Exposure/Response Analysis of an Oral Multi-Node PI3K/AKT/mTOR Pathway Inhibitor Combination of Serabelisib and Sapanisertib

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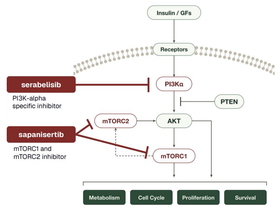
Background

The combination of serabelisib (PI3Kα inhibitor) and sapanisertib (dual mTORC1/mTORC2 inhibitor), known as PIKTOR, is currently in clinical development for multiple solid tumour types, including endometrial (Phase 2, NCT06463028) and breast cancer (Phase 1b/2, NCT07558733).

Whereas single-node inhibitors of the PI3K/AKT/mTOR pathway (such as alpelisib and capivasertib) are constrained by pathway feedback reactivation, resistance mutations, and treatment-induced hyperglycemia, multi-node inhibition approaches achieve more complete pathway inhibition, driving improved efficacy, while allowing reduced relative doses accompanied by lower rates of hyperglycemia (Tyrakis *et. al.,* 2025, Starks *et. al.,* 2022, PIK-201 data snapshot, gedatolisib prescribing information).

An intravenous multi-node PI3K/AKT/mTOR pathway inhibitor, gedatolisib, was recently approved by the FDA for breast cancer. Whilst gedatolisib displays the multi-node hallmarks of improved efficacy coupled with lower rates of hyperglycemia (versus single-node inhibitors), the mTOR related adverse event of stomatitis remains a clinical challenge (gedatolisib prescribing information).

Beyond the advantage of ease of administration, oral dosing offers several potential pharmacokinetic advantages versus other administration routes, including potential for sustained time above efficacy thresholds without excessive C_{max} peaks, which may contribute to on-target class related toxicities such as stomatitis. We sought to characterise the relationship between clinical exposure and efficacy / toxicity thresholds derived from preclinical and clinical data to support the recommended phase 2 dose / schedule (RP2D).



Schematic diagram illustrating simplified PI3K/AKT/mTOR pathway signaling and the multi-node mechanism of action of PIKTOR (serabelisib + sapanisertib)

Goals

Significant legacy pharmacokinetic (PK) data exists for serabelisib and sapanisertib as monotherapies covering a range of doses, dosing intervals, and dosing fasted or with food (Voss *et. al.,* 2020, Moore *et. al.,* 2018, Juric *et. al.,* 2017). However, up to now, there is a lack of published data on the *combined* dosing of serabelisib and sapanisertib at doses and schedules relevant to current clinical development.

The goal of this study is to summarise the PK-PD data most relevant to the current clinical development of PIKTOR, with a focus on:

- Combined dosing of sapanisertib and serabelisib
- RP2D for endometrial cancer: 3 mg sapanisertib + 200 mg serabelisib PO three consecutive days per week (QD3dQW)
- Dosing with food per Phase 1b/2 protocols
- Efficacy benchmarks generated in preclinical endometrial and HR+/HER2- breast cancer models and a human PK-PD study (NCT01899053)

This presentation focuses on milled sapanisertib, introduced after completion of the first in human Phase 1 study (NCT01058707 / Voss *et. al.,* 2020).

Methods

Building on monotherapy PK profiles, plasma exposure profiles were simulated for both agents. Exposures were compared against a panel of *in vitro* and *in vivo* efficacy and pharmacodynamic thresholds derived from cellular dose-response curves, xenograft tumour growth inhibition studies, and clinical data. The following studies have been used to compile this analysis:

