1052P

Phase-Ib Trial of Metformin Combined with Nivolumab for Refractory/Recurrent Solid Tumors

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BACKGROUND

- Addition of metformin to nivolumab, an anti-PD-1 antibody, yielded a substantial tumor regression in mouse model [1] (Fig 1-2).
- Following exposure to metformin, tumor-infiltrating CD8 T cells (CD8 TILs) changed from dominant central memory to effector memory cell types, contributing to acquisition of IL-2, TNF-α, IFN-γ multi-productivity. Almost all CD8 TILs were able to escape apoptosis, thus resisting immune exhaustion [2].
- A combination of metformin and PD-1 blockade has been reported to improve intra tumoral T-cell function and tumor clearance [1].
- Based on these considerations, we have launched an investigator-initiated open-label phase-Ib clinical trial.

Fig 1.

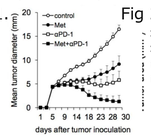


Fig 2.

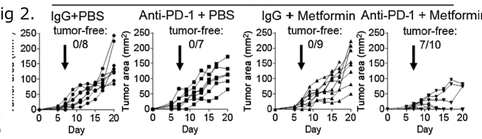


Fig 1. Addition of metoformin to anti-PD-1 antibody suppressed tumor growth *in vivo*. BALB/c mice were inoculated with Meth A cells.
Fig 2. Metabolic remodeling synergizes with checkpoint blockade to affect antitumor immunity. Tumor measurements of C57/BL6 mice inoculated with B16 melanoma.

[1]Scharping NE, et al. Cancer Immunol Res. 2017;5:9-16.
[2]Eikawa S, et al. Proc Natl Acad Sci U S A. 2015;112:1809-14.

OBJECTIVES

The purpose of this study is to investigate the safety, efficacy, and pharmacokinetics of a metformin and nivolumab combination treatment

METHODS

- The recommended dose of metformin combined with nivolumab is determined in part 1, and the safety and efficacy of the optimal dose of metformin combined with nivolumab are examined in part 2.
- Patient eligibility is based on the following criteria: pathological diagnosis of refractory/recurrent solid tumor (part 1), and non-small-cell lung cancer (NSCLC) or pancreatic cancer refractory to standard primary treatment (part 2); ICI-naivety; performance status (PS) 0 or 1; age ≥20 years; and adequate organ function.

<Intervention>

- In part 1, the recommended dose (RD) of Metformin is determined by the conventional 3+3 cohort method at three dose levels, started at a clinically reasonable dose of 750 mg/day and can be increased up to 2,250 mg/day. In part 2, RD is administered (Fig 3). After the determination of RD, patients in part 1 can receive RD.
- In both parts, Metformin is administered orally daily for 14days per non-interrupted cycle. Nivolumab (3 mg/kg) is administered intravenously on day 1 in each cycle. Patients will continue to receive the study treatment until the disease progresses or unmanageable toxic effects develop (Fig 4).

Fig 3.

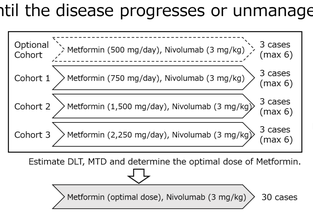
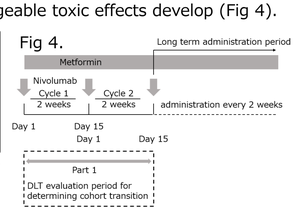


Fig 4.



<Study endpoints>

【Part 1】 1. Safety: maximum tolerated dose (MTD), dose limiting toxicity (DLT), adverse events profile
2. Pharmacokinetics of metformin
【Part 2】 1. Safety: adverse events profile
2. Pharmacokinetics of metformin

<DLT, MTD and RD>

- DLT defined below is evaluated for the first 28 days from day1 in cycle 1.
- MTD is defined as a dose level below that produces any DLT in two or more patients among a maximum of six patients, after which further dose escalation is not permitted.
- RD is defined as MTD or the maximum dose of 2,250 mg/day without detecting MTD for safe administration.

