SUPPLEMENTAL TEXT

Selected Examples of Therapy and Matching Score Methodology

The genomics and treatment of these tumors is complex. Thus, the molecular matches are potentially controversial. However, we consistently followed pre-decided rules in a blinded fashion when matches were called and Matching Scores were determined. Below we have outlined examples of scoring of patients, their treatment regimens, and the rationale for molecular matches where the scoring was complex.

Patient 2 had a tumor with HGF amplification and MET amplification. The patient received crizotinib, a MET inhibitor. Note that MET is the receptor of *hepatocyte* growth factor (*HGF*).[1] This was a 100% match, making the Matching Score >50%.

Patient 22 had a tumor with ERBB2 amplification, ERBB2 T733I, CDK6 amplification, TP53 C135G, APC G1499*, and APC S1400*. Pertuzumab and trastuzumab were matched to ERBB2 amplification and ERBB2 T733I. Per the Methods, two gene alterations that are biologically different were considered separately and so amplifications (which increase expression of the normal gene) and mutations (which alter the function of the normal gene) were considered separately. Together, the biologics pertuzumab and trastuzumab have well-known synergy and are FDA-approved based upon this activity,[2-5] stressing the point of rational combination therapies. This patient (and Patient 122) received pertuzumab and trastuzumab, which are now FDA approved in combination because their joint effects are better than individual effects.[6] Moreover, preclinical data also shows synergy even though they target the same receptor.[3] Hence, we did not consider them as a single agent. Per our rules, and on this basis, we considered 2 “hits” on each appropriate target (amplification and the activating mutation were counted as 4 hit targets). In addition, the patient had a CDK6 amplification and a TP53 mutation. The two APC were both inactivating; hence, per the rules in the Methods, these two APC mutations were considered one hit. Therefore, there were 4 targeted hits on 5 total alterations. Because we felt that this

overamplified the synergy, we routinely also added 2 to the denominator as well (as stated above). Even so, the final calculated matching score was 4 of 7 (not 4 of 5), making the Matching Score >50%.

Patient 47 had a tumor with BRCA1 E1375*, CTNNB1 S37F, NOTCH1 P1770S, NOTCH1 Q1810*, NOTCH1 T1997M, ASXL1 Q748*, CREBBP Q1245*, EPHA3 T215M, FANCE S241F, FANCL splice site 692-1G>A, KDM6A S1400*, KEAP1 R362Q, LRP1B loss exons 12-15, MAGI2 R766*, RB1 S474N, SETD2 R1592*, SLIT2 splice site 611+2T>A, SPTA1 E1707K, TERT promoter -146C>T, and TP53 R342*. The tumor was TMB high and the patient was treated with pembrolizumab. Per our rules and the recent publication by our group,[7] we considered TMB high matched to a checkpoint inhibitor (e.g., pembrolizumab) to be a 100% match. We acknowledge that there is no perfect scoring system, especially for immunotherapy. However, our oversight committee created and followed these rules in a consistent fashion.

Patient 99 had a tumor with KRAS G12D, APC K1165*, APC P1373fs*10, CDKN2A P14ARF S73R, SOX9 Y420*, and TP53 R110L, and the patient was treated with trametinib, palbociclib, and sulindac. Per the matching rules, 5 genomic alterations (APC was counted as 1 since both mutations were inactivating) were counted in the denominator. The KRAS mutation was considered matched to trametinib, a MEK inhibitor, because that alteration is upstream of MEK. The CDKN2A was considered matched to palbociclib, a CDK4/6 inhibitor, because that alteration results in upregulation of CDK4/6.[8-10] The APC mutation was considered matched to sulindac, which targets nuclear β-catenin accumulation in the APC/ β-catenin/TCF pathway (Wnt signaling pathway).[11,12]

Patient 102 had tumor with CDKN2A/B loss, TP53 C176F, TP53 D61fs*62, and EP300 P925T. The tumor was TMB intermediate and the patient was treated with nivolumab and palbociclib. Per our matching rules in the Methods, patients with TMB intermediate, when matched with checkpoint inhibitors, like nivolumab, were scored at 50%. Any additional matches would increase the matching

score over 50%. In this case, the patient also received palbociclib, a CDK4/6 inhibitor, that was matched to CDKN2A/B loss because it upregulates CDK4/6.[8,9]

