Supplemental Table 1: Relationship between protein expression and potential chemotherapy benefit

	Protein Expression	Chemotherapy of Potential Benefit
ERCC1	Negative	Platinum
MGMT	Negative	Dacarbazine, Temozolomide
RRM1	Negative	Gemcitabine
TOP2A	Positive	Doxorubicin, Epirubicin, Etoposide
TOPO1	Positive	Irinotecan, Topotecan
TS	Negative	Fluorouracil, Pemetrexed
TUBB3	Negative	Taxanes*

*TUBB3 positivity predicts taxane resistance

Abbreviations: ERCC1=excision repair complementation group 1, MGMT= O-6-methyl guanine DNA methyltransferase, RRM1=ribonucleotide reductase regulatory subunit M1, TOP2A=topoisomerase 2, TOPO1=topoisomerase 1, TS=thymidylate synthetase, TUBB3=tubulin beta 3

Supplemental Table 2: Methodology for determining various markers shown in Table 1*

	Method	Comment
MSI-H	NGS	Direct analysis of short tandem repeat tracts in the target regions of sequenced genes; High: ≥46 altered microsatellite loci**
TMB-H	NGS	Calculated using nonsynonymous missense mutations; common germline variants excluded; High TMB: ≥17 mutations/Mb**
PD-L1	IHC	Antibody: SP142 (Ventana); Tumor tissue staining with ≥5% considered positive**
ERCC1	IHC	Antibody: 8F1 (Abcam); Positive: staining intensity of 2+ in at least 50% or 3+ in at least 10% or more tumor cells on a given slide
MGMT	IHC	Antibody: MT21.2 (Invitrogen); Positive: staining intensity of ≥ 2+ in at least 50% or more tumor cells on a given slide
RRM1	IHC	Antibody: polyclonal (Proteintech Group); Positive: staining intensity of 2+ or 3+ in at least 35% or more tumor cells on a given slide
TOP2A	IHC	Antibody: 3F6 (Leica Microsystems); Positive: staining intensity of ≥1+ in at least 10% or more tumor cells on a given slide
TOPO1	IHC	Antibody: 1D6 (Leica Microsystems); Positive: staining intensity of 2+ or 3+ in at least 30% or more tumor cells on a given tumor section
TS	IHC	Antibody: TS106 (Dako); Positive: staining intensity of ≥1+ in at least 10% or more tumor cells on a given slide
TUBB3	IHC	Antibody: PRB-435P (BioLegend); Positive: staining intensity of 2+ or 3+ in at least 30% or more tumor cells on a given tumor section

*See also **Methods**

**Gatalica Z, Xiu J, Swensen J, et al: Comprehensive analysis of cancers of unknown primary for the biomarkers of response to immune checkpoint blockade therapy. Eur J Cancer 94:179-186, 2018

Abbreviations: ERCC1=excision repair complementation group 1, MGMT= O-6-methyl guanine DNA methyltransferase, MSI =microsatellite instability, NGS = next generation sequencing; RRM1=ribonucleotide reductase regulatory subunit M1, TMB = tumor mutational burden; TOP2A=topoisomerase 2, TOPO1=topoisomerase 1, TS=thymidylate synthetase, TUBB3=tubulin beta 3

Supplemental Table 3: MSI, TMB, PD-L1 by Cancer Type (bolded percentages are indicative of response to cognate therapy)*

