**Platinum**

### Background

- Tucatinib (ONT-993) is a HER2 selective small molecule pan-HER inhibitor with nanomolar binding affinities with receptor HER2 (K<sub>i</sub> = 11.0 ± 1.0 nM, IC<sub>50</sub> = 11.0 ± 1.0 nM) using a cell-based assay.

### Table/Figure 6. Tucatinib Pharmacokinetic (PK) parameters. Tucatinib was given orally at doses of 300 and 350 mg BID in combination with capecitabine on day 14 (red) and without capecitabine on day 21 (blue). AUC, area under the curve; C<sub>max</sub>, maximum concentration; C<sub>last</sub>, concentration at the last sampling time; CL/F, apparent oral clearance; C<sub>TAU</sub>, time at which AUC is equal to dose; CV%, coefficient of variation; F, bioavailability; GMR, geometric mean ratio; GMR<sub>90</sub>, 90% confidence interval lower limit; GMR<sub>95</sub>, 95% confidence interval lower limit; MRT, mean residence time; T<sub>1/2</sub>, terminal half-life; T<sub>max</sub>, time to peak concentration; V<sub>ss</sub>, apparent volume of distribution; t<sub>1/2</sub>, elimination half-life.

### Table/Figure 5. Effect on DPD activity by tucatinib, ONT-993 and Gimeracil. The table shows the mean percentage inhibition (% Inhibition) of DPD activity at 2 µM of test compounds. The positive control was tested in duplicate and tucatinib and ONT-993 were tested in triplicate. No remarkable inhibition of DPD was observed with either tucatinib or ONT-993.

### Summary and Conclusion

- **In Vivo DDI Results:**
  - Tucatinib did not significantly affect the activity of major enzymes involved in the metabolism of capcitabine or irinotecan.
  - Tucatinib did not have a significant effect on the activity of CYP450 mediated enzymes.
  - In vitro results suggested a low level of significant drug-drug interaction for the combination of tucatinib and capcitabine or irinotecan.

- **Clinical Pharmacokinetic Results:**
  - **Tucatinib:**
    - Tucatinib plasma concentration profiles are dose dependent.
    - Tucatinib levels were similar in both combinations with capecitabine and without capcitabine.
  - **Capcitabine:**
    - Capcitabine plasma concentration profiles did not change after adding tucatinib.

**Conclusions:**

- Capecitabine and tucatinib combination is safe and well tolerated.
- Tucatinib can be added to the current dose of capcitabine with no significant pharmacokinetic interaction.
- The safety data from this study supports the use of the triplet combination (capecitabine + tucatinib + capecitabine) for the pivotal trial HER2CLIMB (NCT02614794).

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**Tucatinib and ONT-993 Do Not Inhibit Thymidine Phosphorylase**

**Tucatinib and ONT-993 Do Not Inhibit Carboxylesterase**

**Tucatinib and ONT-993 Do Not Inhibit Cytidine Deaminase**

**Pharmacokinetic Parameters of Tucatinib**

**Pharmacokinetic Parameters of Capcitabine**

**Evaluation of Drug-Drug Interactions (DDI) Between Tucatinib and Capcitabine in Patients With Advanced HER2+ Metastatic Breast Cancer From a Phase 1b Study**

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