105P Pan-tumor survey of *ROS1* fusions detected by next-generation RNA sequencing

Shannon S. Zhang, MD[1], Misako Nagasaka, MD, PhD[1-3], Yasmine Baca, M.S.[4], Joanne Xiu, PHD[4], Jorge Nieva, MD[5], Ari Vanderwalde, MD, MPH[6], Qing Zhang, PhD[4], Jeffrey J. Swensen, PhD[4], David Spetzler, MS, PhD, MBA[4], W. Michael Korn, MD[4], Stephen V. Liu, MD[7], Sai-Hong Ignatius Ou, MD PhD[1,2]

1. University of California Irvine School of Medicine, Orange, CA, USA; 2. Chao Family Comprehensive Cancer Center, Orange, CA, USA; 3. Division of Neurology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan; 4. Caris Life Sciences, Phoenix, AZ, USA; 5. USC Norris Comprehensive Cancer Center, University of Southern California Keck School of Medicine, Los Angeles, CA, USA; 6. West Cancer Center and Research Institute, Germantown, TN, USA; 7. Georgetown Lombardi Comprehensive Cancer Center, Georgetown University School of Medicine, Washington DC, USA

Background

Two ROS1 tyrosine kinase inhibitors have been approved for *ROS1* fusion positive (*ROS1+*) non-small cell lung cancer (NSCLC). We performed a pan-tumor analysis of the incidence and characteristics of ROS1 fusions across all solid tumors.

Methods

A retrospective analysis was performed on *ROS1* positive solid malignancies identified by either targeted RNA sequencing (Archer prior to 2019) or whole transcriptome sequencing (post 2019) of clinical tumor samples through Caris Life Science (Phoenix, AZ). Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from either tissue collection to last contact or time on treatment (TOT) from start to finish of ICI. Comparison of survival was performed by Kaplan-Meier analysis.

Demographic

Table 1: Distribution of *ROS1* fusion positive tumors in the studied cohort.

** "Other" includes Pancreatic adenocarcinoma, cancer of unknown primary, cholangiocarcinoma, gastric adeno, colorectal adeno, soft tissue, bladder, melanoma, neuroendocrine, ovarian and thyroid.

	All	NSCLC	Glioblastoma	Breast	**Other
N(%)	259	204 (79%)	18 (7%)	7 (3%)	30 (11%)
Age median(range)	63 (18->89)	65 (27-89)	63 (41->89)	60 (40-77)	52.5(18-80)
Male	113 (44%)	86 (42%)	11 (61%)	0 (0%)	16 (53%)
Female	146 (56%)	118 (58%)	7(39%)	7 (100%)	14 (47%)
Sequencing methods					
Targeted RNA (Archer (prior 2019)	55 (21%)	49 (24%)	4 (22%)	1 (14%)	1 (3%)
WTS (post 2019)	204 (79%)	155 (76%)	14 (78%)	6 (86%)	29 (96%)
Mean junction read (SD)	54.7	64 (107.8)	32.2 (55.1)	6.7 (5.2)	25.6 (25.8)
TMB median	4	4	3	5	4

Results

Figure 1A: Fusion partners in all *ROS1+* solid tumors

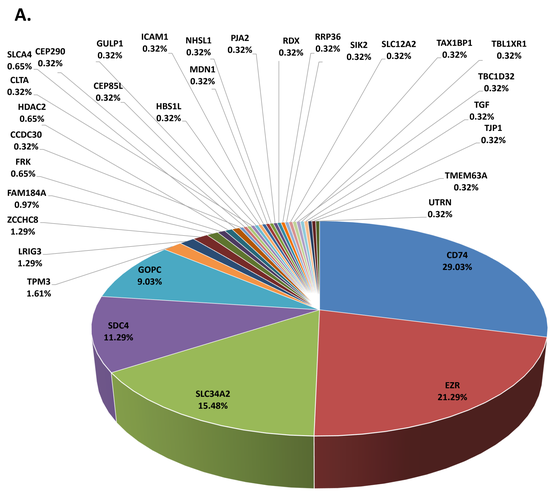


Figure 1B: Frequency of fusion breakpoint by ROS1 exons

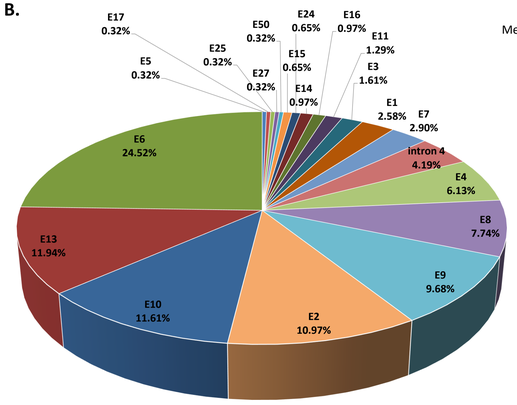


Figure 2: The distribution of PD-L1 (22c3) expression among all *ROS1+* tumors.