	MSI-H**			TMB-H**			PD-L1**		
Type of Cancer	**N**	**Positive**	**Negative**	**N**	**Positive**	**Negative**	**N**	**Positive**	**Negative**
All	28034	**3.3%**	96.7%	27847	**8.4%**	91.6%	22114	**11.0%**	89.0%
Adrenal	40	**0.0%**	100.0%	40	**2.5%**	97.5%	39	**12.8%**	87.2%
Anal	101	**0.0%**	100.0%	100	**6.0%**	94.0%	99	**40.4%**	59.6%
Bladder	298	**0.7%**	99.3%	297	**17.8%**	82.2%	294	**25.2%**	74.8%
Bone	77	**1.3%**	98.7%	77	**1.3%**	98.7%	74	**0.0%**	100.0%
Breast	2427	**0.7%**	99.3%	2397	**3.6%**	96.4%	2293	**5.8%**	94.2%
CNS tumors	171	**0.0%**	100.0%	171	**1.2%**	98.8%	171	**8.8%**	91.2%
Colorectal cancer	3848	**6.3%**	93.7%	3831	**7.3%**	92.7%	3615	**3.5%**	96.5%
Cholangiocarcinoma	434	**1.8%**	98.2%	426	**3.5%**	96.5%	400	**9.0%**	91.0%
Epithelial Ovarian	3855	**1.3%**	98.7%	3818	**1.7%**	98.3%	3674	**6.7%**	93.3%
Esophageal	532	**1.3%**	98.7%	527	**2.5%**	97.5%	497	**12.5%**	87.5%
Extrahepatic cholangiocarcinoma	68	**1.5%**	98.5%	67	**1.5%**	98.5%	65	**3.1%**	96.9%
Female genital tract malignancy	2874	**14.3%**	85.7%	2854	**11.6%**	88.4%	2777	**10.2%**	89.8%
GBM	948	**0.6%**	99.4%	943	**3.0%**	97.0%	910	**15.2%**	84.8%
GIST	154	**0.0%**	100.0%	154	**0.0%**	100.0%	179	**19.0%**	81.0%
Gastric	495	**7.7%**	92.3%	492	**7.5%**	92.5%	459	**10.2%**	89.8%
HCC	179	**1.7%**	98.3%	177	**2.8%**	97.2%	174	**7.5%**	92.5%
Head and Neck	526	**0.6%**	99.4%	523	**6.5%**	93.5%	494	**36.6%**	63.4%
Kidney	353	**0.6%**	99.4%	349	**8.6%**	91.4%	343	**19.8%**	80.2%
Low Grade Glioma	193	**0.5%**	99.5%	193	**1.0%**	99.0%	176	**2.8%**	97.2%
Merkel cell	12	**0.0%**	100.0%	12	**41.7%**	58.3%	12	**0.0%**	100.0%

MFST	9	**0.0%**	100.0%	9	**0.0%**	100.0%	8	**12.5%**	87.5%
Male Genital Tract	56	**0.0%**	100.0%	56	**5.4%**	94.6%	55	**12.7%**	87.3%
Melanoma	812	**0.0%**	100.0%	811	**37.5%**	62.5%	800	**23.2%**	76.8%
Mesothelioma	99	**0.0%**	100.0%	99	**0.0%**	100.0%	96	**24.0%**	76.0%
NET	463	**2.2%**	97.8%	462	**5.0%**	95.0%	437	**4.8%**	95.2%
NSCLC	4754	**0.7%**	99.3%	4752	**15.9%**	84.1%	822	**30.2%**	69.8%
Non-melanoma skin	143	**2.1%**	97.9%	143	**66.4%**	33.6%	141	**34.8%**	65.2%
Cancer with unknown primary	788	**3.0%**	97.0%	779	**11.9%**	88.1%	761	**22.6%**	77.4%
Other	11	**0.0%**	100.0%	11	**0.0%**	100.0%	11	**9.1%**	90.9%
Pancreatic	1261	**1.4%**	98.6%	1248	**1.4%**	98.6%	1174	**10.8%**	89.2%
Peritoneal	17	**0.0%**	100.0%	17	**11.8%**	88.2%	17	**23.5%**	76.5%
Prostate	463	**3.7%**	96.3%	456	**3.7%**	96.3%	443	**3.4%**	96.6%
Retroperitoneal sarcoma	115	**0.0%**	100.0%	113	**0.0%**	100.0%	107	**11.2%**	88.8%
SCLC	220	**0.5%**	99.5%	220	**6.4%**	93.6%	191	**4.7%**	95.3%
Soft tissue sarcoma	613	**1.0%**	99.0%	607	**4.1%**	95.9%	573	**13.4%**	86.6%
Small intestinal	218	**10.1%**	89.9%	214	**7.9%**	92.1%	205	**12.2%**	87.8%
Thymic	52	**3.8%**	96.2%	52	**1.9%**	98.1%	49	**73.5%**	26.5%
Thyroid	108	**1.9%**	98.1%	108	**0.1%**	99.9%	99	**33.3%**	66.7%
Uveal melanoma	112	**0.9%**	99.1%	111	**2.7%**	97.3%	105	**4.8%**	95.2%
Non-Epithelial Ovarian	135	**0.7%**	99.3%	132	**0.8%**	99.2%	127	**3.1%**	96.9%

