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Table S1. Clinical characteristics, genomics and protein analyses among patients presented at Rare Tumor Clinic (N=40).

ID	Age/ Gender	Cancer Diagnosis	Rare/Ultra-Rare	Tissue Next Generation Sequencing *	Protein analyses§	ctDNA †
1	69/W	Ampullary Carcinoma	Ultra-rare	*APC* G1499* *APC* S1400* *CDK6* amplification *ERBB2* amplification *ERBB2* T733I *TP53* C135G		
2	76/M	Ameloblastoma	Ultra-rare	*FGFR2* Y375C *MLL2* E1675* *MLL2* E4957* *SETD2* G1659V *SMO* L412F	EGFR (+) ERCC1 (-) PGP (-) RRM1 (-) TLE3 (+) TOPO1 (+) TS (-) **Pathline:** PD-L1 (+)	None detected.
3	61/W	Anal Squamous Cell Carcinoma	Ultra-rare	*FAT1* K2138* *PIK3CA* K111N *STK11* 126fs*20	EGFR (+) PGP (-) TLE3 (+) TOP2A (+) TOPO1 (+) TUBB3 (-)	*ATM* R3008C
4	58/M	Basal Cell Carcinoma, metastatic	Rare	**Sample #1:** *CDKN1A* R140Q *CDKN2A p16INK4a* P81L	**Sample #1:** MGMT (-) RRM1 (-)	*TP53* P278S

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CTNNA1 R383H
LRP1B splice site variant 9121-1G>A
NOTCH1 W287*
PTCH1 Q1366*
PTCH1 W197*
SLIT2 K325*
SMARCA4 Q1166*
TP53 P278S

TOPO1 (+)
TUBB3 (-)

Sample #2:
TOP2A (+)
TOPO1 (+)
TS (-)

Sample #2:
CD274 (*PD-L1*) amplification
CDKN1A R140Q
CDKN2A p16INK4a P81L
CTNNA1 R383H
FLT1 E487K
JAK2 amplification
LRP1B W2334*
LRP1B splice site 9121-1G>A
MLL2 splice site 4132-1G>A *NOTCH1* W287*
PDCD1LG2 (*PD-L2*) amplification
PDGFRA E459K
PIK3R2 Q412*
PTCH1 Q1366*
PTCH1 W197*
SLIT2 K325*
SMARCA4 Q1166*
TERT promoter-139_-138CC>TT
TP53 P278S

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				Microsatellite instability: Stable Tumor mutation burden: High, 104 mutations per megabase		
5	42/M	Castleman's Disease	Ultra-rare	Insufficient sample.		None detected.
6	52/W	Castleman's Disease	Ultra-rare	*JAK1* V310I		
7	68/W	Castleman's Disease	Ultra-rare			None detected.
8	36/W	Desmoid Tumor	Ultra-rare	*CTNNB1* S45N	ERCC1 (-) MGMT (-) PGP (-) PTEN (-) TS (-)	None detected.
9	66/W	Endometrial Stroma Sarcoma	Ultra-rare	**Sample #1:** *ZC3H7B-BCOR* fusion *CDKN2A p14ARF* P72L *CDKN2A p16INK4A* R58* **Sample #2:** *CDKN2A p14ARF* P72L *CDKN2A p16INK4a* R58* *FRS2* amplification *MDM2* amplification **NantOmics:** *PIK3C2G* amplification	**Sample #1:** EGFR (+) ERCC1 (-) MGMT (-) RRM1 (-) TLE3 (+) TOP2A (+) TUBB3 (-) **Sample #2:** EGFR (+) ERCC1 (-) MGMT (-) RRM1 (-)	None detected.

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					TLE3 (+) TOP2A (+) TUBB3 (-) PR (+)	
10	51/W	Erdheim Chester Disease[¥]	Ultra-rare			None detected.
11	53/M	Erdheim Chester Disease[¥]	Ultra-rare			None detected.
12	54/M	Erdheim Chester Disease	Ultra-rare	*ASXL1* R693* *BRAF* V600E *U2AF1* Q157P		*JAK2* V617F
13	57/M	Erdheim Chester Disease[¥]	Ultra-rare	**UCSD NGS:** None detected.	MGMT (-) TOPO1 (+) TS (-) TUBB3 (-)	None detected.
14	67/W	Erdheim Chester Disease	Ultra-rare	Insufficient sample.	**Emerge:** PD-L1 (+) **Pathline:** PD-L1 (+)	None detected.
15	87/W	Merkel Cell Carcinoma	Ultra-rare	*ARID1A* splice site 4004+1G>A *ATR* W1883* *BCOR* rearrangement intron 6 *BRCA1* inversion exon 4 *DICER1* S1344L *FAM123B* G303D *MUTYH* G382D *RB1* Q597* *TP53* L194fs*14	ERCC1 (-) PGP (-) PTEN (-) RRM1 (-) TOPO1 (+) TS (-) TUBB3 (-) **Pathline:**	