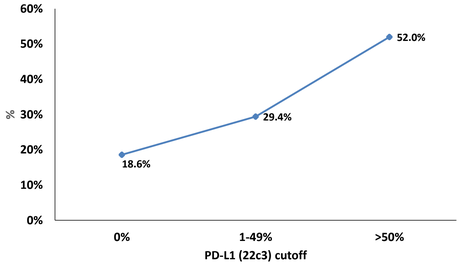
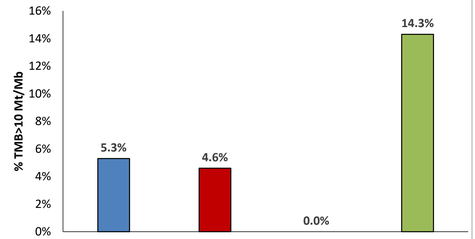


Figure 3: TMB for *ROS1+* tumors



	all ROS1+	NSCLC	Glioblastoma	Breast
Mean TMB (mt/Mb)	4.8	5.7	3.6	5.7
SD	2.9	3.4	1.5	3.6

Figure 4: Most prevalent co-alterations in *ROS1+* tumors by cancer type.

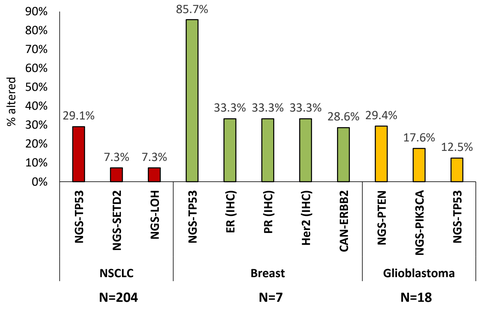


Figure 5: KM showing ROS1+ vs ROS1- glioblastoma.

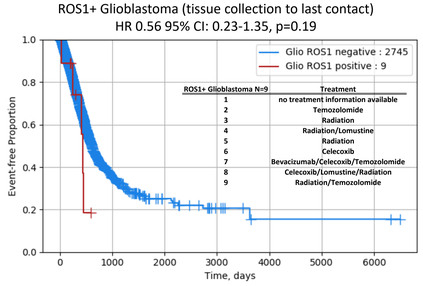
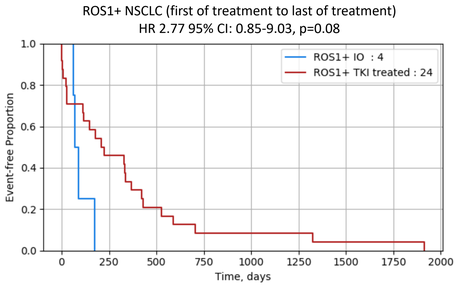


Figure 6: Time on Treatment for IO therapy vs TKI treated ROS1+ NSCLC.



Conclusions

- A total of 259 *ROS1+* tumor samples across 17 solid malignancies were identified from 175,350 tumors that underwent sequencing (88% from whole transcriptome; 12% from targeted RNA).
- *ROS1+* NSCLC constituted 78.8% of the *ROS1+* solid malignancies, followed by glioblastoma (6.9%) and breast cancer (2.7%).
- The frequency of *ROS1* fusion was approximately 0.47% among NSCLC, 0.29% for glioblastoma and 0.04% for breast cancer.
- The distribution of PD-L1 (22C3) expression among all *ROS1+* malignancies were 0% (18.6%), 1%-49% (29.4%), and ≥ 50% (52.0%).
- The mean tumor mutation burden for all *ROS1+* tumors was 4.8 mutations/Mb (SD 2.8), in NSCLC 5.7 (SD 3.4), glioblastoma 3.6 (SD 1.5) and breast 5.7 (SD 3.6).
- The most prevalent fusion partners in *ROS1+* tumors were CD74 (29.03%), EZR (21.29%) and SLC34A2 (15.48%). The most prevalent fusion breakpoint by ROS1 exons were E6 (24.52%), E13 (11.94%) and E10 (11.61%).
- The most common genetic co-alterations of *ROS1+* NSCLC were *TP53* (29.1%) and *SETD2* (7.3%) while in breast TP53 co-mutations were 85.7%. Most prevalent co-mutations in glioblastoma were PTEN (29.4%) PIK3CA (17.6%) and TP53 mutations (12.5%).
- Although the analysis was limited in sample size, *ROS1+* in glioblastoma may represent a potential poor prognostic factor (HR 0.56 95% CI: 0.23-1.35, p=0.19).
- *ROS1* fusions occurred at a low frequency among a diverse range of solid tumors.

ESMO September 2022