*Percentage of patients positive for the marker

** PD-L1 positivity as well as MSI-H and TMB-H is associated with sensitivity to checkpoint inhibitors (therefore, for all cancers, 3.3%, 8.4 % and 11.0% of patients, respectively, would be expected to be responsive.
Abbreviations: CNS=central nervous system; GIST=gastrointestinal stromal tumor; GBM=glioblastoma multiforme; HCC=hepatocellular carcinoma; MFST=malignant solitary fibrous tumor of the pleura; MSI =microsatellite instability, NET=neuroendocrine tumor; NSCLC=non-small cell lung cancer; PD-L1=programmed death-ligand 1, SCLC=small cell lung cancer; TMB = tumor mutational burden

Supplemental Table 4: Protein Expression by Cancer Type (bolded percentages are indicative of response to cognate therapy)*

	ERCC1**			MGMT**			RRM1**			TOP2A**			TOPO1**			TS**			TUBB3**		
Type of Cancer	**N**	**+**	**-**	**N**	**+**	**-**	**N**	**+**	**-**	**N**	**+**	**-**	**N**	**+**	**-**	**N**	**+**	**-**	**N**	**+**	**-**
All	21802	21%	**79%**	5200	55%	**45%**	17205	20%	**80%**	12907	**76%**	24%	22211	**59%**	41%	20491	34%	**66%**	19863	57%	**43%**
Adrenal	39	41%	**59%**	9	44%	**56%**	33	30%	**70%**	39	**69%**	31%	14	**43%**	57%	39	67%	**33%**	39	39%	**62%**
Anal	97	32%	**68%**	12	58%	**42%**	77	47%	**53%**	99	**97%**	3%	32	**56%**	44%	99	64%	**36%**	99	38%	**62%**
Bladder	290	20%	**80%**	43	54%	**47%**	266	26%	**74%**	293	**93%**	7%	85	**47%**	53%	292	46%	**54%**	292	51%	**49%**
Bone	76	40%	**61%**	65	75%	**25%**	69	20%	**80%**	74	**55%**	45%	71	**58%**	42%	42	48%	**52%**	73	47%	**53%**
Breast	2300	28%	**72%**	336	73%	**27%**	1058	29%	**71%**	0	**.**	.	1911	**69%**	31%	1957	33%	**67%**	0	.	**.**
CNS tumors	169	25%	**75%**	27	70%	**30%**	111	14%	**86%**	167	**37%**	64%	77	**38%**	62%	167	34%	**66%**	168	52%	**48%**
Colorectal cancer	3506	18%	**82%**	1133	60%	**41%**	296	37%	**63%**	532	**92%**	9%	3502	**59%**	41%	3664	24%	**76%**	529	45%	**55%**
