Phase 1 study of GR antagonist mifepristone in combination with eribulin in advanced solid tumors, with dose expansion in patients with GR-positive triple-negative breast cancer (TNBC)

Sharon T. Wilks[1], Manuel Modiano[2], Alexander Spira[3], Carlos Becerra[4], Fadi Braiteh[5], Hyo Han[6], Elisavet Paplomata[7], Timothy Pluard[8], Donald Richards[9], Joyce O'Shaughnessy[4], Jackie Walling[10], Dat Nguyen[11], Gabrielle M. Baker[12], Suzanne D. Conzen[12], Rita Nanda[12]

INTRODUCTION

- The glucocorticoid receptor (**GR**) is highly expressed in TNBC[1]
  - Data suggest significant GR expression as defined by >10% IHC positivity in >80% of TNBC single-tissue samples (data on file, Corcept)
- High expression of GR mRNA is associated with a significantly shorter relapse-free survival in patients with estrogen receptor (**ER**) negative early-stage breast cancer[2]
- Mifepristone (**MIFE**, Korlym®, Corcept Therapeutics), a GR antagonist, has been shown to increase the cytotoxic effects of concomitant chemotherapy in both preclinical in-vitro and in-vivo models of GR-positive TNBC[1]
- Early clinical study of MIFE plus nab-paclitaxel in advanced TNBC shows encouraging activity in patients with GR-positive tumors[4]
- We hypothesized that GR antagonism with MIFE in combination with eribulin (**E**) would be a regimen with low propensity for a drug-drug interaction and would enhance cytotoxicity in TNBC

OBJECTIVES

- **Primary**: Establish maximum tolerated dose (**MTD**) and recommended phase 2 dose (**RP2D**) of MIFE in combination with E
- **Secondary**: Characterize safety and pharmacokinetics; obtain preliminary antitumor activity in a cohort of patients with GR-positive metastatic TNBC

STUDY DESIGN

- **Phase 1**: Standard 3 + 3 dose escalation in patients with solid tumors to establish MTD/RP2D
- **Phase 2**: Dose expansion at MTD/RP2D in a 20-patient GR-positive TNBC cohort
- Following 7-day lead-in of MIFE alone, MIFE given daily in combination with E administered intravenously on days 1 and 8 of a 21-day cycle
- Dose limiting toxicity (**DLT**) assessed in first 28-cycle

PATIENT ELIGIBILITY

Key inclusion criteria:

- Consented patients, ≥18 years of age, ECOG -PS ≤1 (Eastern Cooperative Oncology Group Performance Status)
- Phase 1 Dose Escalation tumor types: breast cancer
- Phase 2 Dose Expansion cohort:
  - TNBC (< 1% cells positive for ER/progesterone receptor, and HER2 IHC score of 0/1, or FISH HER2+ ratio of less than 1.8)
  - ≥1 – 5 prior chemotherapy regimens for metastatic or locally advanced tumor
  - Tumor must be GR-positive TNBC (≥10% positive cells by IHC)
  - Assays performed by U. Chicago & QualTek

Table 1. Patient Characteristics

	Phase 1 Dose Escalation n=16	Phase 2 TNBC Expansion n=12	Overall N=28
Gender (F)	16	12	28
Median age (range)	56 (42-79)	57 (44-81)	56 (42-81)
ECOG-PS			
0	8	6	14 (50%)
1	8	6	14 (50%)
Indication			
Breast/TNBC	16/4	12/12	28/16
Median time from initial diagnosis (months)	64	34.5	41
Median # of prior chemotherapy (range)	3 (2-4)	2 (1-5)	2 (1-5)
Prior chemotherapy			
Anthracycline	11	7	18 (64%)
Taxanes	16	11	27 (96%)
Carboplatin	6	8	14 (50%)
Eribulin	2	2	4 (14%)
GR IHC*			
Positive	11 (69%)	11 (92%)	22 (79%)
Negative	2	0	2
Unknown	3	1	4

ECOG-PS=Eastern Cooperative Oncology Group Performance Status
*During screening, 33/40 breast cancer and 27/28 TNBC patients were IHC GR-positive

RESULTS

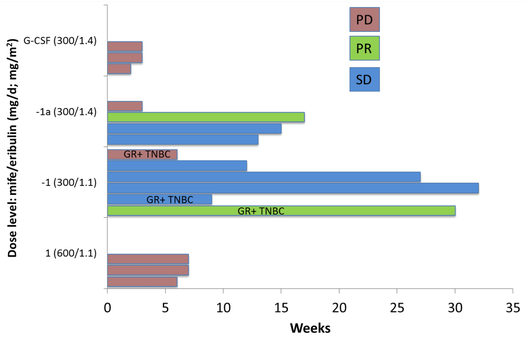
Phase 1 Dose-Escalation

- Included 16 patients with breast cancer (Table 1)
  - 4/16 had TNBC, of whom 3 were GR-positive
- The MTD/RP2D was established to be mifepristone 300 mg/d + eribulin 1.1 mg/m^2 with no DLTs (Table 2)