NCT / Study no.	Phase	Summary	Paper where avilable
NCT01058707	Phase 1	First-in-human dose-escalation of single-agent sapanisertib across four schedules in advanced solid tumours	Voss *et. al.,* 2024
NCT01449370	Phase 1	First-in-human dose-escalation of single-agent serabelisib in advanced solid malignancies	Juric *et. al.,* 2017
NCT02412722	Phase 1	Milled sapanisertib QD/QW ± paclitaxel; food-effect and milled-vs-unmilled PK in solid tumours	Moore *et. al.,* 2018
NCT01899053	Phase 1b	Dose-escalation of sapanisertib + serabelisib combination; safety, PK, DDI, skin PD	NA
NCT03154294	Phase 1b	Sapanisertib + serabelisib + paclitaxel dose-escalation in heavily pretreated solid tumours	Starks *et. al., 2022*
FTH-SER-102	Phase 1	Serabelisib single-dose food-effect, two-way crossover in healthy subjects	NA
NCT06463028	Phase 2	PIKTOR + paclitaxel ± insulin-suppressing diet in advanced/recurrent endometrial cancer; recruiting	NA
NCT07558733	Phase 1b/2	PIKTOR + fulvestrant/other agents umbrella study in HR+/HER2– advanced breast cancer; recruiting	NA
NA	Preclinical	Sapanisertib + Serabelisib preclinical evaluation in endometrial and breast cancer models	Tyrakis *et. al., 2025*

Monotherapy PK

Figure 1. Monotherapy pharmacokinetics of sapanisertib and serabelisib

A. NCT02412722 (Moore *et. al.,* 2018) was an open-label phase I study in patients with advanced solid tumours, evaluating sapanisertib given once daily, once weekly, or three-days-weekly with paclitaxel. A QD run-in crossover assessed food effect and milled-versus-unmilled sapanisertib PK. Data shown for sapanisertib 4mg capsule given with food (n=19 patients). Absorption was rapid, with a geometric-mean terminal half-life of approximately 8h. Taking with food reduced peak concentration (C_{max}) by ~40%, but total exposure was essentially unchanged. Milled versus unmilled capsules were comparable when both were dosed fasted. Food therefore slowed the absorption rate without meaningfully reducing the overall extent of absorption.

B. A Phase 1 study evaluated the food effect on serabelisib pharmacokinetics in n=16 healthy subjects. Using an open-label, randomized, two-way crossover design with a 7-day washout, each subject received a single 200 mg oral dose (2 × 100 mg tablets) both fasted and after a meal. Fasted absorption was rapid, and the terminal half-life rose modestly when taking with food. In contrast to sapanisertib, taking with food increased total exposure by roughly 33–36%, while peak concentration was essentially unchanged.

Combination PK-PD Analysis in Human Subjects

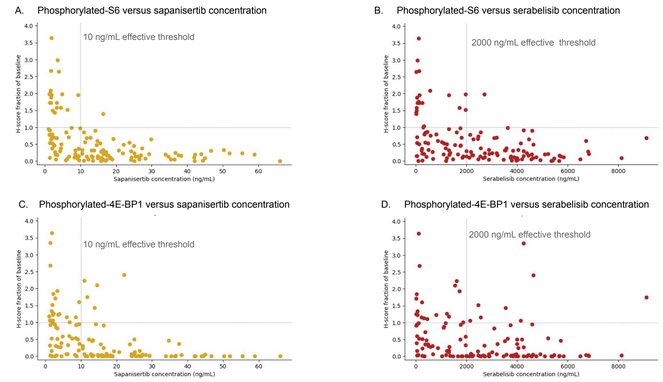


Figure 2. Pharmacokinetic-Pharmacodynamic (PK-PD) analysis of sapanisertib + serabelisib in human subjects.

A safety and pharmacokinetic study of sapanisertib in combination with serabelisib was done in adults with advanced nonhematologic malignancies (NCT01899053). This study paired serial plasma PK with skin-punch biopsies as the pharmacodynamic readout. Biopsies taken at baseline and at 2, 8, and 24 hours post-dose were immunohistochemically stained (H-score) for PI3K/mTOR pathway phosphoproteins, including the key PI3K/AKT/mTOR pathway downstream proteins 4E-BP1 and S6. Change from baseline of the H-score is plotted versus drug concentrations to characterize the exposure–response relationship for sapanisertib (A, C) and serabelisib (B, D). These plots provide estimated pharmacodynamically active thresholds for the concentration of each drug, i.e. 10 ng/mL for sapanisertib and 2000 ng/mL for serabelisib, above which PI3K/AKT/mTOR pathway signalling activity is effectively inhibited. Notably, the combination of sapanisertib + serabelisib inhibited *both* S6 and 4E-BP1 phosphorylation. Preclinical experiments have established that while single-node pathway inhibitors effectively inhibit S6 phosphorylation, they have limited ability to simultaneously inhibit 4E-BP1 phosphorylation. Whereas, multi-node inhibition potently inhibits both S6 and 4E-BP1 phosphorylation, a property which correlates with drug potency (IC_{50}) in cellular dose response assays (Tyrakis *et. al.,* 2025).