Cholangio-carcinoma	392	27%	**73%**	68	65%	**35%**	379	8%	**92%**	84	**64%**	36%	390	**67%**	33%	400	29%	**72%**	397	58%	**42%**
Epithelial Ovarian	3664	12%	**88%**	200	79%	**22%**	3683	16%	**84%**	3751	**77%**	23%	3629	**52%**	48%	632	51%	**49%**	3751	50%	**50%**
Esophageal	506	36%	**64%**	46	54%	**46%**	30	33%	**67%**	513	**96%**	4%	500	**79%**	21%	513	43%	**57%**	513	48%	**52%**
Extrahepatic cholangiocarcinoma	65	17%	**83%**	8	100%	**0%**	62	7%	**94%**	10	**70%**	30%	60	**52%**	48%	65	25%	**75%**	66	49%	**52%**
Female genital tract malignancy	2693	13%	**87%**	156	44%	**56%**	2767	31%	**69%**	2817	**87%**	13%	2641	**47%**	53%	2803	53%	**47%**	2820	57%	**44%**
GBM	915	22%	**79%**	44	25%	**75%**	90	23%	**77%**	139	**63%**	37%	899	**58%**	42%	405	52%	**48%**	400	91%	**10%**
GIST	80	48%	**53%**	41	73%	**27%**	26	12%	**89%**	41	**34%**	66%	43	**37%**	63%	44	43%	**57%**	41	44%	**56%**
Gastric	473	28%	**72%**	74	66%	**34%**	54	26%	**74%**	480	**81%**	19%	466	**68%**	32%	482	36%	**64%**	483	32%	**69%**
HCC	169	24%	**76%**	28	61%	**39%**	126	6%	**94%**	168	**51%**	49%	66	**49%**	52%	171	26%	**74%**	170	13%	**87%**
Head and Neck	494	36%	**64%**	62	68%	**32%**	468	33%	**67%**	200	**68%**	32%	88	**56%**	44%	503	40%	**60%**	504	44%	**56%**
Kidney	335	24%	**76%**	61	54%	**46%**	317	4%	**96%**	347	**37%**	63%	127	**43%**	57%	134	21%	**79%**	345	50%	**50%**
Low Grade Glioma	183	13%	**87%**	6	17%	**83%**	9	0%	**100%**	18	**0%**	100%	181	**37%**	64%	76	5%	**95%**	76	76%	**24%**
MC	12	8%	**92%**	2	50%	**50%**	6	83%	**17%**	12	**100%**	0%	10	**80%**	20%	7	71%	**29%**	6	100%	**0%**
MFST	8	13%	**88%**	8	88%	**13%**	7	14%	**86%**	8	**50%**	50%	8	**38%**	63%	2	100%	**0%**	8	25%	**75%**
Male Genital Tract	53	19%	**81%**	8	50%	**50%**	40	35%	**65%**	54	**82%**	19%	20	**55%**	45%	54	44%	**56%**	54	52%	**48%**