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				TP53 V147I *TP53* W146*	PD-L1 (+)	
16	49/W	Neuroendocrine tumor of the uterine (high-grade, large cell)	Ultra-rare	*ABL2* P497fs*7 *ATRX* D1940fs*15 *BLM* N515fs*16 *FBXW7* R465H *FGF6* V127M *JAK1* K860fs*16 *JAK1* P430fs*2 *MEN1* R521fs*7 *MLL2* P2302fs*20 *MLL3* K2797fs*26 *MSH2* E48* *MSH2* Q324* *NOTCH1* R1586H *PIK3CA* E545D *PREX2* S565fs*3 *PTEN* K267fs*9 *PTEN* R130Q *QKI* A338T *SETD2* F636fs*6 *SMARCA4* Q214* *SMARCA4* T296fs*7 *STK11* W332* *TET2* R1440fs*38 *TET2* R550* Microsatellite instability: High Tumor mutation burden: High, 54 mutations per megabase	ERCC1 (-) MSH2 (-) MSH6 (-) PGP (-) TOP2A (+) TOPO1 (+)	*PTEN* R130Q *FBXW7* R465H *PIK3CA* E545D *PIK3CA* R88Q *NRAS* Q61R *CTNNB1* S33A

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17	62/W	Yolk Sac Tumor of the Liver	Ultra-rare	*AKT2* amplification *CCNE1* amplification *TP53* D281E		**Sample #1:** *CCNE1* amplification *CDK6* amplification *EGFR* amplification *MYC* amplification *PIK3CA* amplification **Sample #2:** None detected. **Sample #3:** None detected.
18	55/M	Thymoma, type B3	Ultra-rare	*DNMT3A* R882H	PD-L1 (+) TS (-) TUBB3 (-) **Pathline:** PD-L1 (+)	None detected.
19	54/W	Fallopian Cancer	Ultra-rare	*FANCC* truncation exon 8 *MYC* amplification *NF1* S821fs*5 *TP53* S166*	ER (+) RRM1 (-) TOPO1 (+) TS (-) **Clarient:** EGFR (+) **Pathline:** PD-L1 (+)	*BRAF* amplification *MET* amplification *MYC* amplification *PIK3CA* amplification *TP53* S166* *TP53* V147G
20	73/M	Myxofibrosarcoma	Ultra-rare	*FRS2* amplification *IGF1R* amplification	Only PD-L1 testing was done which was	None detected.

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				MDM2 amplification *PIK3R2* M476I Microsatellite instability: Stable Tumor mutation burden: Low, ≤1 mutation per megabase **NantOmics:** *BRCA2* K3326 *IGF1R* 17X amplification	negative.	
21	62/M	Basal Cell Carcinoma, locally advanced, surgically unresectable	Rare	*ASXL1* Q760* *INPP4B* W521* *KEL* R130Q *PIK3R1* R534* *PTCH1* splice site 1504-1G>T *PTEN* splice site 210 2A>T *RAC1* P29S *TERT* promotor- 124C>T *TP53* Q100* *TP53* R196* *WT1* C350R Microsatellite instability: Stable Tumor mutation burden: High, 53 mutations per megabase	AR (+) EGFR (+) ERCC1 (-) MGMT (-) PGP (-) PTEN (-) RRM1 (-) TLE3 (+) TOP2A (+) TOPO1 (+) TS (-) TUBB3 (-)	None detected.
22	37/W	Papillary serous carcinoma of ovary	Rare	*KRAS* G12V Microsatellite instability: Unknown Tumor mutation burden: Low, 5 mutations per megabase	**Sample #1:** ER (+) MGMT (-) PGP (-) RRM1 (-)	*KRAS* G12V

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					TOP2A (+) TS (-) TUBB3 (-) **Sample #2:** ER (+) ERCC1 (-) RRM1 (-) TS (-) TUBB3 (-)	
23	68/W	High-grade serous ovarian Cancer	Rare	*FANCC* N152fs*9 *TP53* V173M Microsatellite instability: Stable	EGFR (+) ER (+) RRM1 (-) TLE3 (+) TS (-) TUBB3 (-)	*BRAF* amplification *CCND2* amplification *CCNE1* amplification *CDK4* amplification *CDK6* amplification *EGFR* amplification *ERBB2* amplification *FGFR2* amplification *KRAS* amplification *MET* amplification *MYC* amplification *PIK3CA* amplification *TP53* V173M *TP53* R273H
24	51/M	Adenoid Cystic Carcinoma	Rare	**Washington University NGS:** *AKT1* L52R		None detected.
25	62/W	Papillary serous carcinoma of	Rare	*AURKA* amplification *GNAS* amplification	ER (+) RRM1 (-)	*ATM* R3008H *TP53* Y236D

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		ovary		*LYN* amplification *PRKCI* amplification *TERC* amplification *TP53* R273H *ZNF217* amplification Microsatellite instability: Stable Tumor mutation burden: Low, 5 mutations per megabase	TLE3 (+) TOP2A (+) TOPO1 (+) TS (-)	
26	71/W	High-grade serous fallopian tube adenocarcinoma	Ultra-rare	*KRAS* amplification *TP53* P250_I251del *CCNE1* amplification	ERCC1 (-) TLE3 (+) TOP2A (+) RRM1 (-)	None detected.
27	63/W	Liposarcoma	Ultra-rare	*AKT1* amplification *CDK4* amplification *MDM2* amplification *CDC73* rearrangement intron 14 *FRS2* amplification *ZRSR2* R446_R448>R	ERCC1 (-) MGMT (-) RRM1 (-) TS (-)	TP53 L130V
28	31/W	Castleman's Disease	Ultra-rare	Insufficient tissue.	Only PD-L1 testing was done which was negative.	None detected.
29	66/W	Metaplastic carcinoma of breast	Ultra-rare	*EGFR* F795C *HRAS* G13R *CDKN2A/B* loss *PIK3R1* K567_L570del *TP53* R282W	EGFR (+) ERCC1 (-) MGMT (-) TLE3 (+) TOPO1 (+)	None detected.