DLT

(1) Hematological toxicity
  a. Grade 4 neutropenia lasting >7 days or longer
  b. Grade 4 thrombocytopenia requiring platelet transfusion
(2) Non-hematological toxicity
  a. ≥ Grade 3 febrile neutropenia
  b. ≥ Grade 2 hypoglycemia
  c. ≥ Grade 3 other non-hematological toxicity

RESULTS

Table 1. Patient characteristics

- Seventeen and twenty-four patients were enrolled in parts 1 and 2, respectively.
- Of the 17 cases registered in part 1, 15 cases were selected for DLT evaluation.

	n=41
Age, years	
Median (range)	62 (33-76)
Sex	
Male / Female	24 / 17
Cancer type	
Pancreatic cancer	26
Thymic epithelial tumor	3
Non-small cell lung cancer	2
Others*	10
Stage	
I / II / III / IV / post ope rec	1 / 4 / 9 / 26 / 1
ECOG PS	
0 / 1	19 / 22
PD-L1 status (28-8)	
<1 / 1-49 / ≥50 (%)	26 / 8 / 3
PD-L1 status (22C3)	
<1 / 1-49 / ≥50 (%)	26 / 8 / 2

Others: Rectal cancer, breast cancer, esophageal cancer, intrahepatic bile duct cancer, prostate cancer
ECOG: Eastern Cooperative Oncology Group, PS: performance status

- Mean relative Dose Intensity of nivolumab: 96.14±10.73%
- Mean relative Dose Intensity of metformin: 67.51±29.21%

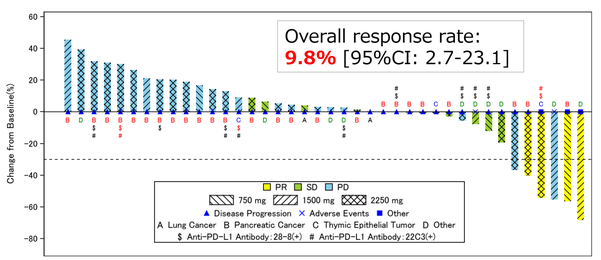
Table 2. DLT evaluation in Part1

Dose level of metformin	750mg/day (n=6) (%)	1500mg/day (n=6) (%)	2250mg/day (n=3) (%)
Increased pancreatic enzymes	0	1* (16.7)	0
Abnormal liver function	0	1* (16.7)	0
pleural effusion	1 (16.7)	0	0

- The recommended dose of metformin for part 2 was determined to be 2250 mg/day.

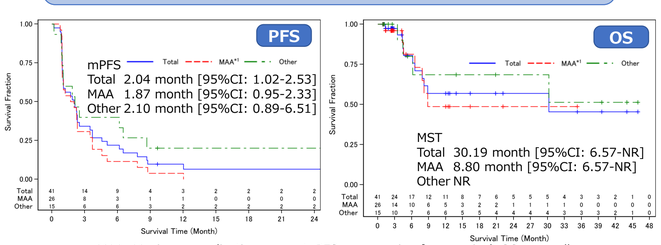
* These events were occurred in a patient in cohort 2.

Fig 5. Waterfall plot of response



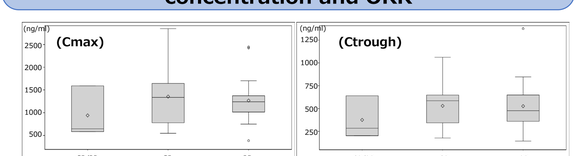
PR: partial response, SD: stable disease, PD: progressive disease

Fig 6. PFS and OS curve



MAA: Maximum application amount, PFS: progression free survival, OS: over all survival, MST: median survival time, CI: confidence interval

Fig7. Relationship between metformin blood concentration and ORR



ORR: overall response rate

Fig 8. Swimmer Plot

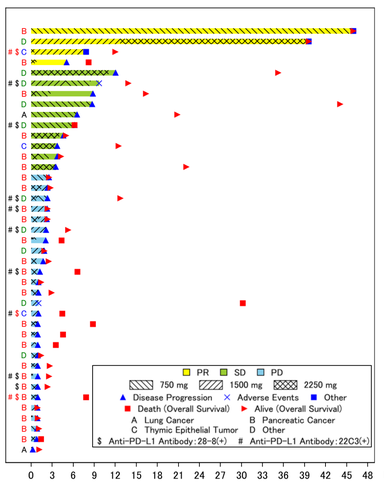


Table 3. Severe Adverse Event related with this combination therapy

	Any (%)	G3 (%)	G4 (%)
Pneumonia	2.4	2.4	0
Impetigo	2.4	2.4	0
Encephalitis	2.4	0	0
Abnormal liver function	2.4	2.4	0
Hypopituitarism	2.4	2.4	0
Adrenocorticotropin deficiency	2.4	2.4	0
Pleural effusion	2.4	2.4	0
Pneumonitis	2.4	0	0
Increased pancreatic enzymes	2.4	0	2.4
Lactic acidosis	2.4	2.4	0

There were no Grade 5 adverse events.

CONCLUSIONS

- This combination therapy was well tolerated and demonstrated clinically meaningful efficacy in selected patients.
- In the future, further verification of the mechanism in cases in which treatment was effective is required.

CONFLICT OF INTERESTS

TK received honoraria from Ono Pharmaceutical, Bristol-Myers Squibb.

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- Contact: t-kubo@cc.okayama-u.ac.jp
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