Adverse Events

- Majority of AEs were disease-related & of mild or moderate severity (Table 3)
- No patient experienced a drug-related SAE
- Brisk recovery from dose-limiting neutropenia with growth-factor support

Figure 1. Phase 1: Dose Escalation



Pharmacokinetics

- Comparison of eribulin PK to that reported in the literature showed no impact of mifepristone on eribulin pharmacokinetics
- No major difference in MIFE exposure at 300 mg in combination with either eribulin dose level 1.1 or 1.4 mg/m^2 (Figure 3)

Table 2. Phase 1: Dose-Escalation and MTD/RP2D (N=16)

Dose (MIFE/E [mg/d; mg/m^2])	N	Median Duration (Wks)	# of DLTs	Response
600/1.1	3	6.9 (6-7)	**2:** G3/4 neutropenia (2nd E infusion omitted)	3 PD
300/1.1 (Selected as MTP/RP2D)	6	18.5 (6-32)	0	1 PR 4 SD 1 PD
300/1.4	4	13 (3-18)	**2:** G4 neutropenia (2nd E infusion omitted)	1 PR 2 SD 1 PD
300/1.4 + G-CSF	3	2 (1-2)	**2:** G4 neutropenia (2nd E infusion omitted)	3 PD

PR= Partial Response; SD=Stable Disease; PD=Progressive Disease
G-CSF=Granulocyte-Colony Stimulating Factor

Table 3. Most Common Adverse Events (N=26)*

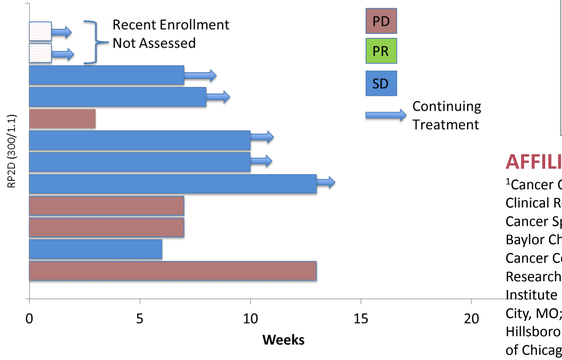
	Number of Patients				
Adverse Events	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All Grades**
Neutropenia	0	0	9	10	19
Fatigue	5	5	4	0	14
Hypokalemia	6	2	3	0	11
Nausea	7	4	1	0	12
Alopecia	7	2	0	0	9
Neuropathy	5	1	2	0	8

Additional grade 3 drug-related AEs: febrile neutropenia (1); hypomagnesemia (1); onycholysis (1)
* Two recently enrolled patients were not included

Phase 2 Dose Expansion in TNBC

- Recruitment is ongoing, preliminary results presented below (Figure 2)

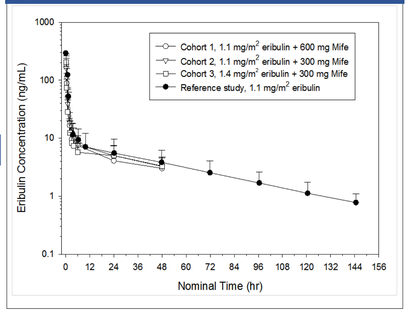
Figure 2. Phase 2: GR-Positive TNBC Patients Treated with R2PD



OVERALL CONCLUSIONS

- The combination of mifepristone and eribulin is well tolerated and appears to be an active treatment regimen
- RP2D is 300 mg mifepristone daily, 1.1 mg/m^2 eribulin days 1, 8 every 21 days
- Dose-limiting toxicity is neutropenia with the majority of AEs being disease-related and of mild or moderate severity
- Pharmacokinetics of both agents were unaltered
- Out of 15 GR-positive TNBC patients treated with 300 mg MIFE + 1.1 mg/m^2 eribulin: 1 PR, 7 SD, 5 PD, 2 not yet assessed
- The study is ongoing

Figure 3. Pharmacokinetic Profile of Eribulin



AFFILIATIONS

[1]Cancer Care Centers of South Texas, San Antonio, TX; [2]ACRC/Arizona Clinical Research Center and Arizona Oncology, Tucson, AZ; [3]Virginia Cancer Specialists Research Institute, Fairfax, VA; [4]Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX; [5]Comprehensive Cancer Center of Nevada, Las Vegas, NV; [6]Moffitt Cancer Center & Research Institute, Tampa , FL; [7]Emory University Winship Cancer Institute Midtown, Atlanta, GA; [8]Saint Luke's Cancer Institute, Kansas City, MO; [9]Texas Oncology-Tyler, Tyler, TX; [10]JW Consulting, Hillsborough, CA; [11]Corcept Therapeutics, Menlo Park, CA; [12]University of Chicago Medicine Chicago, IL

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