Patient 115 had a tumor with KRAS G12V, ATM H448fs*36, PIK3CA I1058F, APC R876*, APC T1556fs*3, DNMT3A W860, and SOX9 S403fs*1. The tumor was TMB intermediate and the patient was treated with nivolumab, trametinib, and sulindac. Similar to Patient 102, TMB intermediate, when matched with checkpoint inhibitors, like nivolumab, was scored at 50%. Any additional matches would increase the matching score over 50%. We considered trametinib matched to the KRAS mutation and sulindac matched to the APC mutation for the reasons outlined for Patient 99.[11,12]

Patient 121 had a tumor that was TMB high and was treated with nivolumab, a checkpoint inhibitor. Per our rules and the recent publication by our group,[7] we considered TMB high matched to a checkpoint inhibitor (e.g., nivolumab) to be a 100% match.

Patient 122 had a tumor with KRAS G12V, ERBB2 amplification, ERBB2 D769Y (kinase), ERBB2 S310Y (extracellular), PARK2 Q34fs*5, APC E1494fs*13, APC R876*, CDKN1B Q163, and SMAD V128M. As per Patient 22, pertuzumab and trastuzumab were matched to ERBB2 amplification, ERBB2 D769Y (kinase domain), ERBB2 S310Y (extracellular domain). Together, these biologics have well known synergy and are FDA-approved based upon this activity.[2-5] Therefore, we counted each drug as two hits for each ERBB2 target. One ERBB2 mutation was in the kinase domain and one was in the extracellular domain. Thus, they functioned differently. Based on these 3 alterations, a total of 6 targets were counted in the numerator. In addition, there were five more alterations in KRAS, PARK2, two inactivating APC (counted as 1 since they are functionally the same), CDKN1B and SMAD4. Thus, the denominator is 6 plus 5 (additional noted in prior sentence). Thus, 6/11 was a Matching Score >50% by our rules. It should be noted that SMAD4 also upregulates ERBB2 resulting in a score of at least 7 of 11 or if the synergy is considered, 8 of 12.[2-5,13] Whether the synergy should be considered for the impact on SMAD4 was debated because the SMAD4 data regarding ERBB2 amplification was newer

and the upregulation of ERBB2 indirect. However, while we debated as to the actual final score, all scores were over 50% by the rules in the Methods.

Patient 141 had a tumor with CD274 (PD-L1) amplification, CDK4 amplification, KDR amplification, KIT amplification, MET amplification, PDCD1LG2 (PD-L2) amplification, PDGFRA amplification, MDM2 amplification, CDKN2A/B loss, FRS2 amplification, JAK2 amplification, and RB1 splice site 2107-1G>C. The patient was treated with nivolumab and cabozantinib. CD274 (PD-L1) amplification was matched to nivolumab[7] and was scored at 50% per our rules. Any additional matches would increase the matching score over 50%. In this case, cabozantinib targets KDR and MET amplifications.

Patient 155 had a tumor that was TMB high and was treated with nivolumab, a checkpoint inhibitor. Per our rules and the recent publication by our group,[7] we considered TMB high matched to a checkpoint inhibitor (e.g., nivolumab) to be a 100% match.

Patient A011 had a tumor that was MSI high and was treated with pembrolizumab, a checkpoint inhibitor.[14-16] Per our rules, (supported by the more recent FDA approval of pembrolizumab for MSI-high tumors), we considered MSI high matched to a checkpoint inhibitor (e.g., pembrolizumab) to be a 100% match.

Patient A016 had a tumor with AKT2 amplification, PIK3CA H1047R, CD274 (PD-L1) amplification, FLT4 amplification, PDCD1LG2 amplification, AURKA amplification, MYC amplification, AXL amplification, CCNE1 amplification, GNAS amplification, JAK2 amplification, LYN amplification, and TP53 E171del. The patient was matched with trametinib, and pembrolizumab. Like Patient 141, CD274 (PD-L1) amplification was matched to a checkpoint inhibitor, pembrolizumab,[7] and was scored at 50% per our rules. Any additional matches would increase the matching score over 50%. GNAS is known to activate the MEK pathway. Thus, GNAS was considered matched to the MEK inhibitor, trametinib.

