Table: 391P Clinical outcomes comparision of ROS1 tyrosine kinase inhibitor vs chemotherapy

Cohort (n=)	Median follow up (95% CI) in months	Median PFS(95% CI) in months	3 years PFS/5 years PFS	Median OS(95% CI) in months	3 years OS/5 years OS
ROS1 TKI in 1st line (n=38)	27.4 (95% CI 13.0-50.8)	27.07(95% CI 24.28-NA)	41.8%/23.9%	48.59 (95% CI 37.85-NA)	71.8%/46.6%
Chemotherapy (n=20)	14.5 (95% CI 12.1-NA)	6.87 (95% CI 5.55-14.5)	10.53%/5.26%	10.9 (95% CI 7.16-NA)	36.7%/36.7%

Conclusions: In India, access to the ROS1 TKI is currently limited. The use of ROS1 TKI improves the outcomes though statistically not significant. To further improve outcomes, future trials should pay special attention to patients with poor PS and find a way for increased access to TKI.

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392P A phase II study of SAF-189s in patients with advanced ROS1 fusion-positive non-small cell lung cancer

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Background: ROS1 fusions (ROS1+) are enriched in 1-2% of non-small cell lung cancer (NSCLC) cases. SAF-189s is a novel, next-generation ALK/ROS1 inhibitor which overcomes multiple resistance mutations. We explored the efficacy and safety of SAF-189s in phase (Ph) 2 study in patients (pts) with ROS1 fusion NSCLC, with or without ROS1 inhibitor treatment.

Methods: This multicenter, single-arm, open-label, Ph2 study enrolled Chinese patients with advanced ROS1+ NSCLC. The study included 2 cohorts: ROS1 inhibitor (ROS1i)-naïve or crizotinib-pretreated pts in a Ph2a cohort receiving SAF-189s with dose escalation (80, 120, 160 and 210 mg doses QD), and ROS1i-naïve pts alone in a Ph2b cohort receiving 160 mg QD. The primary endpoint was Independent Review Committee (IRC)-assessed overall response rate (ORR).

Results: Between Dec 12, 2021 and Mar 25, 2022, 48 and 56 pts were enrolled in the Ph2a and 2b cohorts, respectively. IRC-confirmed ORR in ROS1i-naïve pts were 94.1% and 80.4% and DCR were 94.1% and 96.4% in pts in Ph2a and Ph2b respectively. Notably, confirmed ORRs and DCRs were similar in pts with and without brain metastasis (Table). Median PFS was 16.5 mo in Ph 2a and not reached in Ph 2b. In crizotinib-pretreated pts in Ph2a, confirmed ORR was 40% and median PFS was 5.5 mo. The majority of treatment-related adverse events (TRAEs) were grade 1 or 2. Grade ≥3 TRAEs were observed in 29.2% and 21.4% of pts in the two cohorts, respectively. Only one pt experienced a grade 4 TRAE in 210 mg dosage of Ph2a. Treatment related SAEs were reported in 10.4% and 8.9% of pts, respectively. No treatment-related deaths were reported.

Conclusions: These findings demonstrate the promising clinical activity and a tolerable toxicity profile of SAF-189s in pts with advanced ROS1+ NSCLC, with or without crizotinib treatment. Clinical trial identification NCT04237805.

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394P Research of the algorithm for rare driver genes in non-small cell lung cancer using pathological images and artificial intelligence

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Background: Target therapy for driver gene-positive cases is one of the standard treatments in advanced or recurrent non-small cell lung cancer (NSCLC). However, there is a need for a simple method to find rare driver genes due to their rarity. We developed and evaluated the algorithm to detect rare driver gene in NSCLC comprehensively using pathological images and AI.

