.(2)
- A recent study in patients with refractory breast cancer showed that tumor profiling resulted in a revision of the original treatment decision for all patients and tumor profiling-based therapy resulted in a clinical benefit in 52% of heavily pretreated patients. (3)
- Similar outcomes were recently reported in pancreatobiliary cancer (clinical benefit in 37.5%) and adenoid cystic carcinoma (response in 4/11) patients treated in line with tumor profiling results.(4,5)
- A review of all patients treated in a single center in Australia resulted in clinical and survival benefits in over half of the patients and confirmed the role of molecular profiling in a clinical practice setting. (6)
- The aim of this study was to retrospectively assess the impact of using molecular profiling to guide treatment choice in patients with rare or refractory cancer in routine clinical practice at a single center in Lebanon.

Methods

Objectives
- Describe the Epidemiological characteristics of patients whose tumors underwent Molecular Profiling (MP)
- Evaluate the Duration of response (DR) using therapy directed by MP
- Report Response type.

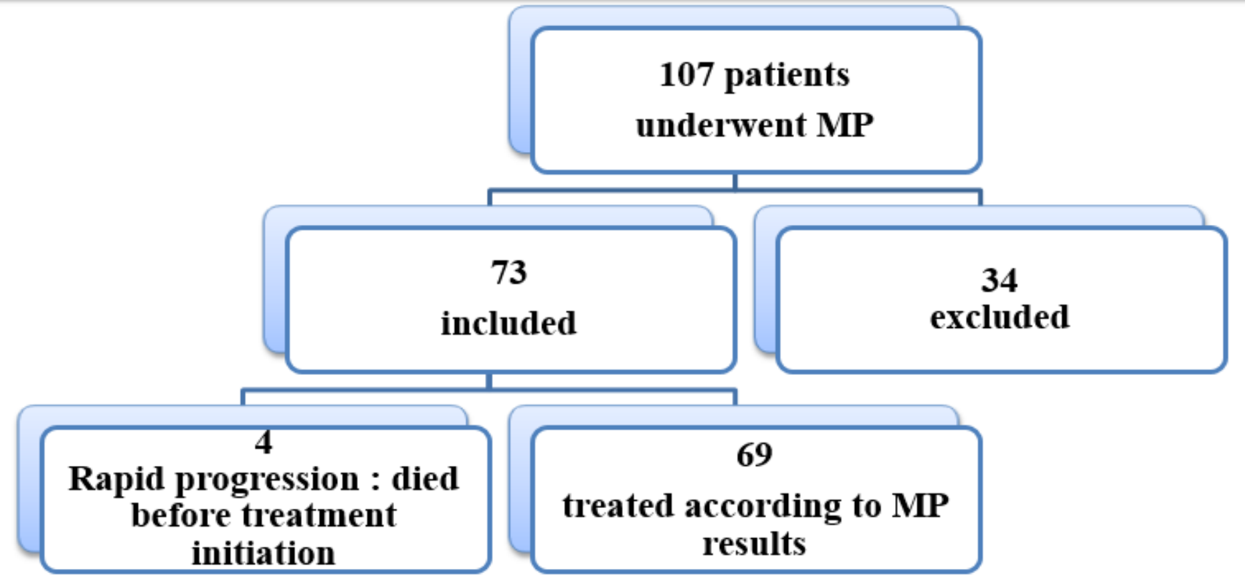
Design
- September 2013 to July 2015 (inclusion still ongoing to date)
- Refractory or progressing metastatic solid tumors
- Progressing according to RECIST criteria and/or biologic progression
- After at least two prior regimens for advanced disease.
- Evaluation every 2 months / Response type according to RECIST criteria

Eligibility criteria
- Informed consent
- Age ≥18 years;
- Life expectancy ≥3 months;
- PS ≤2
- Measurable or evaluable disease
- Patient capability to finance the test (third party payers didn't cover the fees)