Patient A032 had a tumor with BRAF V600E, CCND2 amplification, FAT1 Y2288*, SMAD4 R445*, and TP53 V73fs*76. The patient was treated with dabrafenib, trametinib, and cetuximab. Dabrafenib and trametinib have well known synergy for targeting BRAF V600E.[17-20] EGFR overexpression is known to be an escape pathway. Therefore, adding an EGFR monoclonal antibody to a BRAF inhibitor has synergistic activity.[21-23] This led to it being including in the NCCN guidelines for colorectal cancer. Moreover, the FDA has granted a breakthrough therapy designation to the combination of the BRAF inhibitor encorafenib (Braftovi), the MEK inhibitor binimetinib (Mektovi), and the EGFR inhibitor cetuximab (Erbitux) for the treatment of patients with *BRAF* V600E–mutant metastatic colorectal cancer following one or two prior lines of treatment in the metastatic setting. Therefore, we considered this a triple hit on BRAF. In addition, SMAD4 alterations upregulate EGFR with some publications showing that this change occurs with upregulation of the MAPK pathway.[24-26] In this patient's tumor, we targeted both of those effects. Thus, 3 points for BRAF plus 1 point for SMAD4 equals 4 targeted hits out of 7 alterations. Thus, the matching score was over 50%.

Patient A034 had a tumor with CCND1 amplification, AURKA amplification, FGF19 amplification, FGF3 amplification, FGF4 amplification, GNAS amplification, and ZNF217 amplification, as well as alterations ESR1 D538G, ESR1 E380Q, ESR1 L536P, and ESR1 Y537N. The patient was treated with matched therapy that included fulvestrant, everolimus, palbociclib, pazopanib. This case was difficult to score. CCND1 amplification results in activation of both the cell cycle and mTOR pathways. Therefore, there were two hits on the CCND1 activated pathways via palbociclib, a CDK4/6 inhibitor of the cell cycle, and everolimus, an mTOR inhibitor. In addition, the patient has FGF19, FGF3, and FGF4 amplifications that activate multiple FGF receptors. Pazopanib is a potent FGFR2 inhibitor in vitro and in vivo and also inhibits other FGFR receptors. Thus, counting CCND1 twice (in the numerator and denominator), plus each FGF amplification being counted once, 5 of 8 targets are hit. Regarding the ESR1, there are fulvestrant-sensitive and -resistant mutations. ESR1 E380Q, ESR1 L536P, and ESR1 D538G are fulvestrant-sensitive. ESR1 Y537N is fulvestrant-resistant.[27] We counted all three sensitive alterations as 1 and the one resistant one was 1. Thus, 6 of 10 targets are hit. Alternatively, one could argue that

if one is resistant, then all are resistant. In that case, we would count them all as one. The score would be 5 of 9 targets hit. We debated internally, but in all situations, the Matching Score would be >50%.

Patient A035 had a tumor with KIF5B-RET fusion, MYC amplification, NFKBIA amplification, NKX2-1 amplification, and TP53 S241. The tumor was TMB intermediate and PD-L1 positive by IHC. The patient was treated with matched therapy that included lenvatinib and atezolizumab. Similar to Patients 102 and 115, TMB intermediate, when matched with checkpoint inhibitors, like atezolizumab, was scored at 50%. Any additional matches would increase the matching score over 50%. In this case, lenvatinib inhibits RET, as well as VEGFR1, 2, and 3. TP53 aberrations may be indirectly targeted with VEGF inhibitors.[10,28,29]

Patient A037 had a tumor with KRAS G12C, NF2 truncation exon 7, CDKN2A B Loss, TET2 truncation exon 11, TP53 R306. The tumor was TMB intermediate and the patient was administered nivolumab. The patient also received trametinib for a KRAS alteration bringing the score to over 50%. We realize that at least in monotherapy, these matches have not worked in an ideal fashion. However, for MEK inhibitor matches to KRAS, preclinical and clinical data exist.[30] For instance, on the clinical side, a patient with Rosai Dorfman and a single KRAS mutation was reported in a New England Journal of Medicine article to respond to a MEK inhibitor (i.e., cobimentinib).[31] Finally, there is data to suggest a role for combination treatment with MEK and CDK4/6 inhibitors.[32]

In summary, these patients have complex genomic alterations in their tumors. The Matching Score system is not always straightforward, but we followed the designated rules for consistency.

