Real-world evidence provides clinical insights on tissue-agnostic approvals of therapies

[1]George W. Sledge Jr., [2]Takayuki Yoshino, [1]Joanne Xiu, [1]Anthony Helmstetter, [1]Sergey Klimov, [1]Brady Gilg, [1]Matthew James Oberley, [1]Milan Radovich, [1]Jim Abraham, [1]David Spetzler

[1]Caris Life Sciences, Phoenix, AZ; 2National Cancer Center Hospital East, Kashiwa, Japan

Background

- Many tissue-agnostic (TA) approvals were based on clinical trials with limited patient numbers without covering all tissue types (TT), raising the question of whether these indications were truly tissue agnostic.
- Real world evidence (RWE) offers an opportunity to investigate TTs not included in clinical trials/studies to answer this question.
- Herein we investigate the seven TA approvals to date in a large real-world database and report clinical outcomes.

Tissue-Agnostic FDA Approvals		
Therapy	**Biomarker**	**FDA Approval Date**
Pembrolizumab	MSI-H/dMMR	May-17
Pembrolizumab	TMB-H	Jun-20
Larotrectinib	Ntrk Fusion	Nov-18
Entrectinib	Ntrk Fusion	Aug-19
Dostarlimab-gxly	dMMR	Feb-22
Dabrafenib + trametinib	BRAF V600E Mutation	Jun-22
Selpercatinib	RET gene fusion	Sep-22

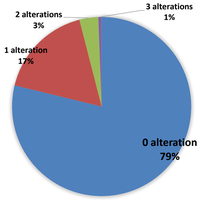
Methods

- A total of 186,581 tumors from over 47 tissue types (TTs) tested with comprehensive molecular profiling including NextGen sequencing of DNA and RNA were investigated for TA alterations (Caris Life Sciences, Phoenix, AZ)
  - TMB-High (≥10 mutations/MB)
  - MSI-H/MMRd
  - BRAF V600E mutations
  - NTRK1/2/3 fusions
  - RET fusions
- Time-on-treatment (TOT) from RWE was obtained from insurance claims and calculated from treatment start to finish.
- Kaplan-Meier estimates were calculated for molecularly defined patient cohorts. Significance was determined as p values of < 0.05.

Results

1. How common are TA indications across cancer types?

- Shown in table are cancer types with >=100 tumors comprehensively profiled for biomarker alterations
- 21% of tumors carried at least one TA indication, subtracting tissue-specific indications, 8.5% of tumors have TA indications.
- Cancer types-specific approvals are highlighted in **green**; cancer type and biomarker-specific approval in **orange**
- Pie chart shows prevalence of cases carrying 0-3 alterations per tumor