- 107 patients with rare or refractory cancer being treated at Hôtel Dieu De France –Saint Joseph University were referred to Caris Life Science for comprehensive tumor profiling between September 2013 and July 2015.
- Specific testing was performed on tumor biopsy samples from all patients per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (IHC), gene amplification (CISH or FISH), and/or RNA fragment analysis.
- IHC analysis was performed on formalin-fixed paraffin-embedded tumor samples using commercially available detection kits, automated staining techniques (Benchmark XT, Ventana, and AutostainerLink 48, Dako), and commercially available antibodies.
- Fluorescent in-situ hybridization (FISH) was used for evaluation of the HER-2/neu [HER-2/CEP17 probe], EGFR [EGFR/CEP7 probe], and cMET [cMET/CEP7 probe] (Abbott Molecular/Vysis). HER-2/neu and cMET status were evaluated by chromogenic in-situ hybridization (INFORM HER-2 Dual ISH DNA Probe Cocktail; commercially available cMET and chromosome 7 DIG probe; Ventana). The same scoring system was applied as for FISH.
- Direct sequence analysis was performed on genomic DNA isolated from formalin-fixed paraffin-embedded tumor samples using the Illumina MiSeq platform. Specific regions of 45 genes of the genome were amplified using the Illumina TruSeq Amplicon Cancer Hotspot panel.

Results

Demographics



Patient's flowchart

- 107 patients in total (56 female, 51 male)
- Average age = 59.8 yrs (median 61 yrs, range 21-81).
- The majority of patients had an ECOG performance status of 0 or 1.
- Median prior lines of therapy – 2 (range 0 – 10)
- Average time to testing from biopsy = 172 days (median 18 days, range 7-2551).
- 71% of biopsies assessed were taken from a metastatic site.

Primary Site	n	Primary Site	n
Breast	17	Unknown primary site	3
Lung	19	Endometrium	5
Ovary	10	Urinary	10
Colon	7	Thyroid	2
Connective, subcutaneous and other soft tissues	13	Biliary ducts	4
Pancreas	6	ENT	2
Stomach	4	Other	5

Feasibility of CMI Testing

- The report provided actionable information in all cases.
- 99% of patients had at least one treatment associated with potential benefit
- A median of 11 treatments across 5 drug classes were associated with potential benefit
- A median of 16.5 drugs in 5 drug classes were associated with potential lack of benefit.

Tests and Treatments Associated with Potential Benefit

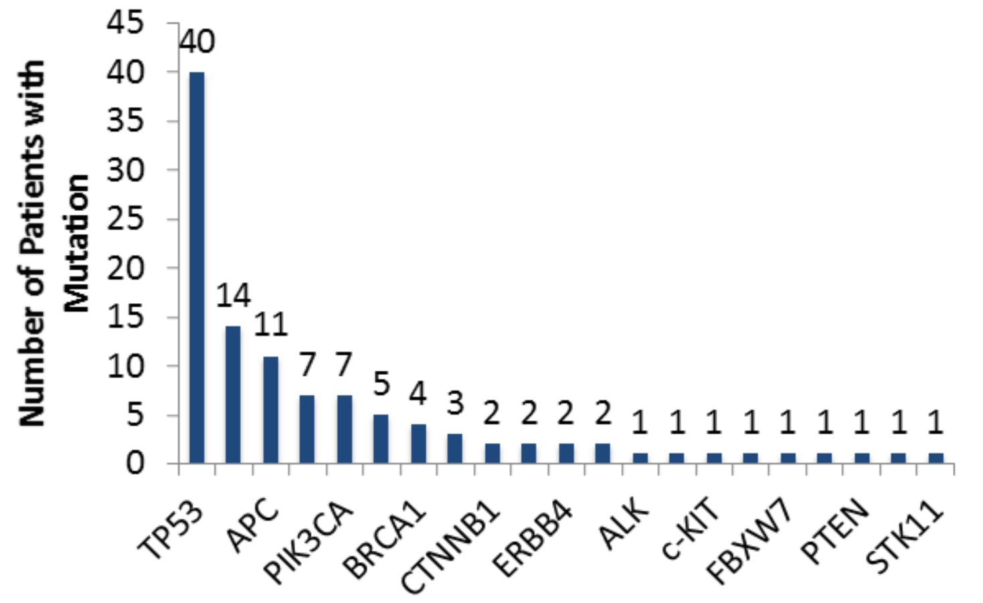
	IHC	ISH	NGS	Total Treatments	Drug Classes	Cytotoxic (n, %)	Hormone (n, %)	Targeted (n, %)
Average	6.7	0.6	0.5	12	4.7	8.8 (80.8%)	2.7 (15.3%)	0.6 (3.9%)
Median	7	1	0	11	5	9	0	0
Min-Max	0-12	0-2	0-4	0-25	0-8	0-14	0-16	0-6