Selected Examples of Immunotherapy with Alternative Matching Score Methodology

TMB High

Patient 47 had a tumor with BRCA1 E1375*, CTNNB1 S37F, NOTCH1 P1770S, NOTCH1 Q1810*, NOTCH1 T1997M, ASXL1 Q748*, CREBBP Q1245*, EPHA3 T215M, FANCE S241F, FANCL splice

site 692-1G>A, KDM6A S1400*, KEAP1 R362Q, LRP1B loss exons 12-15, MAGI2 R766*, RB1 S474N, SETD2 R1592*, SLIT2 splice site 611+2T>A, SPTA1 E1707K, TERT promoter -146C>T, and TP53 R342*. The tumor was TMB high and the patient was treated with pembrolizumab. Per our alternative rules and the recent publication by our group,[7] we considered TMB high matched to a checkpoint inhibitor (e.g., pembrolizumab) to be a 58% match. We acknowledge that there is no perfect scoring system, especially for immunotherapy. However, our oversight committee created and followed these rules in a consistent fashion.

Patient 121 had a tumor that was TMB high and was treated with nivolumab, a checkpoint inhibitor. Per our alternative rules and the recent publication by our group,[7] we considered TMB high matched to a checkpoint inhibitor (e.g., nivolumab) to be a 58% match.

Patient 155 had a tumor that was TMB high and was treated with nivolumab, a checkpoint inhibitor. Per our alternative rules and the recent publication by our group,[7] we considered TMB high matched to a checkpoint inhibitor (e.g., nivolumab) to be a 58% match.

Patient A011 had a tumor that was MSI high and was treated with pembrolizumab, a checkpoint inhibitor.[14-16] Per our alternative rules, (supported by the more recent FDA approval of pembrolizumab for MSI-high tumors), we considered MSI high matched to a checkpoint inhibitor (e.g., pembrolizumab) to be a 58% match.

TMB Intermediate

Patient 102 had tumor with CDKN2A/B loss, TP53 C176F, TP53 D61fs*62, and EP300 P925T. The tumor was TMB intermediate and the patient was treated with nivolumab and palbociclib. Per our alternative matching rules in the Methods, patients with TMB intermediate, when matched with checkpoint inhibitors, like nivolumab, were scored at 31%. One additional match out of 4 genes (25%)

would increase the matching score over 50%. In this case, the patient also received palbociclib, a CDK4/6 inhibitor, that was matched to CDKN2A/B loss because it upregulates CDK4/6.[8,9]

Patient 115 had a tumor with KRAS G12V, ATM H448fs*36, PIK3CA I1058F, APC R876*, APC T1556fs*3, DNMT3A W860, and SOX9 S403fs*1. The tumor was TMB intermediate and the patient was treated with nivolumab, trametinib, and sulindac. Similar to Patient 102, TMB intermediate, when matched with checkpoint inhibitors, like nivolumab, was scored at 31%. Two additional matches out of 6 (33%) would increase the matching score over 50%. We considered trametinib matched to the KRAS mutation and sulindac matched to the APC mutation for the reasons outlined for Patient 99.[11,12]

Patient A035 had a tumor with KIF5B-RET fusion, MYC amplification, NFKBIA amplification, NKX2-1 amplification, and TP53 S241. The tumor was TMB intermediate and PD-L1 positive by IHC. The patient was treated with matched therapy that included lenvatinib and atezolizumab. Similar to Patients 102 and 115, TMB intermediate, when matched with checkpoint inhibitors, like atezolizumab, was scored at 31%. Two additional matches out of 5 (40%) would increase the matching score over 50%. In this case, lenvatinib inhibits RET, as well as VEGFR1, 2, and 3. TP53 aberrations may be indirectly targeted with VEGF inhibitors.[10,28,29]

Patient A037 had a tumor with KRAS G12C, NF2 truncation exon 7, CDKN2A B Loss, TET2 truncation exon 11, TP53 R306. The tumor was TMB intermediate and the patient was administered nivolumab, giving a score of 31%. The patient also received trametinib for a *KRAS* alteration. One additional match out of 5 (20%) would increase the matching score over 50%. We realize that at least in monotherapy, these matches have not worked in an ideal fashion. However, for MEK inhibitor matches to KRAS, preclinical and clinical data exist.[30] For instance, on the clinical side, a patient with Rosai Dorfman and a single KRAS mutation was reported in a *New England Journal of Medicine* article to respond to a MEK inhibitor (i.e., cobimentinib).[31] Finally, there is data to suggest a role for combination treatment with MEK and CDK4/6 inhibitors.[32]

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SUPPLEMENTARY TABLES

Supplementary Table 3. Reasons for not administering molecularly matched therapy to 10 "No Match Administered" patients.

