SUPPLEMENTAL MATERIAL

Phase I study exploring the safety, effect on the tumor microenvironment, and efficacy of itacitinib in combination with epacadostat or parsaclisib in advanced solid tumors

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| TEAE, n (%) | Group A: itacitinib + epacadost | Group B: itacitinib + parsaclisib |
|-------------|---------------------------------|---------------------------------|
|             | Part 1a                          | Part 1b                          | Part 1a                          | Part 1b                          | Part 2                          |
|             | Dose-escalation                  | Dose-expansion                    | Dose-escalation                  | Dose-expansion groups             | Dose-expansion                    |
|             | Group A                          | Groups A-1 and A-2                | Group B                          | B-1 and B-2                       | Groups B-3, B-4, and B-5          |
| (N=12)      | (N=35)                           | (N=42)                           | (N=23)                           | (N=30)                           |
| Any grade   | Fatigue                          | Nausea                           | Vomiting                         | Decreased appetite                | Abdominal pain                    |
| ≥3          | 4 (33.3)                         | 3 (25.0)                         | 4 (33.3)                         | 1 (8.3)                           | 2 (16.7)                          |
| Any grade   | 20 (57.1)                        | 17 (48.6)                        | 13 (37.1)                        | 9 (25.7)                          | 8 (22.9)                          |
| ≥3          | 2 (5.7)                           | 2 (5.7)                           | 2 (5.7)                           | 0 (0)                             | 3 (8.6)                           |
| Any grade   | 16 (38.1)                        | 11 (26.2)                        | 9 (21.4)                         | 11 (26.2)                        | 7 (16.7)                          |
| ≥3          | 2 (4.8)                           | 0 (0)                             | 2 (4.8)                           | 0 (0)                             | 1 (2.4)                           |
| Any grade   | 12 (52.2)                        | 9 (39.1)                         | 9 (39.1)                         | 11 (47.8)                        | 4 (17.4)                          |
| ≥3          | 1 (4.3)                           | 3 (13.0)                         | 3 (13.0)                         | 1 (4.3)                           | 2 (8.7)                           |
| Any grade   | 10 (33.3)                        | 12 (40.0)                        | 7 (23.3)                         | 5 (16.7)                          | 5 (16.7)                          |
| ≥3          | 2 (6.7)                           | 0 (0)                             | 0 (0)                             | 0 (0)                             | 0 (0)                             |
| Anemia      | 1 (8.3)                           | 8 (22.9)                          | 2 (5.7)                           | 8 (22.9)                          | 1 (8.3)                           |
|             | 1 (8.3)                           | 5 (11.9)                          | 8 (19.0)                          | 5 (16.7)                          | 4 (33.3)                          |
|             | 2 (5.7)                           | 1 (2.4)                           | 3 (7.1)                           | 1 (8.3)                           | 0 (0)                             |
|             | 16 (38.1)                        | 5 (21.7)                          | 3 (13.0)                         | 0 (0)                             | 0 (0)                             |
|             | 3 (13.0)                          | 0 (0)                             | 7 (23.3)                         | 0 (0)                             | 0 (0)                             |
|             | 7 (23.3)                          | 2 (6.7)                           | 2 (6.7)                           | 7 (23.3)                          | 0 (0)                             |
|             | 3 (10.0)                          | 0 (0)                             | 0 (0)                             | 3 (10.0)                          | 0 (0)                             |
|             | 2 (6.7)                           | 0 (0)                             | 0 (0)                             | 0 (0)                             | 0 (0)                             |