Tests and Treatments Associated with Potential Lack of Benefit

	IHC	ISH	NGS	Total Treatments	Drug Classes	Cytotoxic (n, %)	Hormone (n, %)	Targeted (n, %)
Average	5.4	1.4	1.3	17.3	5.0	4.5 (31.2%)	7.5 (33.2%)	5.3 (35.7%)
Median	5	1	1	16.5	5	5	7	6
Min-Max	0-11	0-4	0-5	3-35	1-9	0-11	0-18	0-12

Results of Next Generation Sequencing Analysis

- Tumors with at least one mutation = 63, wildtype tumors = 21
- Average number of genes with alterations = 1.3 (median 1, range 0-4)
- Average number of genes tested with no alterations found = 42 (median = 43, range 0 – 46)
- Average number of genes tested with indeterminate results = 1.7 (median 0, range 0-42)



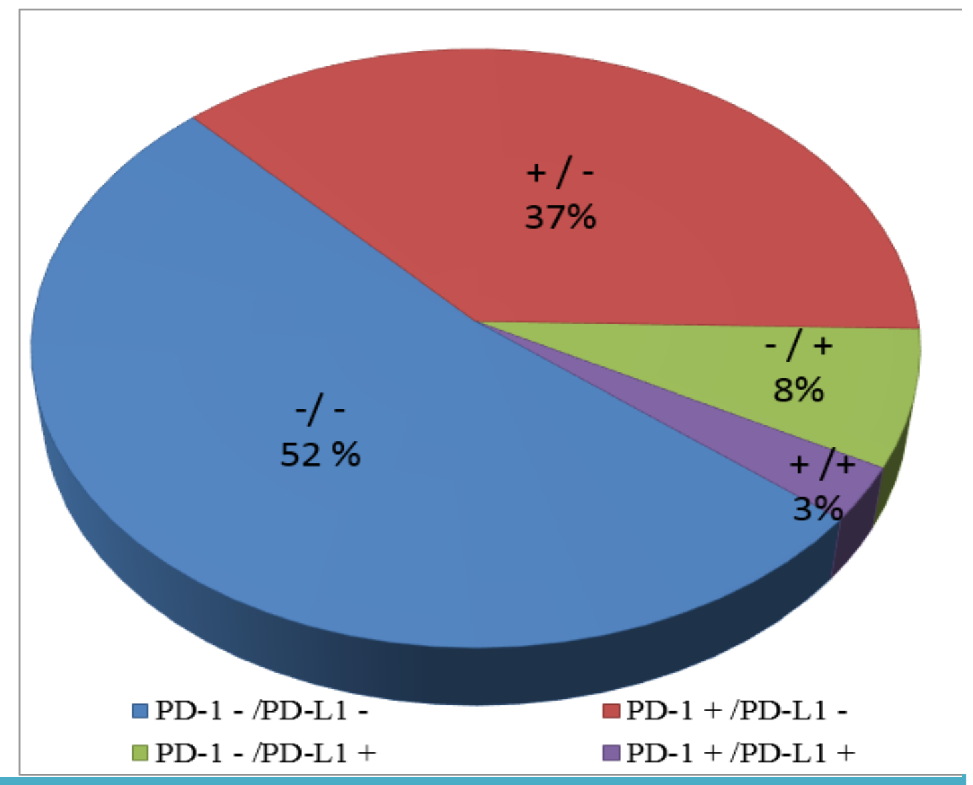
Gene	Protein Changes Found
TP53	K101X, R110fs, T137Q, 140fs, P153A, G154fs, G154V, V157F, R175H (x3), C176F, R181C, Q192X, Y205C, R209fs, N235_Y236del, C238N, N239D, T241F, G242fs, G242Y, G245S, R248Q (x2), R248W (x2), V272L, R273C (x2), R273H, R273L (x2), A276G, C277F, R282W, E285K (x2), E298X, P301fs, R342X, c560-7_560del (x2), c.376-2A>C
KRAS	G12C (x3), G12D (x4), G12F, G12R, G12V (x3), G13D (x2), K117N
APC	R876X, I1307K (x3), E1317Q (x2), P1381S, S1407fs, R1450X, S1465fs, T1556fs
BRCA2	I505T, N1344T, T1354M, R2108C, D2900V, D3170G, K3226X
PIK3CA	E542K, E545K, D549H, H1047L, H1047R (x3)
SMAD4	E330K, F339fs, R361H (x2), G365A
BRCA1	T77M, E542K, 190X, D1482N, W1815K
ATM	P604S (x2), R2453H
CTNNB1	D32Y, S37F
EGFR	G614S, K714fs
ERBB4	M250I, D931Y
JAK3	V722I (x2)
ALK	F1174I
BRAF	G464V
c-KIT	V560D
ERBB2	D769Y
FBXW7	I433F
GNAQ	P170A
PTEN	N340fs
SMO	S354L
STK11	E57fs

Treatments Associated with Potential Benefit and Potential Lack of Benefit

The drug classes most commonly associated with benefit were commercially available and approved in at least one cancer type.