Reasons	N	Percent
Treating oncologists' choice	4*	36.4%
Patient preference	4*	36.4%
Patient co-morbidities	0	0%
Potential drug toxicities	1	9.1%
Insurance payor coverage of off-label agent(s)	0	0%
Investigational agent in other clinical trial availability	2	18.2%

*Patient 123 was not administered matched therapy due to a combination of the "treating oncologists' choice and the patient preference."

Supplementary Table 4. Matched patients and matched drug classes according to molecular test results.

	All Matched Patients (N=73)*					Patients with Matching Score >50% (N=28)*				
	Evaluated	**Test Result**	**N (% of evaluated)**	**Drug Class Administered**	**N (% matched)**	**Evaluated**	**Test Result**	**N (% of evaluated)**	**Drug Class Administered**	**N (% matched)**
Genomic alterations	73	≥ 1 alteration	73 (100%)	Genomically targeted	67 (91.8%)	28	≥ 1 alteration	28 (100%)	Genomically targeted	25 (89.3%)
PD-L1 (IHC)**	34	Positive	7 (20.6%)	Checkpoint inhibitor	4** (57.1%)	15	Positive	4 (26.7%)	Checkpoint inhibitors	4** (100%)
***CD274* (PD-L1) amplification**	73	Positive	3 (4.1%)	Checkpoint inhibitor	3** (100%)	28	Positive	2 (7.1%)	Checkpoint inhibitor	2** (100%)
TMB**	49	High/Intermediate	20 (40.8%)	Checkpoint inhibitor	11** (55%)	19	High/Intermediate	11 (57.9%)	Checkpoint inhibitors	8** (72.7%)
MSI**	47	High	1 (2.1%)	Checkpoint inhibitor	1** (100%)	16	High	1 (6.3%)	Checkpoint inhibitors	1** (100%)
Total characterized genomic alterations	73	≥8 with unknown PD-L1 IHC, TMB, and MSI	5 (6.8%)	Checkpoint inhibitor	1** (20%)	16	≥8 with unknown PD-L1 IHC, TMB, and MSI	1 (6.3%)	Checkpoint inhibitors	1** (100%)

* Some patients received several classes of matched drugs.
** Of the 28 patients with Matching Score >50%, a checkpoint inhibitor was given (alone or in combination with other drugs) to 10 patients (35.7%). Some patients had overlapping immune biomarkers, e.g., one patient had both MSI high and TMB high; three additional patients were both TMB intermediate and PD-L1 positive on IHC.

Note: Four patients (5.5%) in the matched group (with matching score >50%) were treated with hormone therapies in combination with molecularly targeted drugs based on positive hormone status.

Abbreviations: IHC: immunohistochemistry; MSI: microsatellite instability; N= number; TMB: tumor mutational burden.

Supplementary Table 5. Median follow up of all enrolled cohorts. Patients were followed until progression of disease, treatment intolerability, or death.

Group	Median Follow Up (months)	95% Confidence Interval
Matching Score >50% [N=28]	10.5	7.5-13.5
Matching Score ≤50% [N=45]	18.8	12.6-25.0
Treated patients who received no matched therapy [N=10]	7.6	5.7-9.5
Inevaluable [N=66]	10.8	2.9-18.6
All Patients [N=149]	10.8	6.9-14.6

Supplementary Table 6. Effect of the time interval between the biopsy used for matching and treatment start date on outcomes. Only patients matched to therapy [N=73 (Matching Score >0) were included].