Melanoma	794	26%	**74%**	798	38%	**62%**	31	13%	**87%**	84	**71%**	29%	81	**44%**	56%	233	68%	**32%**	803	69%	**31%**
Mesothelioma	94	38%	**62%**	19	58%	**42%**	79	15%	**85%**	95	**39%**	61%	34	**65%**	35%	95	34%	**66%**	96	67%	**33%**
NET	435	12%	**88%**	344	45%	**55%**	79	25%	**75%**	441	**52%**	48%	158	**53%**	48%	445	27%	**74%**	182	76%	**24%**
NSCLC	0	.	**.**	327	64%	**36%**	4074	15%	**85%**	368	**79%**	22%	4102	**66%**	34%	4233	25%	**75%**	4236	71%	**30%**
Non-melanoma skin	139	34%	**66%**	14	36%	**64%**	105	34%	**66%**	141	**85%**	15%	46	**48%**	52%	141	42%	**58%**	141	71%	**29%**
Cancer with unknown primary	751	28%	**72%**	85	60%	**40%**	726	23%	**78%**	256	**78%**	22%	726	**70%**	30%	764	33%	**67%**	759	62%	**38%**
Other	11	27%	**73%**	4	50%	**50%**	8	0%	**100%**	11	**36%**	64%	5	**40%**	60%	10	40%	**60%**	11	18%	**82%**
Pancreatic	1161	26%	**75%**	154	81%	**19%**	1142	10%	**90%**	184	**65%**	35%	1141	**58%**	42%	1189	18%	**82%**	1180	60%	**41%**
Peritoneal	17	0%	**100%**	1	0%	**100%**	16	31%	**69%**	17	**77%**	24%	14	**36%**	64%	6	67%	**33%**	17	77%	**24%**
Prostate	442	18%	**82%**	34	53%	**47%**	25	28%	**72%**	150	**47%**	53%	36	**69%**	31%	40	23%	**78%**	446	26%	**74%**
Retroperitoneal sarcoma	98	36%	**64%**	97	46%	**54%**	99	11%	**89%**	99	**67%**	33%	95	**45%**	55%	29	41%	**59%**	99	32%	**68%**
SCLC	201	10%	**90%**	171	25%	**75%**	20	60%	**40%**	206	**97%**	3%	62	**69%**	31%	210	50%	**51%**	62	87%	**13%**
Soft tissue sarcoma	574	30%	**70%**	558	54%	**46%**	553	13%	**87%**	586	**64%**	36%	570	**51%**	49%	235	50%	**50%**	584	53%	**47%**
Small intestinal	200	18%	**83%**	35	66%	**34%**	88	16%	**84%**	125	**80%**	20%	141	**52%**	48%	206	37%	**63%**	128	45%	**55%**
Thymic	49	16%	**84%**	11	82%	**18%**	42	21%	**79%**	49	**84%**	16%	18	**56%**	44%	49	49%	**51%**	49	20%	**80%**
Thyroid	99	23%	**77%**	13	62%	**39%**	14	14%	**86%**	99	**42%**	58%	16	**31%**	69%	18	17%	**83%**	17	88%	**12%**
Uveal melanoma	90	46%	**54%**	91	52%	**48%**	1	0%	**100%**	21	**33%**	67%	21	**48%**	52%	16	38%	**63%**	91	40%	**60%**
Non-Epithelial Ovarian	128	14%	**86%**	7	43%	**57%**	129	21%	**79%**	129	**42%**	58%	125	**54%**	46%	21	71%	**29%**	128	32%	**68%**

*Percentage of patients positive for the protein marker

** ERCC1 negativity is associated with platinum response (therefore, for all cancers, 79% of patients would be expected to be responsive) (1,2); MGMT negativity which is associated with response to dacarbazine(3) and temozolomide (4,5) (therefore, for all cancers, 45% of patients would be expected to be responsive); RRM1 negativity is associated with gemcitabine response (therefore, for all cancers, 80% of patients would be expected to be responsive) (6); TOPO2A positivity which is associated with doxorubicin response (therefore, for all cancers, 76% of patients would be expected to be responsive) (7); TOPO1 positivity is associated with irinotecan or topotecan response (therefore, for all cancers, 59% of patients would be expected to be responsive) (8) TS negativity is associated with response to fluorouracil/pemetrexed/capecitabine (therefore, for all cancers, 66% of patients would be expected to be

responsive) (9-12); TUBB3 positivity is associated with taxane resistance (therefore, for all cancers, 43% of patients would be expected to be responsive) (13-15)

Abbreviations: CNS=central nervous system; ERCC1=excision repair complementation group 1, GIST=gastrointestinal stromal tumor; GBM=glioblastoma multiforme; HCC = hepatocellular carcinoma; MFST=malignant solitary fibrous tumor of the pleura; MGMT= O-6-methyl guanine DNA methyltransferase, NET=neuroendocrine tumor; NSCLC=non-small cell lung cancer; RRM1=ribonucleotide reductase regulatory subunit M1; SCLC = small cell lung cancer; TOP2A=topoisomerase 2; TOPO1=topoisomerase 1; TS=thymidylate synthetase; TUBB3=tubulin beta 3

