Phase II study of Eribulin in Combination with Gemcitabine for Triple Negative Breast Cancer. ERIGE Trial on behalf of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC)

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Background: There are no well-established chemotherapy regimens for metastatic triple negative breast cancer. The combination of a microtubule inhibitor (eribulin) with a nucleoside analog (gemcitabine) may synergistically induce tumor cell death, especially in tumors like triple negative breast cancers (TNBC) characterized by high cell proliferation, aggressive tumor behavior, and chemo-resistance.

Methods: This is an open-label, national multicenter phase II study evaluating the combination of eribulin (0.88 mg/m^2) plus gemcitabine (1000 mg/m^2) on day 1 and 8, q21 as either first- or second-line treatment of locally advanced or metastatic TNBC. The primary endpoint was the objective response rate (ORR) for evaluable patients (pts). The study was designed according to the Simon's two stage optimal design. We chose the lower activity (p^0) of 0.20 and target activity level (p^1) of 0.35. A prospective, molecular correlative study has been being carried out on germinal DNA of study population to assess the role of BRCA mutations and DNA polymorphisms in predicting efficacy and toxicity of the combination regimen.

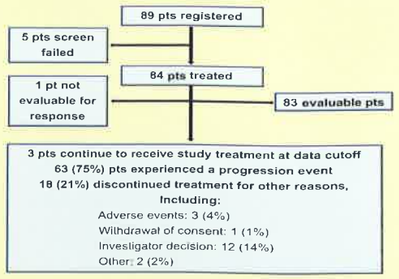
Results: From July 2013 to September 2016, 83 evaluable pts (37 in the first stage, 46 in the second one) were enrolled. They received a median number of 6 cycles of treatment (range 1-24). The ORR (CR+PR) was 37.35% (90% CI: 28.47-46.93) and the clinical benefit rate (CR+PR+SD ≥ 24 wks) was 48.78% (90% CI: 39.24%-58.39%). The most common grade 3-4 adverse events (> 10% of patients) were neutropenia and liver toxicity. With a median follow-up of 20.1 months, the median progression-free survival (PFS) and overall survival (OS) were 5.1 months (95% CI: 4.1-6.4) and 14.8 months (95% CI: 10.6-20.1), respectively. BRCA1/2 deleterious mutations were observed in 15 (22%) out of 68 genotyped pts. Women with BRCA1/2 mutations were associated with worse ORR, PFS and OS than those with BRCA1/2 wild-type.

Baseline Characteristics

Parameter	Evaluable Population (total, n = 83) n (%)
Age (years)	
Median	56
Range	23-81
BRCA1/2 mutational status	
Pathogenic mutation	15 (18)
Wild type	53 (64)
Missing/VUS	15 (18)
ECOG performance status	
0	74 (89)
1	9 (11)
Prior (neo)adjuvant therapy	
Anthracycline	60 (72)
Taxane	48 (58)
Prior lines of chemotherapy for metastatic disease	
0	66 (80)
1	17 (20)
Sites of metastatic disease	
1 site	11 (13)
≥ 2	73 (87)
Bone and visceral	23 (27)
Visceral only	61 (73)
Brain	7 (8)

VUS, variant of unknown significance

Patient Disposition



Dose Modification Related to Study Drugs

Parameter	Safety Population (total, n = 84) n (%)
Treatment delay	60 (71)
Eribulin dose reduction	52 (62)
Eribulin dose omission	41 (49)
Gemcitabine dose reduction	49 (58)
Gemcitabine dose omission	52 (62)
Missing	0

Adverse Events in>10% of pts

	Grade 1 – 2 n (%)	Grade 3 – 4 n (%)
Anemia	35 (42)	1 (1)
Neutropenia	30 (36)	20 (24)
Thrombocytopenia	24 (29)	2 (2)
Fatigue	51 (61)	5 (6)
Nausea	30 (36)	1 (1)
Vomiting	9 (11)	1 (1)
AST/ALT elevation	28 (33)	21 (25)
Fever without neutropenia	29 (35)	0
Alopecia	17 (20)	3 (4)
Diarrhea	16 (19)	0
Constipation	14 (17)	1 (1)
Rash	10 (12)	2 (2)
Peripheral neuropathy	10 (12)	1 (1)
Mucositis/stomatitis	9 (11)	0

Safety population includes all patients (n=84) who received at least 1 dose of study drugs

Efficacy Results

Best response	Evaluable Population (total, n = 83) n (%)
Complete response (CR)	2 (2)
Partial response (PR)	29 (35)
Stable disease (SD) ≥ 24 wks	9 (11)
SD < 24 wks	19 (23)
Progressive disease (PD)	20 (24)
Not assessed	3 (4)
Missing value	1 (1)

Objective Response Rate (ORR)

Overall responses	Total	Percentage	90% CI
31	83	37.35%	28.47%-46.93%

Clinical Benefit Rate (CBR)

Clinical benefit	Total	Percentage	90% CI
40	82	48.78%	39.24%-58.39%

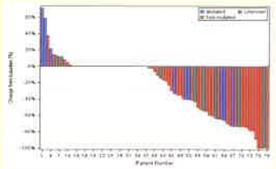
ORR: CR + PR; CBR: CR + PR + SD ≥ 24 wks

Progression-free Survival by BRCA Status

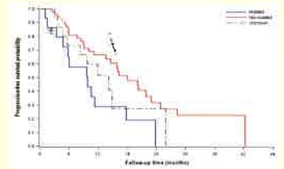
Efficacy Results by BRCA Status

Best response	BRCA-negative (total, n = 53) n (%)	BRCA-positive (total, n = 15) n (%)	Total Genotyped (total, n = 68) n (%)
Complete response (CR)	1 (2)	0	1 (1)
Partial response (PR)	21 (40)	4 (27)	25 (37)
Stable disease (SD) ≥ 24 wks	8 (15)	0	8 (12)
SD < 24 wks	11 (21)	3 (20)	14 (21)
Progressive disease (PD)	9 (17)	7 (47)	16 (24)
Not assessed	2 (3)	1 (6)	3 (4)
Missing value	1 (2)	0	1 (1)

Best Change from Baseline Target Lesions



Overall Survival by BRCA Status



Conclusions

- The combination of eribulin and gemcitabine shows promising activity and a moderate toxicity profile in metastatic TNBC.
- According to previously reported data, in our cohort of pts with metastatic TNBC (unselected for family history) the BRCA1/2 mutation rate was 22%.
- ORR, PFS and OS were systematically worse for BRCA1/2 mutation carriers in comparison with BRCA1/2 wild-type.
- Correlative analyses of DNA polymorphisms and eribulin plus gemcitabine benefit /toxicity are ongoing.
- La combinazione di un inibitore dei microtubuli (eribulina) con un analogo dei nucleosidi (gemcitabina) ha un accettabile profilo di tossicità e una promettente attività clinica, specialmente nei tumori triplo-negativi con assenza di mutazione per BRCA e conseguente adeguata capacità di riparazione del DNA.

Sponsorship

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