#9027: Base Excision Repair (BER) Inhibitor TRC 102 (Methoxyamine) Combined with Pemetrexed (PEM)-Based Chemo-Radiation (CRT) for Locally Advanced Non-Squamous Non-Small Cell Lung Cancer (NS-NSCLC): Results of a Phase 1 Trial

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Background:

- About 35% of all NSCLC presents with locally advanced disease.
- Chemo-radiation results in 5-year OS of only ~31%.
- PEM-platinum combination is approved in stage IV NSCLC.
- This combination has similar efficacy to platinum-etoposide in stage 3 NSCLC and a favorable toxicity profile (Proclaim trial).
- TRC102 is an oral small molecule inhibitor of BER. TRC102 potentiates the cytotoxicity of antimetabolites and alkylators and reverses chemotherapy resistance by rapidly and covalently binding to chemotherapy-induced abasic sites in DNA.
- TRC102 increased radio-sensitization by PEM of NSCLC cell lines and H1299 and A549 xenografts.

Methods:

- Between 11/2015 and 5/2019, 15 patients were enrolled in a 3+ 3 design: 12 with stage III and 3 with oligometastatic stage IV NS-NSCLC.
- Primary objective was to determine dose-limiting toxicities (DLT's) and recommended Phase 2 dose (RP2D) of TRC102 in combination with PEM, cisplatin and radiotherapy.
- Secondary objectives were to assess toxicity, tumor response and PFS at 6 months. Based on pre-clinical data, PEM-TRC102 was given on day 1, and cisplatin/ radiotherapy was initiated on day 3.
- Above schedule was duplicated on day 21 and day 23 of the second cycle.
- After completion of radiotherapy, two additional cycles of PEM-cisplatin were given.
- Toxicities were assessed by NCI CTACAE version 4 and 5.

Conclusion:

- RP2D of TRC102 was 200 mg when given with cisplatin/radiotherapy and Pemetrexed (PEM).
- PEM-TRC102 combined with cisplatin/ radiotherapy in non-squamous NSCLC was safe and well tolerated, and did not cause safety signals beyond those expected from CRT.
- Preliminary response data and PFS in this cohort are encouraging.

Future Direction for Research:

- A phase 2 trial, integrating post-CRT immunotherapy with this aggressive DNA-damaging regimen is warranted.

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Results:

- Median patient age was 69 years (45-79) and median follow up was 16.6 months (3.1-38.6).
- There were no DLTs or grade 5 toxicity. Hematologic and GI toxicities were the most common adverse events (**Table 1**) and radiation pneumonitis was not seen.
- Of 15 evaluable patients, 3 had CR (20%) and 12 had PR (80%) (**Figure 1**).
- 2-year PFS rate was 49%.

Table 1: Toxicity profile of the treated patients.

	Grade 1	Grade 2	Grade 3	Grade 4	Total (n=15)
Hematological toxicity					
Anemia	6	4	3		13
Lymphopenia		3	7	3	13
Decreased neutrophil count			6	1	7
Decreased Platelet count	10	2			12
GI toxicity					
Nausea	5	6			11
Vomiting	1	3			4
Dehydration		3	2		5
Esophagitis	1	7			8
Fatigue	1	3	1		5
Anorexia	2	2	3		7
Weight Loss			3		3
Pulmonary Toxicity					
Pneumonitis					0
Cough	1	2			3
Skin toxicity					
Dermatitis	2	2			4

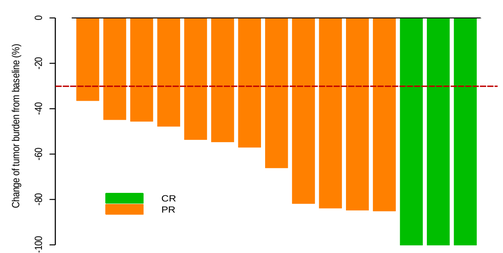

Figure 1: Waterfall plot - Best response for target lesions by patient, based on maximal percentage of tumor reduction. CR – complete response, PR – partial response by RECIST = Response Evaluation Criteria in Solid Tumors.