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Clinical utility of whole transcriptome sequencing for fusion detection in advanced solid tumors: SCRUM-Japan MONSTAR-SCREEN-2

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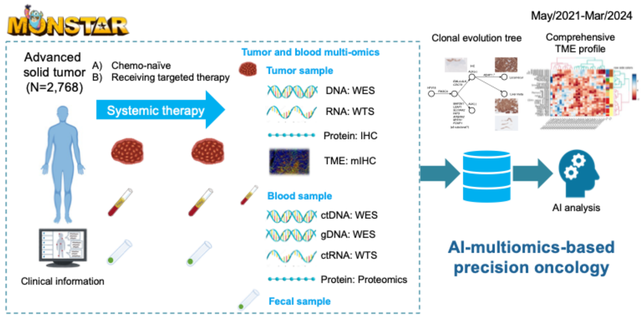
Background

- Fusion variants represent established therapeutic targets in precision oncology yet are incompletely captured by conventional targeted DNA panel sequencing.
- Recent studies have reported that RNA sequencing enables detection of oncogenic fusions and structural variants that escape conventional DNA panel sequencing, particularly complex rearrangements occurring in intergenic regions.
- Herein, we evaluated the landscape of fusion variant detection by whole transcriptome sequencing (WTS) in advanced solid tumors from the SCRUM-Japan MONSTAR-SCREEN-2, a nationwide molecular profiling project (UMIN000043899).

Methods

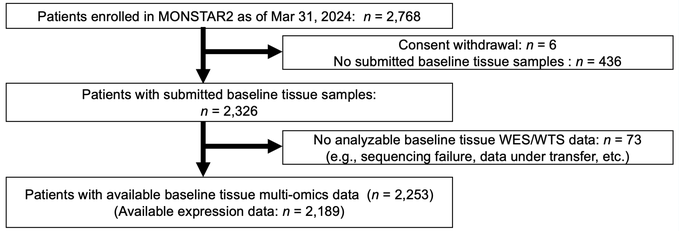
- Patients with advanced solid tumors were enrolled; tumor tissues were profiled using whole exome/transcriptome sequencing (MI CancerSeek, Caris Life Sciences, Phoenix, AZ, USA).
- For fusion detection comparison, we performed an in silico analysis cross-referencing each fusion detected by WTS against publicly available information from conventional DNA panels including both target gene lists and breakpoint information where available, to evaluate theoretical detectability.

Figure 1. Study schema of MONSTAR-SCREEN-2 study



Results

Figure 2. Flow diagram: selection of the patients



Cancer Types	n (%)
Colorectal cancer (CRC)	520 (23.1%)
Gastric cancer (GC)	306 (13.6%)
Breast cancer (BC)	198 (8.8%)
Prostate cancer (PRAD)	177 (7.9%)
Pancreatic cancer (PDAC)	156 (6.9%)
Urothelial carcinoma (UC)	128 (5.7%)
Renal cell carcinoma (RCC)	109 (4.8%)
Biliary tract cancer (BTC)	99 (4.4%)
Head and neck squamous cell carcinoma (HNSCC)	88 (3.9%)
Ovarian cancer (OV)	73 (3.2%)
Esophageal cancer (EC)	53 (2.4%)
Endometrial cancer (UCEC)	49 (2.2%)
Cervical cancer (CESC)	32 (1.4%)
NET / NEC (NET / NEC)	32 (1.4%)
Non-Squamous Head and Neck Cancer (NonSqHNC)	32 (1.4%)
Hepatocellular carcinoma (HCC)	31 (1.4%)
Melanoma (MEL)	30 (1.3%)
Small bowel cancer (SBC)	26 (1.2%)
Sarcoma (SARC)	23 (1%)
Thyroid carcinoma (THCA)	17 (0.8%)
Others	74 (3.3%)