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					TOP2A (+) PD-L1: (+)	
30	70/M	Chondrosarcoma	Ultra-rare	*CDKN2A/B* loss exon 2 *SETD2* splice site 4455-2_4456delAGAA	PR (+) RRM1 (-) TLE3 (+) TOPO1 (+)	*TP53* V272M
31	58/M	Ocular melanoma	Ultra-rare	*GNAQ* Q209L *SF3B1* R625C	ERCC1 (-) PD-L1 (+) RRM1 (-) TLE3 (+) TOP2A (+) TOPO1 (+) TUBB3 (-)	**Sample #1:** *MYC* amplification *BRAF* amplification *MET* amplification *ERBB2* amplification **Sample #2:** *GNAQ* Q209L 9.6% *MYC* amplification *BRAF* amplification *MET* amplification *ERBB2* amplification
32	55/W	Glioblastoma	Rare	*CDKN2A/B* loss *EGFR* amplification, G598V *PIK3R1* I571fs*31 *TERT* promoter -124C>T **UCSD NGS:** *CDKN2A/B* homozygous deletion *EGFR* G598V *NF2* L54Q *PIK3R1* I571fs*31	ERCC1 (-) RRM1 (-) TLE3 (+) TS (-) TUBB3 (+)	

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33	68/W	High grade serous ovarian cancer	Rare	*RB1* V554L *TP53* M160_A161 ins AIYK, Q166*	ER (+) ERCC1 (-) RRM1 (-) TOPO1 (+) TOP2A (+) TS (-) TUBB3 (-)	*BRAF* amplification *CCNE1* amplification *CDK6* amplification *EGFR* amplification *MET* amplification
34	39/W	Myoepithelial carcinoma	Ultra-rare	*EWSR1-NFATC2* fusion	ERCC1 (-) TLE3 (+) TOPO1 (+) TUBB3 (-)	None detected.
35	59/W	High grade serous ovarian cancer	Rare	*BRCA1* K519fs*13 *TP53* H179R	AR (+) ER (+) ERCC1 (-) RRM1 (-) TOPO1 (+) TS (-) TUBB3 (-)	*BRAF* amplification *TP53* H179R *TP53* K132N
36	36/W	Angiosarcoma of breast	Ultra-rare		ERCC (-) RRM1 (-) TOP2A (+)	
37	39/W	Fibromyxoid sarcoma	Ultra-rare	*CRKL* amplification *EWSR1- CREB3L2* fusion		None detected.
38	48/W	Poorly differentiated	Rare	*APC* 1309fs*4, splice site 730-1G>A *KRAS* G12V		

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		carcinoma of unknown primary		*MTOR* S2215Y *RB* R661W *TP53* R175H		
39	50/W	Metaplastic breast cancer	Ultra-rare	*ARID1A* Q1334_R1335insQ CDKN2A/B loss *FBXW7* R479G *FRS2* amplification *MDM2* amplification *PIK3CA* E545K *TP53* splice site 1101-88_1158del146	**Emerge**: PD-L1 (+)	
40	70/W	High-grade neuroendocrine carcinoma of unknown primary	Ultra-rare	*CDK4* R24L *FAT1* T1721fs*8 *KRAS* G12C *PTEN* K163* *MYC* amplification – equivocal *RB1* splice site 1499-2A>T *RBM10* E513* *SMAD2* splice site 1136-1_1136GG>TT *TERC* amplification – equivocal *TP53* I251fs*94 Microsatellite instability: Stable. Tumor mutation burden: Intermediate, 12 mutations per megabase	ERCC1 (-) MGMT (-) TOP2A (+) TOPO1 (+)	*BRAF* amplification *CDK4* R24L *KRAS* G12C *MYC* amplification *PTEN* K163*

* Unless specified, tissue next generation sequencing was done through Foundation Medicine (http://www.foundationmedicine.com/). Microsatellite instability and/or tumor mutation burden status were available in N=7 patients.

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[§] Unless specified, protein analyses were done through Caris (http://www.carislifesciences.com/). Only pertinent positive or negative actionable results are listed.

[†] ctDNA was done through Guardant Health (http://www.guardanthealth.com/guardant360/).

[¥] *BRAF* V600E mutation detected by polymerase chain reaction (N=3).

Blank = Not tested.

Abbreviation: NGS, next-generation sequencing.

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Table S2. Number and percentage of patients with pertinent protein abnormalities detected by IHC (n=29).