	Pembrolizumab		Dabrafenib +Trametinib	Entrectinib Larotrectinib	Selpercatinib	Any alteration (N/Total) %
Cancer Type	**TMB-High**	**MSI-H/MMRd**	**BRAF V600E**	**NTRK1/2/3 Fusions**	**RET Fusions**	
Basal Cell Skin Cancer	100 (86.2%)	2 (1.72%)	0	0	0	(100/116) 86.2%
Squamous Cell Skin Cancer	562 (81.0%)	36 (5.19%)	1 (0.14%)	0	0	(565/693) 81.5%
Melanoma*	2971 (56.2%)	19 (0.35%)	1131 (21.4%)	6 (0.11%)	2 (0.03%)	(3736/5282) 70.7%
Thyroid Carcinoma, others	17 (1.09%)	7 (0.44%)	676 (43.3%)	33 (2.11%)	$66 (4.23%)	(790/1559) 50.7%
Anaplastic Thy. Carcinoma	11 (6.96%)	4 (2.53%)	62 (39.2%)	2 (1.26%)	2 (1.26%)	(76/158) 48.1%
NSCLC	14847 (41.8%)	255 (0.71%)	474 (1.33%)	&24 (0.06%)	250 (0.70%)	(15507/35462) 43.7%
Bladder cancer	2228 (39.4%)	113 (2.00%)	15 (0.26%)	3 (0.05%)	0	(2241/5649) 39.7%
Merkel Cell Carcinoma	80 (39.6%)	1 (0.49%)	0	0	0	(80/202) 39.6%
SCLC	417 (30.6%)	12 (0.88%)	1 (0.07%)	0	1 (0.07%)	(422/1360) 31%
Uterine Neoplasms	2848 (24.7%)	2472 (21.4%)	8 (0.06%)	7 (0.06%)	1 (0.00%)	(2938/11512) 25.5%
CUP	1248 (21.3%)	196 (3.35%)	126 (2.15%)	14 (0.23%)	10 (0.17%)	(1379/5842) 23.6%
Non-urothelial Bladder	73 (22.0%)	7 (2.11%)	2 (0.60%)	0	0	(74/331) 22.4%
Cervical Cancer	536 (18.7%)	82 (2.87%)	5 (0.17%)	2 (0.07%)	0	(546/2854) 19.1%
Head and Neck Cancers	674 (17.5%)	38 (0.98%)	7 (0.18%)	0	0	(684/3839) 17.8%
Salivary Gland Tumors	141 (14.5%)	14 (1.44%)	6 (0.61%)	19 (1.96%)	4 (0.41%)	(171/969) 17.6%
Small Intestinal Ca.	207 (16.2%)	132 (10.3%)	17 (1.33%)	1 (0.07%)	1 (0.07%)	(225/1276) 17.6%
Penile Cancer	27 (16.7%)	3 (1.86%)	0	0	0	(27/161) 16.8%
CRC	2970 (11.9%)	1998 (8.03%)	2090 (8.40%)	53 (0.21%)	55 (0.22%)	(4103/24871) 16.5%
Gastric Cancer	459 (14.4%)	337 (10.6%)	11 (0.34%)	1 (0.03%)	0	(477/3173) 15%
Anal Carcinoma	102 (14.1%)	10 (1.39%)	0	0	0	(102/719) 14.2%
Female Genital Tract Ca.	239 (13.0%)	145 (7.90%)	1 (0.05%)	5 (0.27%)	0	(254/1834) 13.8%
Vulvar Cancer	91 (13.2%)	11 (1.60%)	0	0	0	(93/686) 13.6%
Neuroendocrine tumors	256 (8.75%)	49 (1.67%)	44 (1.50%)	8 (0.27%)	2 (0.06%)	(309/2924) 10.6%
Esophageal and GEJ	522 (9.34%)	190 (3.40%)	6 (0.10%)	3 (0.05%)	0	(540/5586) 9.7%
Breast Carcinoma**	1365 (8.87%)	152 (0.98%)	45 (0.29%)	27 (0.17%)	5 (0.03%)	(1460/15388) 9.5%
Others	91 (7.95%)	11 (0.96%)	10 (0.87%)	3 (0.26%)	0	(107/1144) 9.4%
Soft Tissue Tumors	229 (7.61%)	37 (1.23%)	11 (0.36%)	11 (0.36%)	1 (0.03%)	(257/3008) 8.5%
Low Grade Glioma***	11 (1.43%)	3 (0.39%)	35 (4.57%)	12 (1.56%)	0	(59/765) 7.7%
Cholangiocarcinoma	245 (5.13%)	123 (2.57%)	74 (1.55%)	0	4 (0.08%)	(334/4770) 7%
High Grade Glioma	206 (3.61%)	79 (1.38%)	90 (1.57%)	38 (0.66%)	5 (0.08%)	(343/5704) 6%
Male Genital Tract Cancer	9 (4.61%)	1 (0.51%)	1 (0.51%)	0	0	(10/195) 5.1%
Prostate Ca.	329 (4.62%)	306 (4.30%)	0	0	0	(350/7106) 4.9%
Uveal Melanoma	9 (3.06%)	0 (0%)	5 (1.70%)	0	0	(14/294) 4.8%
Ovarian Cancer	446 (3.13%)	195 (1.37%)	129 (0.90%)	6 (0.04%)	2 (0.01%)	(609/14213) 4.3%
Thymic Carcinoma	7 (3.64%)	5 (2.60%)	0	0	0	(8/192) 4.2%
Peripheral Nervous Ca.	3 (2.34%)	1 (0.78%)	0	1 (0.78%)	0	(5/128) 3.9%
Liver HCC	30 (3.31%)	3 (0.33%)	1 (0.11%)	0	0	(33/906) 3.6%
Non Epithelial Ovarian	17 (3.17%)	0 (0%)	0	0	0	(17/535) 3.2%
Kidney Cancer	57 (2.23%)	23 (0.90%)	4 (0.15%)	0	0	(68/2549) 2.7%
Pancreatic Ca,	162 (1.88%)	104 (1.21%)	23 (0.26%)	8 (0.09%)	12 (0.13%)	(214/8579) 2.5%
Malig. Pleural Meso.	8 (2.14%)	0 (0%)	1 (0.26%)	0	0	(9/373) 2.4%
Peritoneal Sarcoma	7 (1.93%)	1 (0.27%)	0	1 (0.27%)	0	(8/362) 2.2%
Ependymoma	0 (0%)	0 (0%)	1 (0.72%)	1 (0.72%)	0	(2/138) 1.4%
GIST	4 (0.34%)	4 (0.34%)	6 (0.51%)	3 (0.25%)	0	(16/1159) 1.4%
Bone Cancer	1 (0.33%)	2 (0.67%)	0	0	0	(3/297) 1%
Meningioma	3 (0.44%)	1 (0.14%)	2 (0.29%)	0	0	(5/680) 0.7%
Liposarcoma	0	0	0	0	0	(0/335) 0%
Total#	**34940 (18.7%)**	**7190 (3.85%)**	**5138 (2.75%)**	**293 (0.15%)**	**423 (0.22%)**	**(39462/186581) 21.1%**

