Broad glutamine pathway inhibition by DRP-104 results in anti-tumor activity in hypermetabolic lung tumors resistant to PD-1 or osimertinib therapy.

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Abstract:
Recent breakthroughs with checkpoint inhibitors (CI) or the third generation tyrosine kinase inhibitor (TKI) osimertinib (OSI) for patients with specific mutations to the epidermal growth factor receptor (EGFR) gene are now able to induce durable responses in non-small cell lung carcinoma (NSCLC) patients1, 2, however, the majority of patients who receive CI or OSI will be either non-responsive to treatment or develop therapy resistance. We sought to identify alternative treatment strategies to overcome therapy resistance by targeting metabolism in aggressive tumors. The interplay of growth in therapy-resistant hyper-metabolic tumors (HMTs) makes them dependent on nutrients to sustain anabolic growth. To demonstrate this dependency, we coupled PET using 18F-FDG and 18C-Glutamine (18C-GLN) with in vivo metabolomics and identified a conserved metabolic signature in which lung squamous cell carcinomas (LUSC) and EGFR mutant lung adenocarcinomas (LUAD) were marked by dependence upon both glucose and glutamine3, 4. Importantly, this metabolic signature predicted of either response or resistance to targeted therapies that inhibit glucose and glutamine metabolism that may be exploited in a clinical setting.

We previously reported that combined targeting of glucose and glutamine metabolism with mTOR kinase inhibitor TAK228 or TKI in combination with the selective glutaminase (GLS) inhibitor CB-839 resulted in significantly suppress glucose and glutamine metabolism in both LUSC and EGFR mutant LUADs resulting in metabolic crisis and tumor cell death5, 6. Here, we tested the novel broad acting glutamine antagonist DRP-104 (sripinlagenstat) in mouse models of lung cancer as a single agent in OSI-resistant EGFR mutant LUAD or in combination with anti-PD-1 in OSI-resistant LUSC.

ID | Strain | Type | Identified Genetic Mutations | Response to DRP-104 | Tumor Volume, mm³ | ns | 53
---|---|---|---|---|---|---
1996b | MLE-12 Syngeneic cell line | Responding | KEAP1lox/lox; KRASG12D | Partial responder | 2785 2 104 | 001
2785 2 104 | Syngeneic cell line | Responding | KEAP1lox/lox; KRASG12D | Partial responder | 0001
2785 2 104 | Syngeneic cell line | Responding | KEAP1lox/lox; KRASG12D | Partial responder | 0001
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Conclusions: DRP-104 (sripinlagenstat) significantly inhibited tumor progression in the 3605 T1 (L Nath /Pten+/+) and 3605 4 (L Nath /Pten+/-) genetically engineered mouse tumor models (GEMMs) but not in the related GEMMs 2785 2 104 (L Nath /Pten+/+ and 1316c (L Nath /Pten+/-). Responsive tumors had a higher KEAP1/NRF2 pathway activity compared to non-responsive tumors. Interestingly, single agent anti-tumor activity of DRP-104 was extended into several xenograft and PDX tumor models with KEAP1 mutations, including models co-harboring mutations in RAS(PTER, Pten) and/or KEAP1: Lusit. In addition, we showed that DRP-104 induced a significant response in an OSI-resistant PDX model of EGFR mutant LUAD. Lastly, in the DRP-104 resistant but anti-PD-1 resistant GEMM tumors, the combination DRP-104 and PD-1 treatment demonstrated therapeutic synergy, suggesting that broad inhibition of glutaminolysis by DRP-104 induced metabolic remodeling of the tumor immune microenvironment and permissiveness for anti-PD-1. DRP-104 demonstrated potential to treat hypermetabolic therapy-resistant LUAD and LUC as a single-agent therapy and in combination with immune EP. Further clinical development of DRP-104 (sripinlagenstat) in this patient population is warranted and a first-in-human clinical trial is currently ongoing.