Pertinent protein abnormalities	Results of IHC considered actionable	Condition for positive IHC results *	Number of patients with affected protein/Patients tested N (%)	Implications of protein markers
RRM1	Negative	Intensity ≥2+ and ≥50% of cells stained	17/21 (81.0%)	Low or loss of RRM1 (ribonucleotide reductase catalytic subunit M1) is potentially targetable with gemcitabine [S1].
ERCC1	Negative	Intensity of ≥3+ with ≥10% or ≥2+ with ≥50% of cells stained	17/24 (70.8%)	Loss of ERCC1 (excision repair cross-complementation group 1) is potential marker for response to platinum [S2].
TLE3	Positive	Intensity ≥2+ and ≥30% of cells stained	12/17 (70.6%)	Positive TLE3 (transducin like enhancer of split 3) is potential marker for response to taxane therapy [S3].
TOPO1	Positive	Intensity ≥2+ and ≥30% of cells stained	16/24 (66.7%)	Positive TOPO1 (topoisomerase I) is potential marker for response to topoisomerase I inhibitors such as irinotecan or topotecan [S4].
PGP	Negative	Intensity ≥1+ and ≥10% of cells stained	7/11 (63.6%)	Negative PGP (P-glycoprotein) may predict response to taxane [S5].
TS	Negative	Intensity ≥1+ and ≥10% of cells stained	15/25 (60.0%)	Negative TS (thymidylate synthase) is potentially

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				targetable with 5-fluorouracil [S6].
TUBB3	Negative	Intensity ≥2+ and ≥30% of cells stained	14/24 (58.3%)	Negative TUBB3 (class III beta-tubulin) is predictive marker for response with taxane-based therapy [S7].
EGFR	Positive	Intensity ≥1+ and ≥10% of cells stained	7/13 (53.8%)	Although there are conflicting data, EGFR (epidermal growth factor receptor) is potentially targetable with anti-EGFR therapy such as cetuximab [S8].
TOP2A	Positive	Intensity ≥1+ and ≥10% of cells stained	13/25 (52.0%)	Positive TOP2A (topoisomerase II alpha) predicts the response to topoisomerase II inhibitor such as doxorubicin [S9].
MGMT	Negative	Intensity ≥1+ and >35% of cells stained	9/23 (39.1%)	Negative MGMT (O(6)-methylguanine-DNA methyltransferase) may predict response to alkylating agents such as dacarbazine [S10].
ER	Positive	Intensity ≥1+ and ≥10% of cells stained	6/24 (25.0%)	Positive ER (estrogen receptor) predicts response to hormone modulator [S11].
PD-L1	Positive	Intensity ≥2+ and ≥5% of cells stained	7/28 (25.0%)	Positive PD-L1 (programmed death-ligand 1) predicts response to immune check point inhibitors [S12].
PTEN	Negative	Intensity ≥1+ and >50%	3/25 (12.0%)	PTEN (phosphatase and tensin

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		of cells stained		homolog) loss is potentially targetable with mTOR inhibitors [S13].
PR	Positive	Intensity ≥1+ and ≥10% of cells stained	2/20 (10.0%)	Positive PR (progesterone receptor) predicts response to hormone modulator [S14]
AR	Positive	Intensity ≥1+ and ≥10% of cells stained	2/24 (8.3%)	Positive AR (androgen receptor) predicts response to hormone modulator [S11].[S15]
MSH2	Negative	Intensity ≥1+ and ≥1% of cells stained	1/20 (5.0%)	Loss of mismatch repair protein (e.g. MSH2 [MutS protein homolog 2] or MSH6 [MutS protein homolog 6]) predicts response to PD-1 blockade [S16].
MSH6	Negative	Intensity ≥1+ and ≥1% of cells stained	1/20 (5.0%)	

Only pertinent positive and negative results were listed. For example, positive, AR, EGFR, ER, PD-L1, PR, TLE3, TOP2A, and TOPO1 as well as negative ERCC1, MGMT, MLH1, MSH2, MSH6, PGP, PTEN, RRM1, TS, and TUBB3 were considered pertinent since they are targetable.

* Condition for positive IHC results according to Caris Life Sciences (www.carismolecularintelligence.com).

Abbreviations:
AR, androgen receptor; EGFR, epidermal growth factor receptor; ER, estrogen receptor; ERCC1, excision repair cross-complementation group 1; MGMT, O(6)-methylguanine-DNA methyltransferase; MSH2, MutS protein homolog 2; MSH6, MutS protein homolog 6; PD-L1, programmed death-ligand 1; PGP, P-glycoprotein; PR, progesterone receptor; PTEN, phosphatase and tensin homolog; RRM1, ribonucleotide reductase catalytic subunit M1; TLE3, transducin like enhancer of split 3; TOPO1**,** topoisomerase I; TOP2A, topoisomerase II alpha; TS, thymidylate synthase; TUBB3, class III beta-tubulin.

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Table S3. Matched targeted therapy and clinical outcome among patients presented in the Rare Tumor Clinic (N=21). Patient ID corresponds to **Figure 2 and Supplemental Table 1**.