<u>Supplemental Table 5</u>: Relationship between MSI-H and protein markers*

Tumor type	Odds Ratio (95% CI)	p-value	N	Comment
MSI-H and TS				
Colorectal cancer	13.86 (10.05 – 19.13)	<0.001	3,665	No for benefit of combination of immunotherapy and fluorouracil/pemetrexed/capecitabine (TS negativity is associated with response to fluorouracil/pemetrexed/capecitabine (9-12). However, data shows that TS positivity was correlated with TMB-H.)
Cholangiocarcinoma	6.51 (1.25 – 34.07)	0.022	400	
Epithelial ovarian Cancer	Infinity (>1.50)**	0.031	632	
Female Genital Tract Malignancy	1.74 (1.40 – 2.17)	<0.001	2,803	
Gastric cancer	3.92 (1.91-8.06)	<0.001	483	
Neuroendocrine tumor	4.33 (1.20-15.61)	0.025	445	
Cancer with unknown primary	10.36 (3.48-30.78)	<0.001	764	
Pancreatic cancer	6.26 (2.30-16.99)	0.001	1,189	
Small intestine cancer	4.56 (1.67-12.43)	0.0027	206	
MSI-H and TOP2A				
Epithelial ovarian	6.46 (1.56 – 26.73)	0.002	3,751	Yes for benefit of combination of immunotherapy and doxorubicin (TOPO1 positivity, which is associated with doxorubicin response (7), was correlated with MSI-H.)
Female Genital Tract Malignancy	1.82 (1.25 -2.64)	0.001	2,817	
Gastric	4.20 (0.99 – 17.83)	0.043	480	
Neuroendocrine tumor	Infinity (>2.40)**	0.004	441	

*Fisher's exact tests were performed for TS and TOP2A since tumor types could not be combined (only significant results are presented in table); if odds ratio of biomarker is less than 1 and p-value is significant, then biomarker negativity is associated with MSI-H

**Due to a zero cell, estimated odds ratio is infinite and the 95% confidence interval is one-sided

Abbreviations: CI=confidence interval, MSI=microsatellite instability, TS=thymidylate synthetase; TOP2A=topoisomerase 2

Supplemental Table 6: Relationship between TMB-H and protein markers*

	Odds Ratio (95% CI)	p-value	N	Comment
TMB-H and RRM1 protein expression				
Small intestinal cancer	14.40 (2.33-89.03)	0.005	88	No for benefit of combination of immunotherapy and gemcitabine. (RRM1 negativity is associated with gemcitabine response (6). However, data shows that RRM1 positivity was correlated with TMB-H.)
Pancreatic cancer	5.25 (1.90-14.49)	0.004	1,133	
Cancer with unknown primary	1.93 (1.19-3.12)	0.010	717	
Non-small cell lung cancer	1.34 (1.07-1.67)	0.012	4,072	
Female genital tract malignancy	3.50 (2.76-4.44)	<0.001	2,755	
Epithelial ovarian cancer	3.77 (2.28-6.22)	<0.001	3,664	
Breast cancer	2.14 (1.03-4.45)	0.043	1,055	
Bladder cancer	2.26 (1.18-4.32)	0.019	265	
Non-melanoma skin cancer	0.38 (0.16-0.88)	0.031	105	Yes for benefit of combination of immunotherapy and gemcitabine. (RRM1 negativity is associated with gemcitabine response (6) and data shows that RRM1 negativity was correlated with TMB-H.)
TMB-H and TS protein expression				
Small Intestinal Cancer	6.30 (1.97-20.10)	0.001	205	No for benefit of combination of immunotherapy and fluorouracil/pemetrexed/capecitabine (TS negativity is associated with response to fluorouracil/pemetrexed/capecitabine (9-12). However, data shows that TS positivity was correlated with TMB-H.)
Pancreatic cancer	4.81 (1.89-12.27)	0.002	1,180	
Cancer with unknown primary	2.08 (1.34-3.24)	0.001	755	
Non-small cell lung cancer	1.63 (1.36-1.94)	<0.001	4,231	
Gastric cancer	4.47 (2.14-9.33)	<0.001	481	
Female Genital Tract Malignancy	1.68 (1.32-2.13)	<0.001	2,791	