Combination Dose Selection Based on Human PK-PD

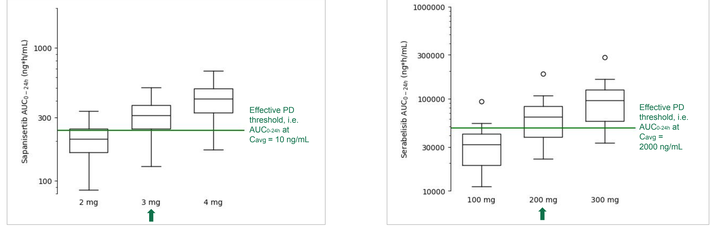


Figure 3. Dose selection based on estimated effective drug thresholds from human PK-PD data. PK data from the study described in Figure 2 was used to compare the exposure (AUC) for (A) sapanisertib at 2 mg, 3 mg and 4 mg doses, and (B) serabelisib at 100 mg, 200 mg and 300 mg doses with the AUCs determined in Figure 2 to be pharmacodynamically effective drug concentrations. The plots show that doses of 3 mg sapanisertib + 200 mg serabelisib represent to lowest doses where the mean AUC is above the effective drug threshold. This data suggests that these doses may provide drug exposures which combine effective on-target PI3K/AKT/mTOR pathway inhibition providing patients with pharmacodynamically effective drug exposures with the lowest risk of drug-related toxicities. 2 mg and 3 mg sapanisertib data are calculated from 4 mg data assuming dose linearity. 100 mg and 300 mg serabelisib data are calculated from 200 mg data assuming dose linearity. Box bottom = 1st quartile; box top = 3rd quartile; lower whisker = data within 1st quartile – 1.5*IQR; upper whisker = data within 3rd quartile + 1.5*IQR; solid line = median.

Combination PK vs. Human PD Thresholds

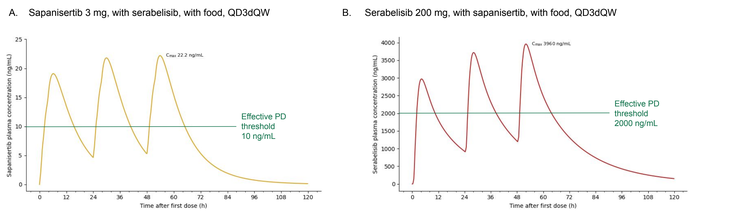
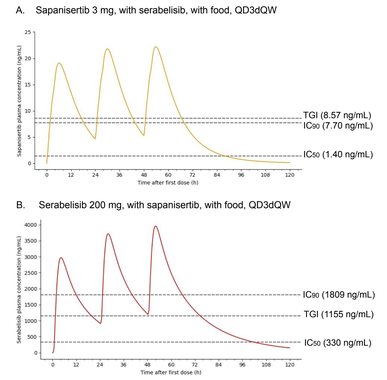


Figure 4. Endometrial cancer-RP2D pharmacokinetics versus human PK-PD thresholds. Based on monotherapy pharmacokinetics (Figure 1), and pharmacokinetic data derived from the combined dose PK-PD study (Figure 2), repeat dose PK simulations were performed for sapanisertib 3 mg + serabelisib 200 mg. In order to accurately simulate Phase 2 dosing the following factors were included in the simulations:

A. Sapanisertib 3 mg pharmacokinetics for QD3dQW dosing schedule, with food, was simulated based on monotherapy data presented in Figure 1A (NCT02412722), and was derived by linear scaling of sapanisertib from 4 mg to 3 mg and increased C_{max} and AUC due to a minor drug interaction with serabelisib: analysis of study NCT01899053 revealed serabelisib and sapanisertib given together produced a 22% increased C_{max} and 29% increased AUC for sapanisertib, with no change in PK for serabelisib. The ongoing Phase 1b/2 studies require dosing with food. A one-compartment model with lag was fitted to individual subject PK data, and using those parameters concentration-time profiles were generated for the QD3QW dosing schedule. Finally, individual concentration profiles were averaged to generate the overall mean concentration over time. Estimated time above 10 ng/mL threshold = 41.2 hours per week, 164.7 hours per 28-day cycle.