ID	Age/ Gender	Cancer Diagnosis*	Therapy and Rationale	Clinical outcome from matched therapy
6	52/W	Castleman's Disease	Siltuximab (anti-interleukin-6 antibody). *JAK1* mutation that alters IL-6 receptor sensitivity to IL-6 [S17]	CR. PFS = 11.9+ months.
21	62/M	Basal Cell Carcinoma, locally advanced, surgically unresectable	Vismodegib (Smoothened homologue inhibitor) for *PTCH1* mutation [S18]. Nivolumab (anti-PD1 antibody) for high tumor mutation burden [S19].	CR. PFS = 4.0+ months.
25	62/W	Papillary serous carcinoma of ovary	Doxorubicin based therapy for TOP2A positive [S9].	PR (82.9% decrease). PFS = 8.6+ months.
4	58/M	Basal Cell Carcinoma, metastatic	Nivolumab for *PD-L1* and *PD-L2* amplification [S12, 19].	PR (77% decrease). PFS = 12.5+ months.
16	49/W	Neuroendocrine tumor of the uterine (high-grade)	Nivolumab for microsatellite instability-high and high mutation burden [S19].	PR (75% decrease). PFS = 9.2+ months.
1	69 /W	Ampullary Carcinoma	Trastuzumab and pertuzumab (anti-Her2 antibodies) for *ERBB2* amplification [S20].	PR (59% decrease). PFS = 15.2+ months.
10	51/W	Erdheim Chester Disease	Vemurafenib for *BRAF* V600E mutation [S21].	PR (36.7% decrease). PFS = 19.7 months. Stopped due to severe uveitis.

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11	53/M	Erdheim Chester Disease	Vemurafenib for *BRAF* V600E mutation [S21].	PR (32.4% decrease). PFS = 26.1+ months.
8	36/W	Desmoid Tumor	Combination of sorafenib plus sulindac. CTNNB1 (beta-catenin) is part of Wnt signaling. In preclinical study, sorafenib was shown to have anti-cancer effect by modulating Wnt/beta-catenin signaling [S22]. Wnt/beta-catenin signaling also has cross-talk between COX-2. Thus it is potentially targetable with sulindac (COX-1/2 inhibitor) [S23].	SD (24% decrease). PFS = 9.1+ months.
35	59/W	High grade serous ovarian cancer	WEE1 inhibitor trial. *BRCA1* mutation is potentially targetable with WEE1 inhibitor [S24].	SD (23% decrease). PFS = 1.5+ months.
9	66/W	Endometrial Stroma Sarcoma	Combination of palbociclib, lenvatinib, anastrozole and doxorubicin. Palbociclib (CDK4/6 inhibitor) for *CDKN2A* alteration. Although some publication indicate *CDKN2A* aberration was not predictive of response to palbociclib [S25], it is	SD (20.7% decrease). PFS = 3.6+ months. CA 125 dropped from 1040 U/ml to 19 U/ml (to reference range).

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			theoretically targetable with CDK4/6 inhibitor [S26]. Lenvatinib (multi-kinase inhibitor including FGFR) targeting *FRS2* amplification [S27]. Anastrozole (aromatase inhibitor) to target PR positive [S14]. Doxorubicin for positive TOP2A [S9].	
31	58/M	Ocular melanoma	Combination of nivolumab, ipilimumab and trametinib. Nivolumab for positive PD-L1 [S12]. Trametinib for *GNAQ* mutation [S28].	SD (15.5% decrease). PFS = 3.2+ months.
23	68/W	High-grade serous ovarian Cancer	Combination of carboplatin, paclitaxel and bevacizumab. Carboplatin for *FANCC* alteration (*FANCC* associated with BRCAness) [S29]. Paclitaxel for TLE3 positive and TUBB3 negative [S3, 7]. Bevacizumab (anti-VEGF antibody)	SD (12.8% decrease). PFS = 1.8+ months.

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			for *TP53* alteration. *TP53* alterations are reported to be associated with higher *VEGF-A* expression [S30]. Patients with *TP53* alteration are also reported to have better clinical outcome with anti-VEGF containing regimen [S31, 32].	
19	54/W	Fallopian Cancer	Gemcitabine for RRM1 negative [S1].	SD (11.4% decrease). PFS = 9.8 months.
24	51/M	Adenoid Cystic Carcinoma	AKT inhibitor clinical trial for *AKT1* alteration.	SD (8% decrease). PFS = 5.5 months.
13	57/M	Erdheim Chester Disease	Vemurafenib and trametinib for *BRAF* V600E mutation [S21].	SD (5% decrease). PFS = 13.9+ months.
26	71/W	High-grade serous fallopian tube adenocarcinoma	Combination of carboplatin, bevacizumab and trametinib. Carboplatin for ERCC1 negative [S2]. Bevacizumab (anti-VEGF antibody) for *TP53* alteration. *TP53* alterations are reported to be associated with higher *VEGF-A* expression [S30]. Patients with *TP53* alteration are also reported to have better clinical outcome with anti-VEGF containing regimen [S31, 32]. Trametinib for *KRAS* amplification. KRAS alteration is potentially targetable with MEK inhibitor [S33].	SD (1.8% increase). PFS = 2.4+ months.