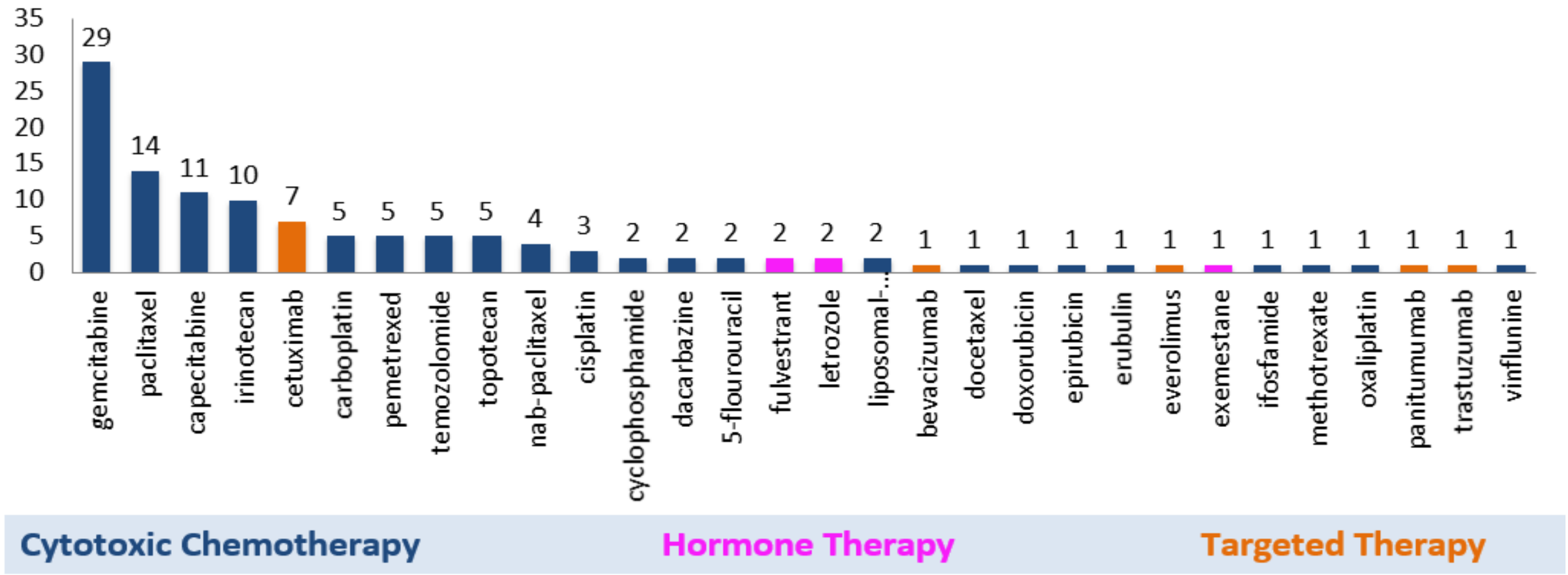
Immunotherapy

- PD-1 and PD-L1 statuses were also assessed in 67 patients.
- 35 patients (52%) were negative for both PD-1 and PD-L1.
- 25 patients had PD-1 expression on the surface of the tumor infiltrating lymphocytes (37%), while a further 5 were PD-L1 positive (8%).
- 2 patients (3%) were positive for both PD-1 and PD-L1.