Epithelial ovarian cancer	Inf (>1.50)**	0.031	633	
Cholangiocarcinoma	3.53 (1.20-10.42)	0.029	397	
Colorectal cancer	10.57 (7.96-14.04)	<0.001	3,652	
Breast cancer	0.53 (0.30-0.95)	0.029	1,940	Yes for benefit of combination of immunotherapy and fluorouracil/pemetrexed/capecitabine (TS negativity is associated with response to fluorouracil/pemetrexed/capecitabine (9-12). Data shows that TS negativity was correlated with TMB-H.)
Merkel cell	0 (<0.97)**	0.048	7	
TMB-H and TUBB3 protein expression				
Non-small cell lung cancer	1.22 (1.01-1.47)	0.035	4,234	No for benefit of combination of immunotherapy and taxanes (TUBB3 positivity is associated with taxane resistance (13-15). Data shows that TUBB3 positivity was correlated with TMB-H.)
Melanoma	1.80 (1.30-2.48)	<0.001	802	
Female genital tract malignancy	0.78 (0.62-0.98)	0.039	2,808	Yes for benefit of combination of immunotherapy and taxanes (TUBB3 positivity is associated with taxane resistance (13-15). Data shows that TUBB3 negativity was correlated with TMB-H.)
Colorectal cancer	0.43 (0.20-0.95)	0.046	529	

*Fisher's exact tests were performed for RRM1, TS, and TUBB3 since tumor types could not be combined (only significant results are presented in table); if odds ratio of biomarker is greater than 1 and p-value is significant, then biomarker positivity is associated with TMB-H; if odds ratio of biomarker is less than 1 and p-value is significant, then biomarker negativity is associated with TMB-H

**Due to a zero cell, estimated odds ratio is zero and the 95% confidence interval is one-sided

Abbreviations: CI=confidence interval, RRM1=ribonucleotide reductase regulatory subunit M1, TMB=tumor mutational burden, TS=thymidylate synthetase; TUBB3=tubulin beta 3

Supplemental Table 7: Relationship between PD-L1 positivity and protein markers*

	Odds Ratio (95% CI)	p-value	N	Comment
PD-L1 positive and ERCC1 protein expression				
Glioblastoma multiforme	1.61 (1.06 - 2.42)	0.030	900	No for benefit of combination of immunotherapy and platinum (ERCC1 negativity, which is associated with platinum response (1,2), however ERCC1 positivity was correlated with PD-L1 positivity.)
Female genital tract malignancy	1.81 (1.31-2.49)	<0.001	2,642	
Esophageal cancer	2.07 (1.21-3.55)	0.010	486	
Gastrointestinal stromal tumor	0.12 (0.014 - 0.99)	0.032	77	Yes for benefit of combination of immunotherapy and platinum (ERCC1 negativity, which is associated with platinum response (1,2), was correlated with PD-L1 positivity.)
PD-L1 positive and RRM1 protein expression				
Non-epithelial ovarian cancer	13.64 (1.35-137.35)	0.025	126	No benefit of combination of immunotherapy and gemcitabine. (RRM1 negativity is associated with gemcitabine response (6); however data shows that RRM1 positivity was correlated with TMB-H.)
Soft tissue sarcoma	2.34 (1.28-4.26)	0.010	537	
Pancreatic cancer	1.84 (1.06 - 3.17)	0.032	1,114	
Female genital tract malignancy	1.38 (1.07 -1.79)	0.016	2,710	
Cholangiocarcinoma	5.06 (2.03 - 12.63)	0.002	372	
PD-L1 positive and TOP2A protein expression				
Non-epithelial ovarian cancer	Inf (>1.28)**	0.029	126	Yes for benefit of combination of immunotherapy and doxorubicin
Soft tissue sarcoma	3.19 (1.71-5.96)	<0.001	570	