B. Serabelisib 200 mg pharmacokinetics for QD3dQW dosing schedule, with food, was simulated based on monotherapy data presented in Figure 1B (NCT02412722). A two-compartment model with lag was fitted to individual subject PK data, and using those parameters concentration-time profiles were generated for the 200 mg QD3QW dosing schedule. Finally, individual concentration profiles were averaged to generate the overall mean concentration over time. Estimated time above 2000 ng/mL threshold = 37.6 hours per week, 150.2 hours per 28-day cycle.

Combination PK vs. Preclinical Efficacy Thresholds



Sapanisertib

	Per week	Per 28-day cycle
Time above IC90 threshold (hours)	44.4	177.5
Time above IC50 threshold (hours)	77.6	310.4
Time above TGI threshold (hours)	43.4	173.6

Serabelisib

	Per week	Per 28-day cycle
Time above IC90 threshold (hours)	42.3	169.3
Time above IC50 threshold (hours)	94.8	379.0
Time above TGI threshold (hours)	62.8	251.0

Figure 5. Estimation of time-above preclinical efficacy thresholds at combined 3 mg sapanisertib + 200 mg serabelisib dose.

Pharmacokinetics of sapanisertib (A) and serabelisib (B) as derived for Figure 4 are shown with efficacy thresholds derived from preclinical experiments. Cellular IC_{50} and IC_{90} values were calculated using data presented in Tyrakis *et. al.,* 2025: IC_{50} threshold values are derived from an average of six cell lines representing clinically relevant models i.e. HR+/HER2- breast cancer cell lines and endometrial cancer cell lines (i.e. MCF7, T47D, AN3CA, HEC1B, MFE-280, MFE-296). IC_{50} and Hill slope values were derived from nonlinear regression of dose-response data fit to a four-parameter logistic (Hill) equation. IC_{90} values were calculated from the fitted IC_{50} and Hill slope according to the relationship $IC_{90} = IC_{50} \times [90/(100-90)]^{(1/HillSlope)}$. Cellular IC_{50}/IC_{90} values are not corrected for plasma protein binding; cellular assays were carried out in the presence of plasma protein (10% FBS) and both drugs have relatively low plasma protein binding (~70-80% plasma protein bound in human plasma). Note that PIKTOR is being evaluated in combination with other therapies (e.g. SERD and CDK4/6 inhibitors in breast cancer, and paclitaxel in endometrial cancer), combinations which may substantially lower IC_{50} and IC_{90} values. Tumour growth inhibition (TGI) thresholds were derived from mouse xenograft experiments using 0.5 mg/kg sapanisertib + 75 mg/kg serabelisib QD3dQW with human HR+/HER2- breast cancer xenograft models; MCF7 (*PIK3CA* mutant) and HCC1428 (*PIK3CA* wild-type), where sapanisertib + serabelisib (without other combination agents) produced TGI of >70% and >60% respectively after 8 weekly treatment cycles. TGI threshold values represent mouse $C_{avg(0\text{-}24h)}$ for 0.5 mg/kg sapanisertib and 75 mg/kg serabelisib in mice and are corrected for differences in mouse/human plasma protein binding.