			Univariable		Multivariable	
Clinical outcomes	**Variable**	**Results**	**OR or HR**	**P-values[4]**	**OR or HR**	**P-values**
Rate of SD ≥ 6 months/PR/CR (%)[1]	**Time between tissue biopsy and treatment initiation** ≥9 months (N=28) <9 months (N=32)	 5/28=17.9% 15/32=46.9%	OR 4.06 (1.23-13.35)	**0.021**	OR 4.17 (1.14-15.25)	**0.031**
	Matching Score >50% (N=20) ≤50% (N=40)	 10/20=50.0% 10/40=25.0%	OR 3.00 (0.97-9.30)	0.057	OR 3.29 (0.93-11.60)	0.065
	Unmatched chemotherapy added YES (N=15) NO (N=45)	 8/15=53.3% 12/45=26.7%	OR 3.14 (0.94-10.55)	0.064	OR 4.49 (1.13-17.76)	**0.033**
Progression-free survival (PFS, median in months, 95% CI)[2]	**Time between tissue biopsy and treatment initiation** ≥9 months (N=34) <9 months (N=39)	 3.5 (2.4-4.6) 3.7 (2.5-5.0)	HR 0.60 (0.35-1.03)	0.059	HR 0.65 (0.38-1.11)	0.117
	Matching Score >50% (N=28) ≤50% (N=45)	 6.5 (3.2-9.9) 3.2 (2.6-3.9)	HR 0.41 (0.23-0.73)	**0.002**	HR 0.42 (0.24-0.76)	**0.004**
	Unmatched chemotherapy added YES (N=16) NO (N=57)	 3.7 (0.0-7.5) 3.7 (3.3-4.1)	HR 0.99 (0.54 -1.80)	0.967	---	---
Overall survival (OS, median in months, 95% CI)[2]	**Time between tissue biopsy and treatment initiation** ≥9 months (N=34) <9 months (N=39)	 7.9 (2.8-13.1) 14.1 (10.1-18.0)	HR 0.65 (0.33-1.30)	0.222	HR 0.69 (0.35-1.38)	0.298
	Matching Score[3] >50% (N=28) ≤50% (N=45)	 NR (after a median follow-up of 8.5 months (95% CI 3.9-13.2)) 10.2 (4.4-16.0)	HR 0.42 (0.18-0.97)	**0.036**	HR 0.43 (0.19-1.00)	**0.050**
	Unmatched chemotherapy added YES (N=16) NO (N=57)	 17.0 (5.6-28.4) 11.8 (6.2-17.4)	HR 0.71 (0.31-1.63)	0.417	---	---

[1] N=60 patients evaluable for the rate of SD ≥ 6 months/PR/CR.
[2] N=73 patients evaluable for PFS and OS analyses.
[3] The cut-off of 50% for the Matching Score was chosen according to the minimum P-value criteria.[1]
[4] Variables with P<0.3 in univariable analysis were included in multivariate analysis.

*Two-sided log-rank analyses were performed. No adjustment for multiple comparisons was made.

Abbreviations: 95% CI: 95% Confidence Interval; CR: Complete response; NR=Not reached; PR: Partial response; SD: Stable disease.

Supplementary Table 7. Effect on outcomes of VEGF and MEK inhibitors in patients matched to *TP53* and *KRAS* mutations, respectively.

			Disease control (DCR, SD≥6mos/PR/CR)		Progression-free Survival (PFS)			Overall Survival (OS)		
Groups	**N**	**Evaluable**	**Rate**	***P***	**Median, months**	**HR (95% CI)**	***P***	**Median, months**	**HR (95% CI)**	***P***
Patients with *TP53* mutations treated with VEGF/VEGFR inhibitor only vs. Patients with *TP53* mutations not matched to any therapy	11 3	10 3	10.0% [1/10] 33.3% [1/3]	0.42	2.8 2.1	1.41 (030-6.58)	0.66	7.2 NR	1.57 (0.18-13.68)	0.68
Patients with *RAS* mutations treated with MEK inhibitor only vs. Patients with *RAS* mutations who were not treated with any matched therapy	3 4	2 4	0.0% [0/2] 25.0% [1/4]	>0.99	3.6 1.9	0.87 (0.14-5.30	0.88	4.5 NR	1.00 (0.06-16.00)	>0.99
Patients with *TP53* + *RAS* mutations treated with VEGF/VEGFR + MEK inhibitors vs. Patients with *TP53* + *RAS* mutations who were not treated with any matched therapy	2 2	2 2	50.0% [1/2] 50.0% [1/2]	>0.99	3.5 2.1	0.71 (0.04-11.79)	0.81	Not available	--	--

*Two-sided log-rank analyses were performed. No adjustment for multiple comparisons was made.