Cancer with unknown primary	17.76 (2.39-131.77)	<0.001	253	(TOPO2A positivity, which is associated with doxorubicin, epirubicin, and etoposide response (7,16), was correlated with PD-L1 positivity.)
Non-melanoma skin	3.78 (1.05-13.55)	0.045	140	
Non-small cell lung cancer	8.55 (1.99-36.73)	<0.001	214	
Neuroendocrine tumor	5.53 (1.60 -19.16)	0.003	427	
Mesothelioma	3.65 (1.34-9.94)	0.013	93	
Kidney cancer	3.94 (2.26-6.87)	<0.001	341	
Head and Neck	3.61 (1.33 - 9.80)	0.010	191	
Female genital tract malignancy	2.65 (1.58 - 4.45)	<0.001	2,760	
PD-L1 positive and TS protein expression				
Small intestinal cancer	3.47 (1.45-8.30)	0.007	205	No for benefit of combination of immunotherapy and fluorouracil/pemetrexed/capecitabine (TS negativity is associated with response to fluorouracil/pemetrexed/capecitabine (9-12). However, data shows that TS positivity was correlated with TMB-H.)
Pancreatic cancer	2.40 (1.58-3.62)	<0.001	1,163	
Cancer with unknown primary	2.08 (1.46-2.97)	<0.001	743	
Non-small cell lung cancer	1.43 (1.03-2.00)	0.036	769	
Neuroendocrine tumor	2.90 (1.17-7.15)	0.035	429	
Melanoma	3.37 (1.35-8.43)	0.006	224	
Kidney cancer	3.79 (1.39 - 10.32)	0.015	130	
Head and neck	2.46 (1.68 - 3.61)	<0.001	478	
Gastric cancer	4.48 (2.34-8.55)	<0.001	456	
Female genital tract malignancy	1.32 (1.03-1.70)	0.031	2,747	
Epithelial ovarian cancer	2.44 (1.25-4.77)	0.008	617	
Cholangiocarcinoma	2.81 (1.40-5.62)	0.006	394	
Colorectal cancer	3.50 (2.44-5.03)	<0.001	3,566	
Breast cancer	2.09 (1.44-3.04)	<0.001	1,933	

Bladder cancer	2.65 (1.53-4.59)	<0.001	290	
PD-L1 positive and TUBB3 protein expression				
Soft tissue sarcoma	1.79 (1.08-2.94)	0.027	568	No for benefit of combination of immunotherapy and taxanes (TUBB3 positivity is associated with taxane resistance (13-15). However, data shows that TUBB3 positivity was correlated with TMB-H.)
Cancer with unknown primary	1.55 (1.07-2.24)	0.019	738	
Non-small cell lung cancer	1.97 (1.36-2.84)	<0.001	763	
Kidney cancer	2.20 (1.26-3.84)	0.006	340	
Head and neck	1.52 (1.04-2.21)	0.035	479	
Gastric cancer	2.86 (1.55-5.27)	0.001	457	
Esophageal cancer	2.23 (1.28-3.89)	0.004	490	
Bladder cancer	2.50 (1.43-4.36)	0.001	291	

*Fisher's exact tests were performed for RRM1, TS, and TUBB3 since tumor types could not be combined (only significant results are presented in table); if odds ratio of biomarker is greater than 1 and p-value is significant, then biomarker positivity is associated with TMB-H; if odds ratio of biomarker is less than 1 and p-value is significant, then biomarker negativity is associated with TMB-H

**Due to a zero cell, estimated odds ratio is infinite and the 95% confidence interval is one-sided

Abbreviations: CI=confidence interval, ERCC1= excision repair complementation group 1, RRM1=ribonucleotide reductase regulatory subunit M1, TMB=tumor mutational burden, TS=thymidylate synthetase; TUBB3=tubulin beta 3