| Diarrhea    | 2 (16.7)                          | 7 (20.0)                          | 7 (20.0)                          | 7 (20.0)                          | 2 (16.7)                          |
|             | 3 (8.6)                           | 3 (8.6)                           | 3 (8.6)                           | 3 (8.6)                           | 0 (0)                             |
|             | 14 (33.3)                         | 14 (33.3)                         | 1 (2.4)                           | 1 (2.4)                           | 6 (20.0)                          |
|             | 1 (2.4)                           | 1 (2.4)                           | 3 (13.0)                         | 3 (13.0)                          | 0 (0)                             |
|             | 3 (13.0)                          | 3 (13.0)                          | 6 (20.0)                          | 6 (20.0)                          | 0 (0)                             |
|             | 5 (21.7)                          | 5 (21.7)                          | 3 (10.0)                          | 3 (10.0)                          | 0 (0)                             |
|             | 4 (33.3)                          | 4 (33.3)                          | 4 (33.3)                          | 4 (33.3)                          | 0 (0)                             |
|             | 0 (0)                             | 0 (0)                             | 0 (0)                             | 0 (0)                             | 0 (0)                             |
| Condition                        | B-1 (16.7) | B-2 (16.7) | B-1 (16.7) | B-2 (16.7) | B-1 (14.3) | B-2 (14.3) | B-1 (11.9) | B-2 (11.9) | B-1 (9.5)  | B-2 (9.5)  | B-1 (17.4) | B-2 (17.4) | B-1 (6.7)  | B-2 (6.7)  |
|---------------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Malignant neoplasm progression  | 2          | 2          | 5          | 5          | 2          | 2          | 5          | 2          | 4          | 4          | 4          | 4          | 2          | 2          |
| Cough                           | 3 (25.0)   | 0 (0)      | 4 (11.4)   | 0 (0)      | 8 (19.0)   | 0 (0)      | 4 (17.4)   | 0 (0)      | 6 (20.0)   | 0 (0)      | 5 (16.7)   | 0 (0)      | 2 (6.7)    | 2 (6.7)    |
| Dizziness                       | 2 (16.7)   | 0 (0)      | 4 (11.4)   | 0 (0)      | 1 (2.4)    | 0 (0)      | 1 (4.3)    | 0 (0)      | 5 (16.7)   | 0 (0)      | 2 (16.7)   | 2 (16.7)   | 4 (11.4)   | 4 (11.4)   |
| Pneumonia*                      | 2 (16.7)   | 2 (16.7)   | 3 (8.6)    | 1 (2.9)    | 1 (2.4)    | 1 (2.4)    | 1 (4.3)    | NR         | 1 (3.3)    | 1 (3.3)    | 3 (13.0)   | 0 (0)      | 2 (6.7)    | 0 (0)      |
| Anxiety                         | 2 (16.7)   | 0 (0)      | 2 (5.7)    | 0 (0)      | 1 (2.4)    | 0 (0)      | NR         | NR         | 1 (3.3)    | 0 (0)      | 5 (16.7)   | 0 (0)      | 2 (6.7)    | 0 (0)      |
| Chills                          | 2 (16.7)   | 0 (0)      | 2 (5.7)    | 0 (0)      | 5 (11.9)   | 0 (0)      | 3 (13.0)   | 0 (0)      | 2 (6.7)    | 0 (0)      | 2 (6.7)    | 0 (0)      | 5 (16.7)   | 0 (0)      |
| Insomnia                        | 3 (25.0)   | 0 (0)      | 2 (5.7)    | 0 (0)      | 2 (4.8)    | 0 (0)      | 1 (4.3)    | 0 (0)      | 1 (3.3)    | 0 (0)      | 5 (16.7)   | 0 (0)      | 2 (6.7)    | 0 (0)      |
| Ear pain                        | 2 (16.7)   | 0 (0)      | NR         | NR         | NR         | NR         | NR         | NR         | 5 (14.3)   | 0 (0)      | 4 (9.5)    | 0 (0)      | 5 (21.7)   | 0 (0)      |
| Muscle spasms                   | 2 (16.7)   | 0 (0)      | NR         | NR         | 1 (2.4)    | 0 (0)      | NR         | NR         | 5 (14.3)   | 0 (0)      | 4 (9.5)    | 0 (0)      | 5 (21.7)   | 0 (0)      |
| Myalgia                         | NR         | NR         | 5 (14.3)   | 0 (0)      | 4 (9.5)    | 0 (0)      | 5 (21.7)   | 0 (0)      | 3 (10.0)   | 0 (0)      | 5 (14.3)   | 0 (0)      | 4 (9.5)    | 0 (0)      |
| Blood alkaline phosphatase increased | 1 (8.3)   | 0 (0)      | 2 (5.7)    | 0 (0)      | 5 (11.9)   | 2 (4.8)    | 4 (17.4)   | 1 (4.3)    | 3 (10.0)   | 0 (0)      | 5 (14.3)   | 0 (0)      | 4 (9.5)    | 0 (0)      |
| Dyspnea                         | 1 (8.3)    | 0 (0)      | 5 (14.3)   | 2 (5.7)    | 7 (16.7)   | 2 (4.8)    | 4 (17.4)   | 1 (4.3)    | 3 (10.0)   | 2 (6.7)    | 1 (8.3)    | 0 (0)      | 1 (2.9)    | 4 (9.5)    |
| Headache                        | 1 (8.3)    | 0 (0)      | 4 (11.4)   | 1 (2.9)    | 4 (9.5)    | 0 (0)      | NR         | NR         | 5 (16.7)   | 0 (0)      | 5 (16.7)   | 0 (0)      | 5 (16.7)   | 0 (0)      |