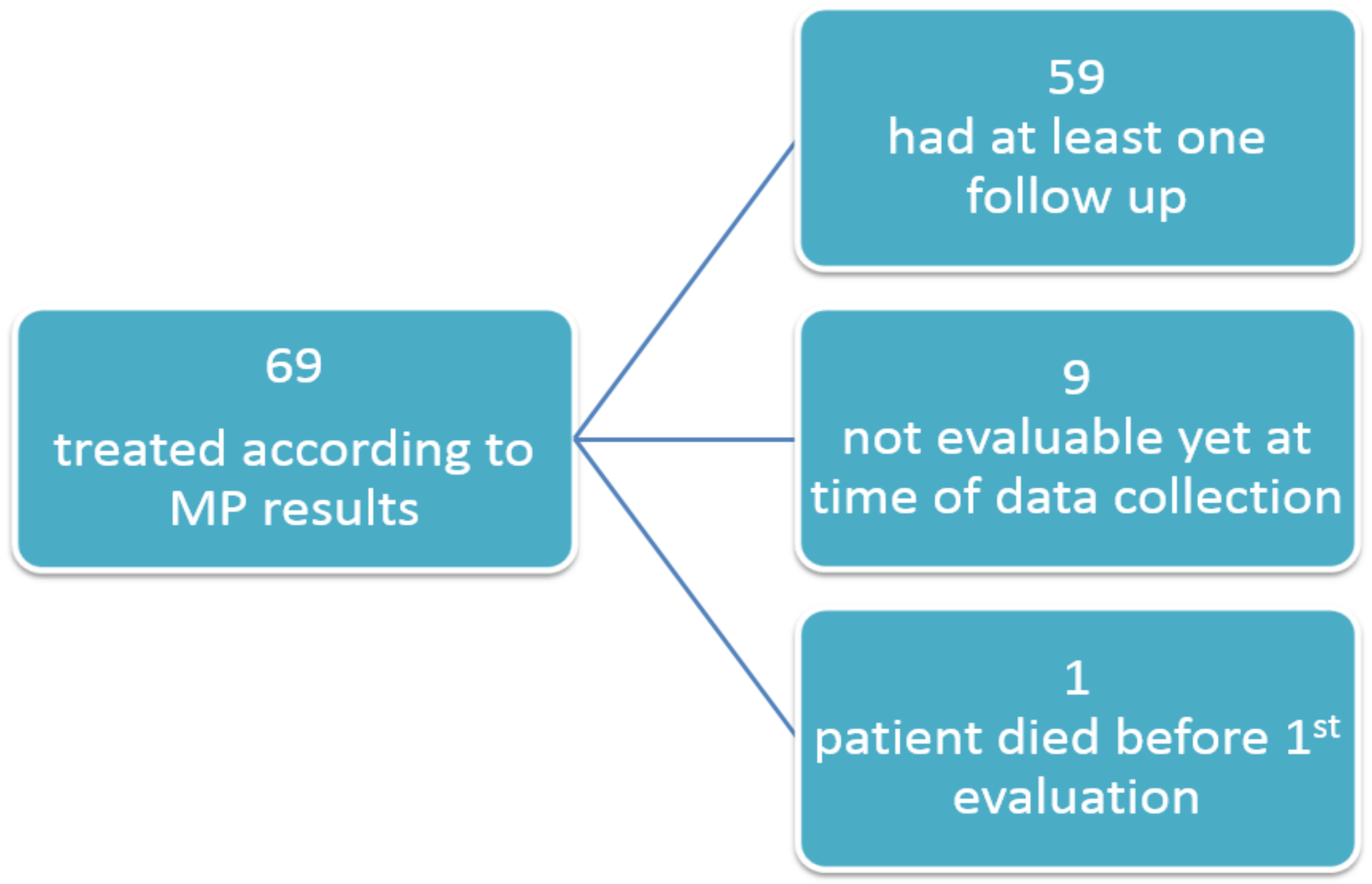


Treatment Selection

- 69 patients were treated according MP results after tumor profiling was performed.
- 47 pts received combined therapy (68 %)
- 29 pts received monotherapy (42%)
- 52 (76%) patients received drugs associated with potential benefit only



Clinical Outcomes



Response Type

Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)
7 (12%)	13 (22%)	21 (36%)	18 (30%)

Disease control rate = 70%

Average Duration of Response	**4.7 months**

Conclusion

- Biomarkers and molecular medicine are replacing nowadays "one size fits all" medicine with tailored medicine. This paradigm shift requires that personalized oncology rapidly implement new validated biomarkers.
- Next generation sequencing is a valuable clinical tool that is on the way of becoming a key player in everyday practice. Its use offers significant orientation in the choice of therapeutic opportunities for patients with metastatic, refractory or progressing solid tumors with good performance status.
- These promising results are a first step toward understanding practical translations of MP into tumor response.

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