DIACCURATE

#4477

DIACC3010, optimized inhibitor of S6 kinase, combined with endocrine therapy, has potent antitumor activity in treatment-resistant ER+ HER2- metastatic breast cancer

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SCAN ME

ABSTRACT

Background: Ribosomal protein S6 kinase (S6K) is a key regulator of estrogen receptor (ER) function, and its high expression is associated with poor clinical outcomes in breast cancer (BC). Recent data have demonstrated that S6K is involved in resistance to CDK4/6 inhibitors in metastatic BC (MBC).

DIACC3010 (formerly M2698) is an oral brain-penetrant potent inhibitor of S6K. By design, DIACC3010 also selectively inhibits AKT1 and AKT3, while sparing AKT2. DIACC3010 was previously evaluated in a phase 1 trial (NCT01971515). We performed exploratory correlative analyses of the phase 1 trial in ER+ HER2-negative MBC patients in addition to nonclinical experiments to evaluate its role in the CDK4/6 and endocrine therapy (ET) resistant setting.

Methods: DIACC3010 was evaluated as monotherapy, or combined with either trastuzumab or tamoxifen, in a multicenter phase 1 trial that accrued 101 patients with advanced/refractory solid tumors (1). The current analysis focused on patients with ER+ HER2-negative MBC and aimed to explore the efficacy of DIACC3010 according to *ESR1* mutational status. DIACC3010 was also evaluated patient-derived xenograft (PDX) mouse models, in monotherapy and combined with tamoxifen or palbociclib, and in xenograft models alone and in combination with elacestrant or abemaciclib.

Results: Twenty patients were evaluable at baseline for their tumor mutational status and included in the analysis. Median age was 60 years and median number of prior lines of therapy was 5.5. Twelve of 20 (60%) patients had received prior treatment with CDK4/6 inhibitors. Nine of 20 patients (45%) had *ESR1* mutations, of whom 4 had received CDK4/6 inhibitor. Median progression free survival was 5.6 months in patients with *ESR1* mutations, and 2.6 months in patients with *ESR1* wild-type tumors.

Among the 13 ER+ BC PDX models evaluated, 12 provided interpretable results. The combination of DIACC3010 with tamoxifen or palbociclib induced respectively 10/12 (83%) and 11/12 (92%) significant tumor growth control in PDX models, of which 42% were resistant to tamoxifen and 50% were resistant to palbociclib.

The combination of DIACC3010 with elacestrant or abemaciclib induced respectively 77% and 75% significant tumor growth control in MCF7 xenograft model.

Furthermore, DIACC3010 monotherapy resulted in significant tumor growth control in 3/5 (60%) of the tamoxifen-resistant PDX models and 5/6 (83%) of the Palbociclib-resistant PDX models.

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INTRODUCTION

Clinical evidence suggests that inhibiting the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) (PAM) signaling pathway is beneficial for the treatment of solid tumors.

The PAM pathway plays a significant role in endocrine resistance of breast cancer.

Currently, there are two products targeting this pathway approved for the treatment of metastatic breast cancer: everolimus combined with exemestane, a rapamycin analog and inhibitor of mTOR; and alpelisib, combined with fulvestrant, an α-selective PI3K inhibitor, approved only for patients with *PI3KCA* mutations.

DIACC3010 was designed with a unique PAM pathway inhibition profile:

- Spares AKT2, to improve safety;
- Potently blocks S6K to control the negative feedback loop

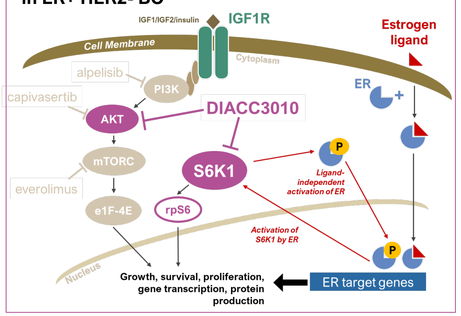
Table 1: DIACC3010 kinase inhibitory profile

Kinase	IC_{50}	Inhibition
AKT1	1.4 nM	✓
AKT2	80 nM	X
AKT3	1 nM	✓
S6K	0.9 nM	✓

S6K is a master regulator of multiple oncogenic pathways, including PAM. It is overexpressed in tumors and associated with poor prognosis (2).

Estrogen-independent activation of ER is tightly controlled by S6K (3). In addition, S6K has been recently associated with resistance to CDK4/6 inhibition (4).

Figure 1: S6K blocks 2 resistance mechanisms in ER+ HER2- BC



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RESULTS

Association between *ESR1* mutational status and clinical response to DIACC3010

Patients (N = 101) with advanced relapsed/refractory metastatic solid tumors were enrolled in a large **Phase 1 trial** (1).

The trial comprised DIACC3010 dose-escalation in monotherapy followed by multiple cohort expansions (1).

The current analysis focuses on the combination cohort of DIACC3010 and tamoxifen in refractory ER+ HER2- metastatic breast cancer.

Prior anticancer therapies included palbociclib, everolimus, fulvestrant and other endocrine therapies.

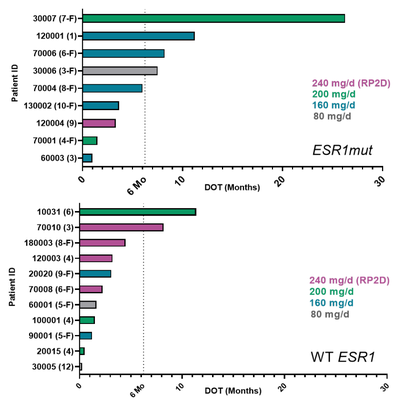
Table 2: Median patient number of prior anticancer therapies (N) and progression-free survival (PFS) per *ESR1* mutational status

	N	PFS (Months)
***ESR1*-mut** (n=9)	6	5.6
WT *ESR1* (n=11)	5	2.6
All (n=20)	5.5	3.9

Twenty patients were evaluable for genomic alterations: 9 patients had detectable *ESR1* mutations at study entry (circulating tumor DNA assessment Guardant360 Assay).