*Severity grade was missing for the patient who experienced a TEAE of pneumonia in Part 1b dose-expansion Group B-1 and B-2.

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; NR, not reported.
### Supplemental table 2

| Serious TEAE by MedDRA preferred term*, n (%) | Group A: itacitinib + epacadostat | Group B: itacitinib + parsaclisib |
|---------------------------------------------|-----------------------------------|----------------------------------|
|                                             | Part 1a Dose-escalation | Part 1b Expansion | Part 1a Dose-escalation | Part 1b Expansion | Part 2 Expansion |
|                                             | (N=12) | (N=35) | (N=42) | (N=23) | (N=30) |
| Anemia                                      | 1 (8.3) | 1 (2.9) | 0 (0) | 2 (8.7) | 0 (0) |
| Anxiety                                     | 1 (8.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Biliary tract infection                     | 1 (8.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Deep vein thrombosis                        | 1 (8.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Encephalopathy                              | 1 (8.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Pneumonia                                   | 1 (8.3) | 1 (2.9) | 1 (2.4) | 0 (0) | 0 (0) |
| Procedural hemorrhage                        | 1 (8.3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Pulmonary embolism                           | 1 (8.3) | 0 (0) | 0 (0) | 2 (8.7) | 0 (0) |
| Respiratory failure                          | 1 (8.3) | 1 (2.9) | 0 (0) | 0 (0) | 0 (0) |
| Abdominal pain                               | 0 (0) | 3 (8.6) | 1 (2.4) | 2 (8.7) | 0 (0) |
| Small intestinal obstruction                 | 0 (0) | 3 (8.6) | 0 (0) | 0 (0) | 1 (3.3) |
| Diarrhea                                     | 0 (0) | 2 (5.7) | 0 (0) | 0 (0) | 0 (0) |
| Dyspnea                                      | 0 (0) | 2 (5.7) | 0 (0) | 1 (4.3) | 2 (6.7) |
| Nausea                                       | 0 (0) | 2 (5.7) | 0 (0) | 3 (13.0) | 1 (3.3) |
Vomiting            0 (0)       2 (5.7)   1 (2.4)   3 (13.0)   1 (3.3)
Dehydration         0 (0)       1 (2.9)   0 (0)    3 (13.0)   0 (0)
Tumor pain          0 (0)       1 (2.9)   0 (0)    2 (8.7)    0 (0)
Acute kidney injury  0 (0)       1 (2.9)   3 (7.1)  1 (4.3)    1 (3.3)
Lung infection      0 (0)       0 (0)     0 (0)    1 (4.3)    2 (6.7)

*Preferred terms are arranged by decreasing order of frequency of TEAEs in Part 1a, Group A. TEAE was defined as any adverse event either reported for the first time or worsening of a pre-existing event after first dose of study drug and until 30 days after the last dose of study drug.

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
**Supplemental figure 1**  Heat map of average Log2 fold change of all proteins identified by paired t-test to be differentially expressed (FDR ≤0.05 and Log2 fold change >0.4 or <−0.4) between C1D1 and C2D1 in any treatment group.

Delta 0.3 mg QD: itacitinib 100 mg (n=23 [Group B-3 and B-5]) or 300 mg (n=2 [Part 1a Group B]) plus parsaclisib 0.3 mg; Delta 10 mg QD: itacitinib 300 mg plus parsaclisib 10 mg (n=12 [Group B-1 and B-2]); Epacadostat: itacitinib 300 mg plus epacadostat 300 mg (n=12 [Group A-1 and A-2]).

C1D1, cycle 1 day 1; C2D1, cycle 2 day 1; delta, parsaclisib; FDR, false discovery rate; QD, once daily.
Supplemental figure 2  
Kynurenine levels were analyzed in baseline (C1D1) versus on-treatment (itacitinib 300 mg QD + epacadostat 300 mg BID) plasma samples (C2D1, C4D1) from Groups A-1 (n=5) and A-2 (n=8).

BID, twice daily; C1D1, cycle 1 day 1; C2D1, cycle 2 day 1; C4D1, cycle 4 day 1; PD, progressive disease; QD, once daily; SD, stable disease.
**Supplemental figure 3**  Representative immunohistochemistry staining for CD8⁺ T cells at screening compared with on-treatment with itacitinib plus low-dose parsaclisib (0.3 mg). Tumor infiltrating CD8⁺ and FoxP3⁺ (forkhead box protein 3) positive cells were quantified by counting cells present within the tumor as assessed by co-localization with pan-cytokeratin staining. (A) Patient with transitional cell carcinoma of urinary tract: 318 CD8⁺/mm² cells at screening (left panel) versus 1681 CD8⁺/mm² cells on-treatment (right panel). (B) Patient with head and neck squamous cell carcinoma: 932 CD8⁺/mm² at screening (left panel) versus 152 CD8⁺/mm² cells on-treatment (right panel).

Orange = panCK (segmentation); green = CD8 (effector T cells); magenta = FoxP3 (regulatory T cells).