Figure 3. Proportion of fusion variants detectable only by WTS

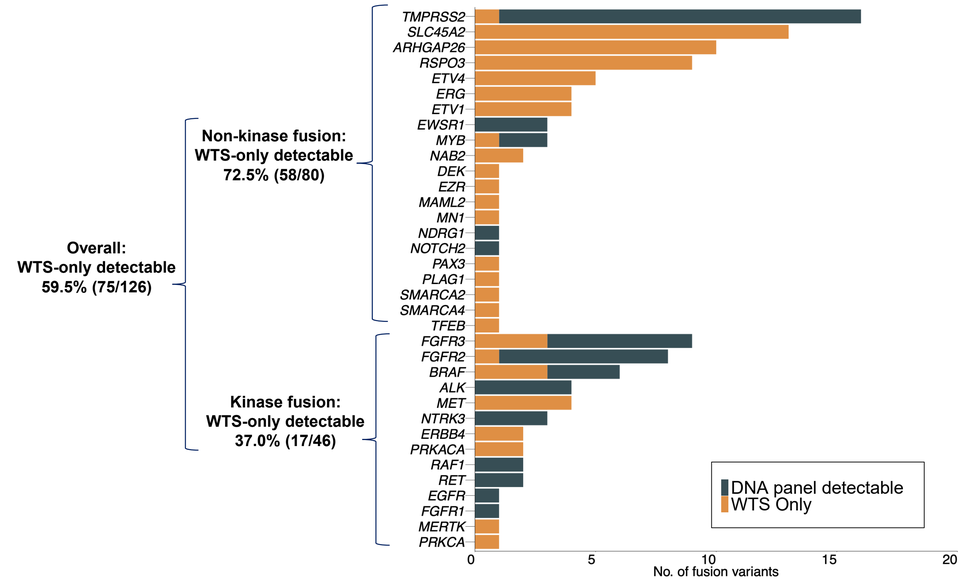
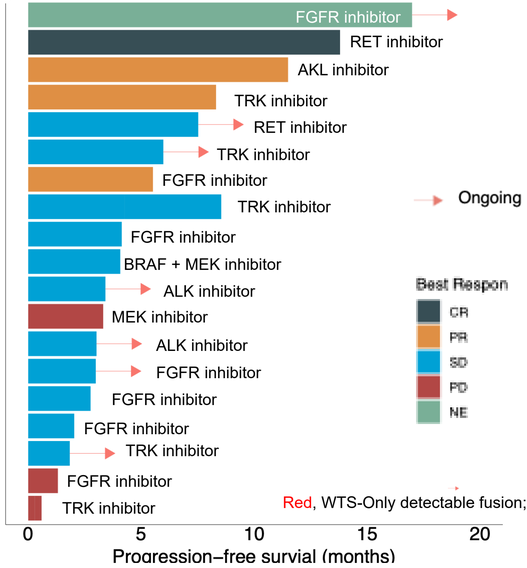


Figure 4. Treatment guided by fusion variants detected with WTS

Cancer Types	Line of Therapy	Target Fusion	Time on Therapy (months)
BTC	1	*FGFR2:AHCYL1*	17
SGC	2	*ETV6:RET*	13.8
BTC	3	*EML4:ALK*	11.5
SGC	1	*ETV6:NTRK3*	8.3
THCA	2	*GOLGB1:RET*	7.5
SGC	2	*ETV6:NTRK3*	6
BTC	2	*FGFR2:HOOK1*	5.5
SGC	2	*ETV6:NTRK3*	4.3
BTC	3	*FGFR2:HOOK1*	4.1
MEL	2	*MYO5A:BRAF*	4.1
THCA	3	*KIAA1217:ALK*	3.4
MEL	4	*TOP2B:RAF1*	3.3
CESC	2	*EML4:ALK*	3
CRC	2	*FGFR2:JUP*	3
BTC	2	*FGFR2:TACC1*	2.8
ESCC	3	*FGFR3:TACC3*	2
CRC	3	*ETV6:NTRK3*	1.8
PDAC	3	*FGFR2:TFCP2*	1.3
SGC	4	*ETV6:NTRK3*	0.3



Summary & Conclusion

- **WTS analysis of 2,253 patients identified 126 pathogenic fusions, 59.5% of which were undetectable by DNA panel sequencing.**
- **Among 18 patients receiving fusion-targeted therapy, ORR was 22.3% and DCR was 83.4%, with a representative *MYO5A-BRAF* fusion case in melanoma achieving stable disease on BRAF/MEK inhibitor therapy.**
- **WTS detected fusion variants at a high frequency, highlighting the importance of WTS in precision oncology.**

Acknowledgement

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