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22	37/W	Papillary serous carcinoma of ovary	Combination of trametinib and tamoxifen. Trametinib for *KRAS* mutation. KRAS alteration is potentially targetable with MEK inhibitor [S33]. Tamoxifen for ER positive [S11].	SD (8.5% increase). PFS = 4.2 months.
30	70/M	Chondrosarcoma	Combination of lenvatinib, palbociclib and anastrazole. Lenvatinib (multi-kinase inhibitor including anti-VEGF) for *TP53* mutation. *TP53* alterations are reported to be associated with higher *VEGF-A* expression [S30]. Patients with *TP53* alteration are also reported to have better clinical outcome with anti-VEGF containing regimen [S31, 32]. Palbociclib (CDK4/6 inhibitor) for *CDKN2A/B* loss. Although some publication indicate *CDKN2A/B* aberration was not predictive of response to palbociclib [S25], it is theoretically targetable with CDK4/6 inhibitor [S26]. Anastrazole or PR positive [S14].	SD (16% increase). PFS = 1.0+ month.

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33	68/W	High grade serous ovarian cancer	Combination of bevacizumab and sorafenib. Bevacizumab and sorafenib (multi-kinase inhibitor including anti-VEGF) for *TP53* mutation. *TP53* alterations are reported to be associated with higher *VEGF-A* expression [S30]. Patients with *TP53* alteration are also reported to have better clinical outcome with anti-VEGF containing regimen [S31, 32].	PD. PFS = 2.1 months (patient died without follow up scan).
20	73/M	Myxofibrosarcoma	Ceritinib for *IGF1R* amplification [S34].	PD with new lung metastases. PFS = 1.8 months.

*Patients are ordered according to the response, which corresponds to **Figure 4**.
Abbreviations: CR, complete response; PD, progressive disease; PFS, progression free survival; PR, partial response; SD, stable disease.

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Table S4. Genomic alterations detected by tissue next generation sequencing (n=33).

	Any alterations N (%)	Mutation N (%)	Amplification N (%)	Loss N (%)	Fusion/Re-arrangement N (%)	Multiple alterations N (%)
TP53	15 (45.5%)	15 (45.5%)	0	0	0	0
CDKN2A/B	4 (12.1%)	0	0	4 (12.1%)	0	0
FRS2	4 (12.1%)	0	4 (12.1%)	0	0	0
MDM2	4 (12.1%)	0	4 (12.1%)	0	0	0
RB1	4 (12.1%)	4 (12.1%)	0	0	0	0
KRAS	4 (12.1%)	3 (9.1%)	1 (3.0%)	0	0	0
MLL2	3 (9.1%)	3 (9.1%)	0	0	0	0
PIK3CA	3 (9.1%)	3 (9.1%)	0	0	0	0
PIK3R1	3 (9.1%)	3 (9.1%)	0	0	0	0
PTEN	3 (9.1%)	3 (9.1%)	0	0	0	0
SETD2	3 (9.1%)	3 (9.1%)	0	0	0	0
TERT	3 (9.1%)	3 (9.1%)	0	0	0	0
AKT1	2 (6.1%)	1 (3.0%)	1 (3.0%)	0	0	0
APC	2 (6.1%)	2 (6.1%)	0	0	0	0
ARID1A	2 (6.1%)	2 (6.1%)	0	0	0	0
ASXL1	2 (6.1%)	2 (6.1%)	0	0	0	0
BCOR	2 (6.1%)		0	0	2 (6.1%)	0
BRCA1	2 (6.1%)	2 (6.1%)	0	0	0	0
CCNE1	2 (6.1%)		2 (6.1%)	0	0	0
CDK4	2 (6.1%)	1 (3.0%)	1 (3.0%)	0	0	0
CDKN2A	2 (6.1%)	2 (6.1%)	0	0	0	0
EGFR	2 (6.1%)	1 (3.0%)	0	0	0	1 (3.0%)
EWSR1	2 (6.1%)		0	0	2 (6.1%)	0
FANCC	2 (6.1%)	2 (6.1%)	0	0	0	0
FAT1	2 (6.1%)	2 (6.1%)	0	0	0	0
FBXW7	2 (6.1%)	2 (6.1%)	0	0	0	0
JAK1	2 (6.1%)	2 (6.1%)	0	0	0	0
MYC	2 (6.1%)	2 (6.1%)	0	0	0	0
NOTCH1	2 (6.1%)	2 (6.1%)	0	0	0	0
PTCH1	2 (6.1%)	2 (6.1%)	0	0	0	0
SMARCA4	2 (6.1%)	2 (6.1%)	0	0	0	0
STK11	2 (6.1%)	2 (6.1%)	0	0	0	0
TERC	2 (6.1%)	2 (6.1%)	0	0	0	0

Included aberrant genes with N ≥ 2.

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Table S5. Genomic alterations detected by ctDNA (Guardant Health) (n=33).