Patients with *ESR1* mutations had median progression free survival of 5.6 months compared to 2.6 months in patients with *ESR1* WT tumors

Figure 2: Individual clinical outcome (durations of treatment, DOT) of patients treated in the Phase 1, per *ESR1* mutations status



DIACC3010 has potent anti-tumoral efficacy in ER+ HER2- breast cancer PDX models

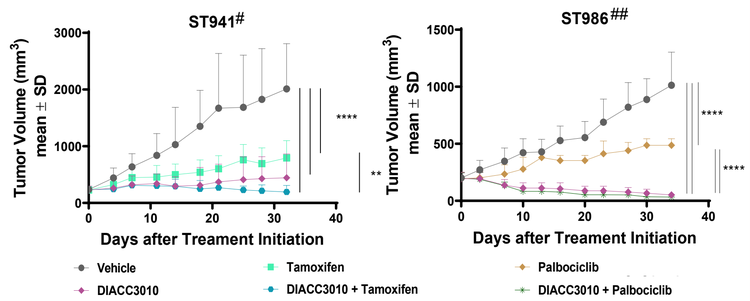
DIACC3010 alone and in combination with **tamoxifen** or **palbociclib** was tested in a panel of **12 breast cancer Patient-Derived Xenograft (PDX)** models.

Six- to 12-week-old female athymic Nude mice (n=4 mice per group) were implanted subcutaneously (SC) with 70 mg tumor fragment.

Dosing regimen, with all drugs administered per os (PO) and daily were:
- DIACC3010 25 mg/kg & tamoxifen 3 mg/kg, n=10 models (#)
- DIACC3010 25 mg/kg & tamoxifen 5 mg/kg, n=2 models
- DIACC3010 30 mg/kg & tamoxifen 1 mg/kg, n=1 model
- DIACC3010 25 mg/kg & palbociclib 40 mg/kg, n=9 models
- DIACC3010 25 mg/kg & palbociclib 75 mg/kg, n=3 models
- DIACC3010 30 mg/kg & palbociclib 75 mg/kg, n=1 model (##)

Five out of 12 PDX models were found resistant to tamoxifen (42%) and 6 were found resistant to palbociclib (50%) (both drugs had no anti-tumor activity as compared to vehicle).

Figure 3: Representative examples of PDX models treated and with DIACC3010 ± tamoxifen (model ST941) or with DIACC3010 ± Palbociclib (model ST986)



Statistical analysis: 2-way ANOVA; Tukey's multiple comparison test. **** p<0.0001 ** p<0.001

DIACC3010 induces significant tumor growth control in more than 83% of tested PDX models.
DIACC3010 has antitumor activity in 60% of tamoxifen-resistant models and in 83% of palbociclib-resistant models.

DIACC3010 has potent anti-tumoral efficacy in MCF7 breast cancer xenograft model

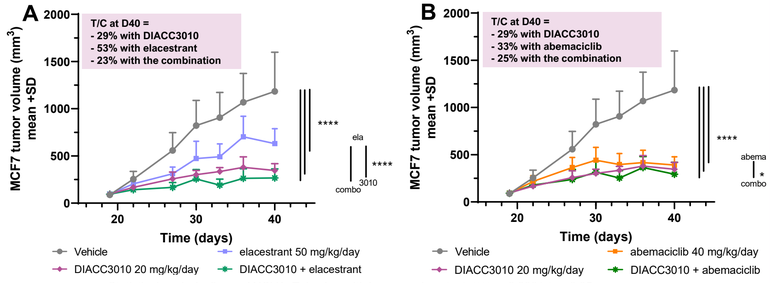
DIACC3010 alone and in combination with **elacestrant** or **abemaciclib** were tested in MCF7 **human breast cancer** (ATCC purchased) **xenograft in Nude mice.**

D-1: Mice were implanted with 0.18 mg b-estradiol containing pellets.
D0: mice were injected with 5.10^6 cells in 200 µl PBS:Matrigel (50:50).

Treatments started on D19 (tumor vol. ~100 mm^3) with all drugs administered PO once daily for 21 days (n=8 mice/group), with the doses presented in Fig. 4.

DIACC3010 induced 71% MCF7 tumor growth inhibition as compared to vehicle, more potently than elacestrant (47%) (Fig. 4.A) and as efficiently as abemaciclib (67%) (Fig. 4.B).

Figure 4: Representative examples of MCF7 models treated with DIACC3010 ± elacestrant (A) or with DIACC3010 ± abemaciclib (B)



Statistical analysis: 2-way ANOVA; Tukey's multiple comparison test. **** p<0.0001 * p<0.05

Both combinations of DIACC3010 to elacestrant and to abemaciclib provided significant tumor growth inhibition (77% and 75%, respectively, as compared to the control group).

CONCLUSIONS

These exploratory analyses from the phase 1 trial, along with nonclinical efficacy in monotherapy and in combination with standard treatments in various models of breast cancer, support further clinical development of DIACC3010 in ER+ HER2- metastatic breast cancer.

A randomized Phase 2/3 study in combination with endocrine therapy will be conducted in the near future.