Abbreviations: 95% CI: 95% Confidence Interval; CR: Complete response; NR=Not reached; PR: Partial response; SD: Stable disease.

Supplementary Table 8. Serious adverse events (SAE) in 83 treated patients according to grade, matching, Matching Score, and relationship to treatment. Green indicates Matching Score >50% and red indicates Matching Score ≤50%. Shades of white to grey distinguish the relationship to treatment.

Study ID	Serious Adverse Event (SAE)	Grade	Received at least one matched therapy	Matching Score >50%	Relationship to Treatment
2	Headache	3	Yes	Yes	Not related
30	Skin infection	3	Yes	No	Not related
44	hematuria	3	Yes	No	Not related
44	Anemia	3	Yes	No	Not related
A001	Hypertension	3	Yes	No	Not related
A012	Vomiting	3	Yes	No	Not related
A012	Gastric outlet obstruction	3	Yes	No	Not related
A021	Pain	3	Yes	No	Not related
A021	Neuropathy	3	Yes	No	Not related
A021	Hypokalemia	3	Yes	No	Not related
33	Stroke	5	Yes	No	Not related
5	Gastric hemorrhage	3	Yes	No	Possible
7	Anemia	3	No	No	Possible
7	Gastric perforation	3	No	No	Possible
19	Gastric hemorrhage	3	Yes	No	Possible
19	Anemia	3	Yes	No	Possible
26	Elevated aspartate aminotransferase	3	No	No	Possible
33	Liver abscess	3	Yes	No	Possible
84	Fatigue	3	Yes	No	Possible
A037	Hyponatremia	3	Yes	Yes	Possible
A038	Ileus	3	Yes	No	Possible
23	Neutropenia	3	Yes	No	Probable
A018	Neutropenia	3	Yes	No	Probable
A018	Hyponatremia	3	Yes	No	Probable
A038	Hypertension	4	Yes	No	Probable

Supplementary Table 9. Serious adverse events (SAE) according to body systems for 83 treated patients.

Body System	Adverse Event	Grade	N of patients
Blood and lymphatic system disorders	Anemia	3	3
	Neutropenia	3	2
Gastrointestinal disorders	Gastric hemorrhage	3	2
	Gastric perforation	3	1
	Gastric outlet obstruction	3	1
	Ileus	3	1
	Vomiting	3	1
Liver disorders	Elevated aspartate aminotransferase	3	1
Infections and infestations	Abscess	3	1
	Skin infection	3	1
Central nerve system disorders	Stroke	5	1
Peripheral nerve system disorders	Neuropathy	3	1
Metabolism and nutrition disorders	Hyponatremia	3	2
	Hypokalemia	3	1
Renal and urinary disorders	Hematuria	3	1
Others	Hypertension	4	1
	Hypertension	3	2
	Headache	3	1
	Fatigue	3	1
	Pain	3	1

Supplementary Table 10. Percentages of serious adverse events (SAE) in various cohorts according to relationships with treatment.

Matching Score (MS)	Patients with any SAE	Patients with SAE related to treatment (possible/probable)	Patients with SAE unrelated to treatment
MS >50%	7.1% (2/28)	3.6% (1/28)	3.6% (1/28)
MS ≤50%	26.7% (12/45)	15.6% (7/45)	11.1% (5/45)
Treated patients who received no matched therapy	20.0% (2/10)	20.0% (2/10)	0% (0/10)

Abbreviation: MS: Matching Score.

EXTENDED DATA FIGURE LEGEND

Extended Data Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram includes the 149 patients that consented to I-PREDICT**.**

* Treated evaluable patients includes patients who received >10 days of treatment for drugs given on a daily basis (generally drugs given by mouth) or at least two doses of a drug normally given every two weeks or more frequently (the latter generally being intravenous drugs). Only patients whose treatment was reviewed and validated by data analysis lock down are included.

** One patient had inadequate tissue for NGS and declined biopsy; he was later re-enrolled after he agreed to undergo biopsy.

Note: One treated patient who initially was believed to have prior therapy was found, after data lockdown analysis, to have not received the prior regimen.

SUPPLEMENTARY REFERENCE

1. Mazumdar, M. & Glassman, J.R. Categorizing a prognostic variable: review of methods, code for easy implementation and applications to decision-making about cancer treatments. *Statistics in medicine* **19**, 113-132 (2000).