Methods: The images of H&E staining were collected from NSCLC patients registered in LC-SCRUM-IBIS. The data included 167 positive cases with one of the 9 driver genes (ALK, ROS1, RET, BRAF, MET, ERBB2, KRAS) and 646 negative cases. To identify the existence of target genes, we initially set a multi-task classification problem where each task consists of a binary classification task for a specific mutation. We used a neural network based on Attention-based Multiple Instance Learning (MIL) as a backbone. In addition to this baseline model, three different approaches were compared: (i) utilization of annotated cancer cells; (ii) unification of clinical pathological conditions; and (iii) training of individual models for the classification of each gene. Three-fold cross validation was applied for the evaluation.

Table: 392P Clinical outcomes of patients receiving SAF-189s in Ph 2a and 2b

	Ph2a (n=48)[a]		Ph2b (n=56)	
	ROS1i-naïve (n=17)	Crizotinib-pretreated (n=25)	ROS1i-naïve (n=56)	Brain metastases at baseline (n=21)
Assessed by IRC (95% CI)				
ORR, %	94.1 (71.3-99.9)	40 (21.1-61.3)	80.4 (67.6-89.8)	85.7 (63.7-97.0)
DCR, %	94.1 (71.3-99.9)	72.0 (50.6-87.9)	96.4 (87.7-99.6)	100 (83.9-100)
PFS, mo	16.5 (5.6-NR)	5.5 (2.8-11.1)	NR	NR
DoR, mo	15.2 (6.9-NR)	7.0 (2.8-NR)	NR	NR
Assessed by investigators (95% CI)				
ORR, %	88.2 (63.6-98.5)	24.0 (9.4-45.1)	75.0 (61.6-85.6)	76.2 (52.8-91.8)
DCR, %	94.1 (71.3-99.9)	76.0 (54.9-90.6)	94.6 (85.1-98.9)	95.2 (76.2-99.9)
PFS, mo	13.8 (5.6-NR)	6.8 (2.8-NR)	NR	NR
DoR, mo	NR	NR	NR	NR

[a]6 pts in Ph2a cohort relapsed with other treatment. NR, not reached.

Results: The mean AUC score of the 9 binary classification tasks for each gene for the baseline approach was 0.612. The mean AUC scores of the additional approaches (i), (ii) and (iii) were 0.593, 0.626 and 0.687, respectively. The first two approaches indicate that the additional annotations to the cancer cells had little effect on the classification task and that the diverse sample conditions might have a negative impact on the task. The last approach showed that we can obtain better models by training individual models for each gene rather than a unified method for the diverse driver genes.

Conclusions: We developed an algorithm using pathological images and AI and examined its performance. The performance was not satisfactory good for practical use. For further improvement, training with additional samples and additional learning methods should be considered.

Clinical trial identification: UMIN:000045992.

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395P Molecular landscape of Indian NSCLC: Is NGS the answer?

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Background: The list of therapeutically relevant biomarkers in NSCLC is continually expanding and hence molecular profiling is of paramount importance. Tissue availability and chance of rebiopsy is a major limitation in lung cancer and sequential single gene assays lead to tissue exhaustion and inadvertent delays in institution of therapy. We sought to compare the performance of targeted next-generation sequencing (NGS) panels with traditional assays and correlate the mutational landscape in an Indian NSCLC cohort.

Methods: 414 consecutive patients who underwent both single gene assay and NGS were included in the study. The NGS panel is a custom made 34 gene panel interrogating for canonical alterations in genes implicated in lung carcinoma, including both DNA and RNA based assays A cost-effectiveness analysis of NGS compared to standard molecular testing was conducted.

Results: 414 samples were evaluated. Median age was 69 years, 52 % were male, 59 % were never smokers, 92.3 % had stage IV disease and 97.9 % had adenocarcinoma histology. In patients profiled with NGS on DNA, EGFR (36.2 %), KRAS (30.6 %), BRAF (5.8 %) and ERBB2 (5.9 %) mutations were found. RNA fusion testing revealed fusions in ALK (6.2 %), RET (5.9 %) and ROS1 (2.1 %). Compared to sequential testing in EGFR, ALK and ROS1 negative patients, upfront NGS testing resulted in an additional 1.2 % of patients with actionable alterations for targeted therapy being identified. However the turnaround time for NGS was a median 14.2 days and cost increment was 19%. However, detection of complex EGFR alterations, variant ALK fusions, and ROS1 fusions also improved by 5.2%, 1.5% and 3.4% respectively. Additionally squamous histology patients also depicted MET exon 14 skipping and KRAS G12C alterations in 2.4% and 4.7% cases, respectively.