	Any alterations N (%)	Mutation N (%)	Amplification N (%)
TP53	7 (21.2%)	7 (21.2%)	0
BRAF	6 (18.2%)	0	6 (18.2%)
MYC	5 (15.2%)	0	5 (15.2%)
MET	4 (12.1%)	0	4 (12.1%)
CCNE1	3 (9.1%)	0	3 (9.1%)
CDK6	3 (9.1%)	0	3 (9.1%)
EGFR	3 (9.1%)	0	3 (9.1%)
PIK3CA	3 (9.1%)	0	3 (9.1%)
ATM	2 (6.1%)	2 (6.1%)	0
CDK4	2 (6.1%)	1 (3.0%)	1 (3.0%)
ERBB2	2 (6.1%)	0	2 (6.1%)
KRAS	2 (6.1%)	2 (6.1%)	0
PTEN	2 (6.1%)	2 (6.1%)	0
CCND2	1 (3.0%)	0	1 (3.0%)
CTNNB1	1 (3.0%)	1 (3.0%)	0
FBXW7	1 (3.0%)	1 (3.0%)	0
FGFR2	1 (3.0%)	0	1 (3.0%)
GNAQ	1 (3.0%)	1 (3.0%)	0
JAK2	1 (3.0%)	1 (3.0%)	0
KRAS	1 (3.0%)	0	1 (3.0%)
NRAS	1 (3.0%)	1 (3.0%)	0
PIK3CA	1 (3.0%)	1 (3.0%)	0

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Table S6. Concordance between ctDNA and tissue NGS (N=27).

Genomic alteration*			
	***TP53* (+) from tissue**	***TP53* (-) from tissue**	**Total**
***TP53* (+) from ctDNA**	4	3	7
***TP53* (-) from ctDNA**	6	14	20
Total	10	17	27
Concordance for *TP53*	**18/27 (66.7%)**		
	***BRAF* (+) from tissue**	***BRAF* (-) from tissue**	**Total**
***BRAF* (+) from ctDNA**	0	6	6
***BRAF* (-) from ctDNA**	1	20	21
Total	1	26	27
Concordance for *BRAF*	**20/27 (74.1%)**		
	***MYC* (+) from tissue**	***MYC* (-) from tissue**	**Total**
***MYC* (+) from ctDNA**	2	3	5
***MYC* (-) from ctDNA**	0	22	22
Total	2	25	27
Concordance for *MYC*	**24/27 (88.9%)**		
	***MET* (+) from tissue**	***MET* (-) from tissue**	**Total**
***MET* (+) from ctDNA**	0	4	4
***MET* (-) from ctDNA**	0	23	23
Total	0	27	27
Concordance for *MET*	**23/27 (85.2%)**		

***Included 4 commonly altered genes found by ctDNA analysis.

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Figure S1. 3D waterfall plot among patients who received matched therapy in the Rare Tumor Clinic (N=21).

Patient ID corresponds to **Supplemental Tables 1 and Table 3** which describes the genomic/protein markers and matched targeted therapy patients received. See **Figure 2** for the waterfall and swimmer plot that correspond to 3D waterfall plot.

