

188TiP Metformin +/- cyclic fasting mimicking diet in combination with platinum-pemetrexed chemotherapy for advanced LKB1 inactive lung adenocarcinoma: The FAME trial

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Background: LKB1 inactive (LKB1i) lung adenocarcinoma (LA) has an aggressive behavior and is resistant to immunotherapy (IO). LKB1i cells are vulnerable to nutrient starvation. Based on preclinical data showing a synergy cisplatin-metformin, we hypothesized that combining platinum-based chemotherapy (CT) with metformin +/- a calorie-restricted, low-carbohydrate, low-protein diet known as Fasting Mimicking Diet (FMD) may improve the efficacy of CT in patients (pts) with LKB1i LA.

Trial design: FAME is a monocentric, open label, double arm, non comparative, randomized, single stage, pick-the-winner phase II trial. Primary objective is Progression Free Survival (PFS), evaluated in comparison with a historical cohort of pts treated with CT. Secondary objectives consist in studying experimental treatment toxicity, response rate, overall survival, metabolic changes in blood, urine and stool, correlation between LKB1 mutation status and LKB1 protein expression. Main inclusion criteria are: advanced LKB1i LA, absence of EGFR mutations and ALK/ROS1 rearrangements, PDL1 expression < 50%, performance status 0-1. Main exclusion criteria are: body mass index < 20 kg/m², weight loss ≥ 5% in the previous 3 months, diabetes mellitus, active brain metastases, baseline fasting glucose ≤ 65 mg/dL, arterial pO₂ < 70 mmHg, high blood lactates. Eligible pts will be randomized 1:1 to up to 4 cycles of platinum-pemetrexed CT + metformin, or up to 4 cycles of platinum-pemetrexed CT + metformin + FMD. After 4 cycles, stable/responding pts will continue pemetrexed + metformin until progression or toxicity. Forty-one pts per arm will be necessary to identify a 4.4 mos increase in median PFS. Brookmeyer-Crowley test will be used with an α tail of .15 and a power of .8 mos. Assuming a dropout rate of 5%, the number of pts to enroll will be 88.

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