Combination Dose Selection in Phase 1b Dose Escalation Study

A Phase 1b dose escalation study of sapanisertib + serabelisib + paclitaxel (NCT03154294, Starks *et. al.,* 2022) enrolled patients with advanced solid tumours, including patients with breast, ovarian and endometrial cancer (n=19) and used following combined doses administered without food:

1. Sapanisertib 2 mg QD3dQW + Serabelisb 100 mg QD3dQW + Paclitaxel 60 mg/m^2 QW (days 1, 8, 15)
2. Sapanisertib 2 mg QD3dQW + Serabelisb 200 mg QD3dQW + Paclitaxel 60 mg/m^2 QW (days 1, 8, 15)
3. Sapanisertib 2 mg QD3dQW + Serabelisb 200 mg QD3dQW + Paclitaxel 80 mg/m^2 QW (days 1, 8, 15)
4. **Sapanisertib 3 mg QD3dQW + Serabelisb 200 mg QD3dQW + Paclitaxel 80 mg/m^2 QW (days 1, 8, 15) → Dose selected for expansion cohort**
5. Sapanisertib 4 mg QD3dQW + Serabelisb 200 mg QD3dQW + Paclitaxel 80 mg/m^2 QW (days 1, 8, 15) → DLT (Hyperglycemia) reported in group 5

Of note the dose selected for the expansion cohort (sapanisertib 3 mg + serabelisib 200 mg QD3dQW) matches the combined dose selected following analysis of the human PK-PD study (Figure 3). This clinical trial also reported an encouraging clinical efficacy signal, as shown in table 1.

Table 1. Best response according to RECIST 1.1 (Starks *et. al.,* 2022, table 4)

N (%)	All Patients (n = 19)	Endometrioid Endometrial Cancer
Complete Response	3 (16%)	3 (60%)
Partial Response	4 (21%)	1 (20%)
Stable Disease	4 (21%)	0
Progressive Disease	4 (21%)	1 (20%)
Not evaluable	4 (21%)	0

Stomatitis Dose / Exposure Relationship

Sapanisertib Monotherapy; Phase 1, NCT01058707

In the first-in-human Phase 1 study of sapanisertib monotherapy, the on-target dose limiting toxicity of grade 3 stomatitis was observed (Voss *et. al.,* 2020), but only at higher doses than currently being used in clinical development.

That is, for cohorts that received QD doses of sapanisertib (i.e. either QD3dQW, QD5dQW, or QD7dQW) the DLT of Grade 3 stomatitis was observed at the following dose levels:

- ≥ 12 mg QD3dQW
- ≥ 10 mg QD5dQW
- ≥ 5 mg QD7dQW

For these QD regimens (i.e. excluding QW regimens, which are not currently being used in clinical development), when assessing correlation of various parameters (i.e. discrete daily dose, average daily dose, total weekly dose, weekly AUC, C_{max}) versus rates of grade 3 stomatitis, the most highly correlated factors were:

- Discrete daily dose (R^2 0.758)
- C_{max} (R^2 0.692)

Sapanisertib + Serabelisib; Phase 1b, Safety & PK Study NCT01899053

In a safety and PK Phase 1b study, combined doses ranging from 2-8 mg sapanisertib + 100-400 mg serabelisib were taken (fasted). Grade 3 stomatitis was observed at the following combined dose level:

- Sapanisertib 4 mg + Serabelisib 200 mg QD3dQW (consecutive days)

Across dose escalation (n=16) and dose expansion (n=20) cohorts, a total of n=36 subjects received this 4 mg / 200mg dose. In these n=36 subjects, rates of stomatitis were:
Any grade: 19.4% (n=7), grade 3: 2.8% (n=1), no cases of grade 4/5 stomatitis were reported.

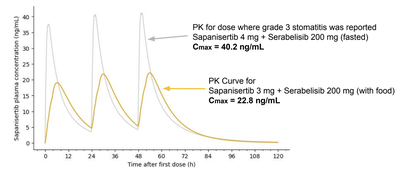


Figure 6. Simulated PK curves for sapanisertib 4 mg + serabelisib 200 mg (fasted) QD3dQW and sapanisertib 3 mg + Serabelisib 200 mg (with food) QD3dQW

Conclusions

We believe this integrated PK-PD approach supports the dose and schedule rationale for the PIKTOR combination endometrial cancer RP2D and provides a translational framework linking preclinical efficacy data to clinical exposure and PK-PD for an oral multi-node PI3K/AKT/mTOR pathway inhibitor approach.

Modeled plasma exposure for both agents exceeded efficacy and pharmacodynamic thresholds for a substantial proportion of each weekly and 28-day dosing cycle, supporting target coverage at the selected dose / regimen.

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