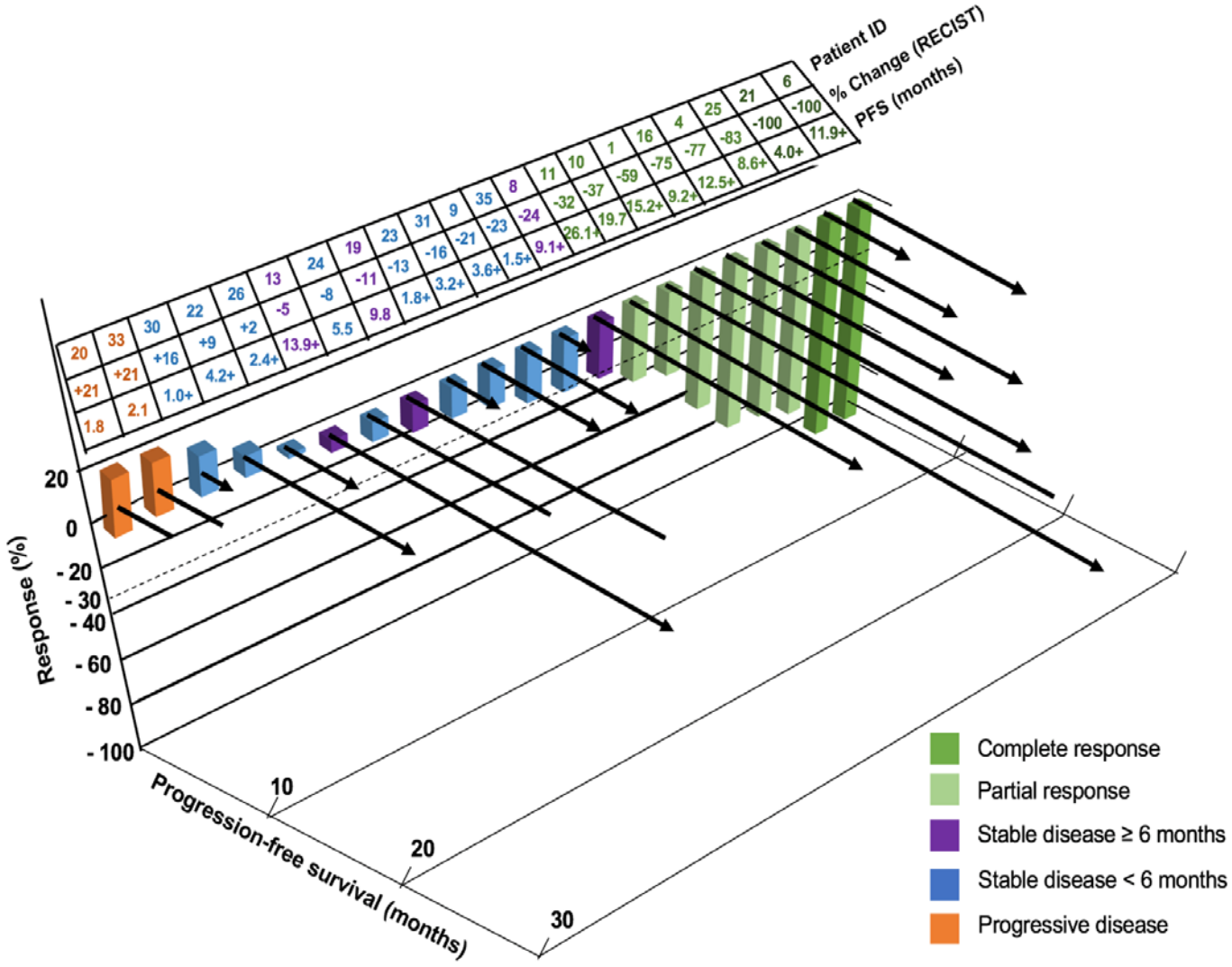

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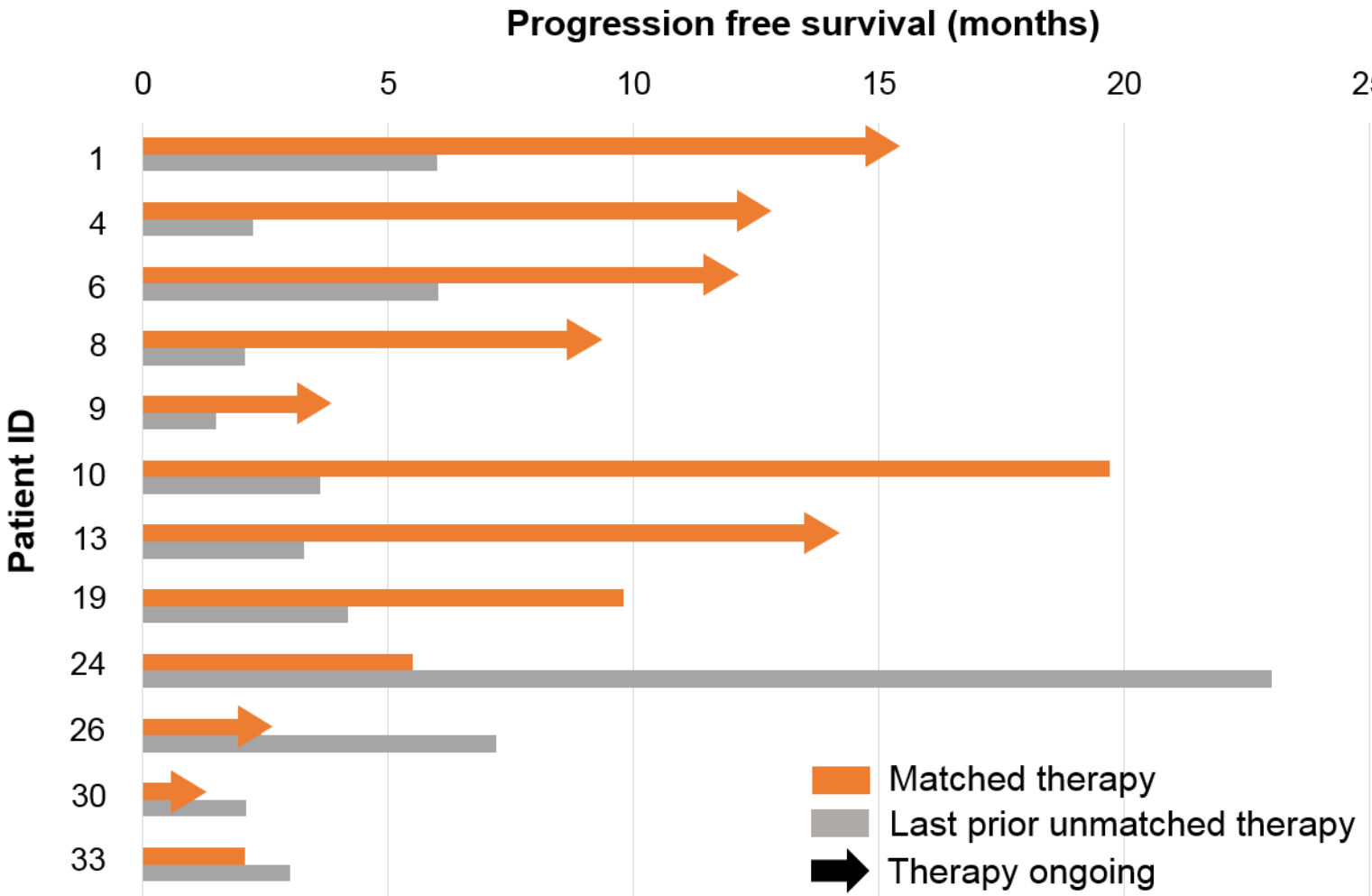
Figure S2. Comparison of PFS between matched vs. prior unmatched therapy (N=12) PFS between matched and unmatched therapies were compared. Eight of 12 patients (66.7%) achieved PFS ratio of ≥ 1.3 (range: 0.23-5.60) (PFS of matched therapy divided by PFS of last prior unmatched therapy).



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