Conclusions: This study underscores the need for upfront NGS testing despite increment in expenditure for the patient. Our results support the implementation of diagnostic NGS in NSCLC to allow patients access to the most appropriate molecularly targeted therapy. In addition, we also advocate performing panel based upfront NGS testing in patients with squamous histology as well, especially in the light of recent approvals of capmatinib and sotorasib fro MET exon 14 skipping and KRAS G12C alterations.

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396P Mutational profiling by next generation sequencing in patients with metastatic non-small cell lung carcinoma

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Background: According to GLOBOCAN 2020 lung cancer is the 2nd most common cancer worldwide (11.4%) accounting for highest cancer related mortality (18%). NSCLC is divided into molecular subtypes based on oncogenic drivers. NCCN strongly recommends performing broad panel-based testing like NGS in mNSCLC patients.

Methods: A hospital based prospective observational study on 88 patients during a period of 1 year. All patients aged 18 years or above, diagnosed as metastatic non small cell lung carcinoma and evaluated for oncogenic driver mutation by NGS method were included in the study. NGS was performed in fresh frozen paraffin embedded (FFPE) tissue block. We had included 5 diver mutations e.g. EGFR, EMLA-ALK, BRAF, MET, ROS1 which are under current recommendations from NCCN guidelines and have specific targeted therapy recommended against them.

Results: Majority of mNSCLC cases were in the age group of 41-50 years (n=30, 34.1%) with average age at presentation being 53.74 years. Male: female ratio was 1.14:1 and most patients were non smokers (n=47, 53.4%). Adenocarcinoma (n=75, 85.2%) was the most common histological subtype followed by squamous cell carcinoma (n=10, 11.4%). mNSCLC cases with adenocarcinoma histology had highest mutational burden (n=55, 62.5%). EGFR (n=32, 56.14%) was the most common mutation detected followed by EMLA-ALK4 (n=19, 33.33%). ROS1 mutation was detected in 4 patients while MET and BRAF V600E mutations were detected in 1 each. Most common variant in EGFR mutation was Exon 19 (n=17, 53.12%) followed by Exon 20 (n=8, 25%) and Exon 21 (n=6, 18.75%). EGFR mutation in Exon 18 was the rarest mutation (n=1, 3.13%). 2 patients with EGFR Exon 20 had upfront T790M mutation. p.Glu746_Ala750 was the most common variant in EGFR Exon 19 mutation while L858R was the commonest variant in EGFR Exon 21 mutation. Skeleton was the most common metastatic site across all subtypes of driver mutations while brain was the most common site in the EMLA-ALK4 mutated patients.

Conclusions: Geographical and demographic differences of the North-Eastern part of India may have impact on the high mutational burden among lung cancer patients. 64.77% of our mNSCLC patients had driver mutation of which 56.14% had EGFR and 33.33% had EMLA-ALK mutation.

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397TiP Phase III LUNAR study: Tumor treating fields (TTFields) with standard of care for the treatment of stage 4 non-small cell lung cancer (NSCLC) following platinum failure

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Background: Tumor Treating Fields (TTFields) therapy is a novel, loco-regional treatment modality approved for use in glioblastoma and malignant pleural mesothelioma. TTFields are electric fields generated by a portable, wearable device, and delivered to the tumor via arrays placed on the skin. TTFields act by disrupting cellular processes critical for cancer cell viability and tumor progression. Preclinical data demonstrated efficacy of TTFields with either chemotherapy or immunotherapy in non-small cell lung cancer (NSCLC), in vitro and in vivo. Results from the EF-15 pilot study of TTFields therapy with pemetrexed in NSCLC showed good efficacy and tolerability, and provided rationale for further investigation in a phase 3 setting.