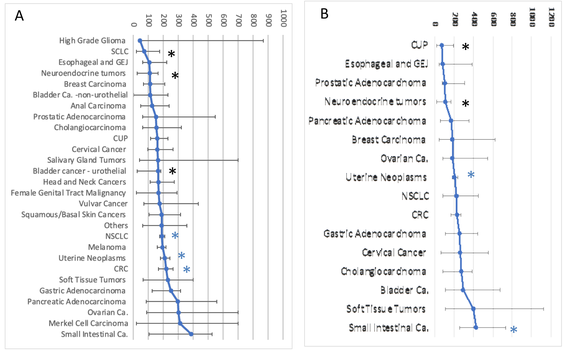
*: Dabrafenib+trametinib indicated in melanoma for V600E/K
**: Pembrolizumab indicated in TNBC tumors
***: Dabrafenib+trametinib indicated in pediatric low grade glioma

$: Selpercatinib indicated in RET-mutated medullary thyroid cancer
&: Entrectinib indicated in ROS1 fusion positive NSCLC
#: Total included additional tumors not shown on the table

Results

2. Are response durations tissue agnostic?

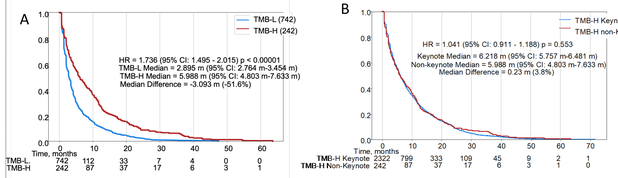
Substantial variability of TOT among TTs was observed among tumors treated with TA indications.
A. TOT of TMB-H tumors ; B. MSI-H/MMRd tumors treated with pembrolizumab(tumor types with black asterisks show significantly shorter TOT than those with blue asterisks)



	TMB-H N	TOT mo (CI%)	MSI-H/MMRd N	TOT mo (CI%)
NSCLC	1556	6.4 (5.8-7) *	30	7.5 (2.8-15.1)
UCEC	363	7 (6.1-8.2) *	399	6.9 (5.9-8) *
MEL	245	6.5 (5.4-7.2)	0	
CRC	237	7.3 (5.6-8.9) *	218	7.7 (5.6-9.1)
BLAC	210	5.5 (0.9-6.1) *	15	9.8 (3.5-22.4)
CUP	111	5.4 (3.9-7.7)	23	2.5 (0.7-6.4) *
CESC	80	5.4 (3.2-8.8)	15	8.8 (2.1-18.4)
STAD	54	8.4 (4.2-10.5)	51	8.6 (3.5-14.9)
SBA	21	12.9 (3.5-17.5)	18	14.3 (8.6-24.5) *
NEC	17	3.7 (0.9-5.5) *	8	3.7 (0.6-5.6) *
SCLC	12	2.4 (0.7-5.8) *	0	

3. Do initial TA indications extend beyond initial study populations?

A: A total of 242 TMB-H tumors of cancer types not included in KEYNOTE158 or Cristescu 2023 retrospective study were treated with pembrolizumab, and showed significantly improved TOT compared to the TMB-L counterpart
B: Similar pembrolizumab TOT was seen in TMB-H tumors on or off KEYNOTE158 trials (and Cristescu 2023)



Results

4. Can RWE extend TA indications to other drugs in the same class?

Pembrolizumab and Nivolumab in TMB-H tumors.

- Shown are Hazard Ratios of TOT in TMB-H vs. TMB-L tumors
- Bolded entries suggest significant findings

	Nivolumab			Pembrolizumab		
Cancer Type	**TMB-H N| TMB-L N**	**HR (CI%)**	**p value**	**TMB-H N| TMB-L N**	**HR (CI%)**	**p value**
Melanoma	**379|407**	**0.846 (0.735-0.973)**	**0.019**	212|174	0.61 (0.704-1.054)	0.146
Lung Non-small cell lung cancer NSCLC	**382|598**	**0.844(0.742-0.96)**	**0.01**	**1311| 2091**	**0.858 (0.8-0.919)**	**<0.0001**
Colorectal Adenocarcinoma	**69| 88**	**0.387 (0.278-0.539)**	**<0.00001**	**202|126**	**0.345 (0.272-0.439)**	**<0.00001**
Cancer of Unknown Primary	31|53	0.752 (0.476-1.189)	0.225	93|127	0.782 (0.597-1.025)	0.074
Lung Small Cell Cancer SCLC	**11|48**	**0.397 (0.228-0.692)**	**<0.001**	9|18	0.595 (0.256-1.38)	0.207
Head and Neck Cancers	26|136	0.816 (0.529-1.259)	0.357	**48| 338**	**0.734 (0.542-0.996)**	**0.048**
Bladder cancer - urothelial	10|46	0.659 (0.393-1.105)	0.113	**175| 293**	**0.819 (0.678-0.988)**	**0.038**
Non-Melanoma, Non-Merkel Skin Cancers	**12|5**	**0.104 (0.024-0.453)**	**0.001**	34|10	0.609 (0.297-1.25)	0.183
Uterine Neoplasms	2|25	0.713 (0.164-3.106	0.658	**318| 663**	**0.533 (0.463-0.614)**	**<0.00001**
All TMB-H tumors considered	1002|2421	**0.762 (0.708-0.820)**	**<0.00001**	**2785|5641**	**0.717 (0.685-0.751)**	**<0.00001**
MSS TMB tumors	784|2139	**0.782(0.720-0.849)**	**<0.00001**	**1997|5375**	**0.756 (0.718-0.796)**	**<0.00001**

Conclusions

- TA indications are common, with one patient in every five tested being a candidate for TA therapy; however, TA frequency varies tremendously across cancer types.
- Response durations (as measured by TOT) may not be tissue agnostic.
- Some TA approvals (e.g., TMB-H) extend beyond the initial study populations.
- RWE may extend TA indications to other drugs in the same class.

References

- Lemetry et al. Ann. Rev. Cancer Biol 2022 'Development of Tissue-Agnostic Treatments for Patients with Cancer'
- FDA, 2022 'Tissue Agnostic Drug Development in Oncology, Guide for Industry"
- Marabelle et al. Lancet Oncology 2020, Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study'
- Cristescu R, et al. J Immunother Cancer 2022 ' Tumor Mutational Burden Predicts the Efficacy of Pembrolizumab Monotherapy'

gsledge@carisls.com

ASCO Annual 2023, Abstract ID: 6589

ASCO Annual 2023, Chicago, IL