Phase 1b/2a clinical trial of the oral BET inhibitor PLX2853 as monotherapy for ARID1A mutated gynecologic cancers and in combination with carboplatin for platinum resistant ovarian cancer

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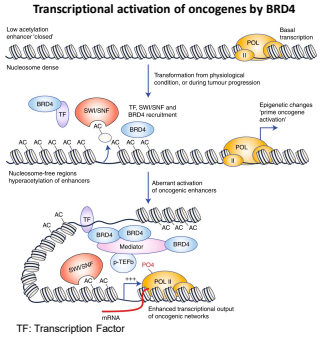
Background

- The aberrant regulation of epigenetic processes has emerged as a common feature underlying many malignancies, with epigenetic regulation of gene expression impacting both the initiation and maintenance of these malignancies.
- The Bromodomain and Extra-Terminal (BET) Domain proteins facilitate the development of many types of human neoplasms by serving as the epigenetic regulators of genes essential for tumor growth and survival.
- It was recently shown that loss of ARID1A sensitizes most ovarian cancer (OC) to BET inhibition. 30-60% of clear cell and endometroid OC and endometrial carcinomas (EC) have ARID1A mutations.
- **PLX2853** is an orally active, small molecule inhibitor of BET bromodomain-mediated interactions that exhibits low nanomolar potency in blocking all 4 BET family members (BRD2, BRD3, BRD4, and BRDT).

Transcriptional activation of oncogenes by BRD4



TF: Transcription Factor

From Shorstovam Foulkes, Witcher, Br J Ca, March, 2021

Methods and Trial Design

A multicenter, open-label, study with two parallel arms

Arms

- Phase 2a study of PLX2853 *monotherapy* in advanced gynecological malignancies with a known pathogenic ARID1A mutation
- Phase 1b/2a *combination* study of PLX2853 plus carboplatin in platinum resistant OC

Eligibility

Inclusion Criteria

Measurable disease by RECIST v1.1
No limit on lines of prior therapy
Refractory or resistant to standard therapies
Willing and amenable to sequential tumor biopsy
Adequate BM, renal, hepatic and thyroid function
ECOG 0 or 1

Exclusion Criteria

Use of strong inhibitors and inducers of CYP3A4 and 2C8
Inability to tolerate oral meds or significant malabsorption
Platinum sensitive OC

Treatment

- Included safety lead-in of 6 patients **PLX-2853** at **80 mg orally daily**
- Phase 1b dose escalation in standard 3+3 design
  Phase 2a expansion at **80mg daily**
  PLX2853 + Carboplatin q21 days at SOC dosing

Patient Demographics

Characteristic	Phase 2a Monotherapy (N=14) n (%)	Phase 1b/2a Combination (N=23) n (%)	Total (N=37) n (%)
Age			
<65 years	10 (71.4)	14 (60.9)	24 (64.9)
≥65 years	4 (28.6)	9 (39.1)	13 (35.1)
Ethnicity			
Hispanic or Latino	3 (21.4)	0	3 (8.1)
Not Hispanic or Latino	9 (64.3)	21 (91.3)	30 (81.1)
Unknown	2 (14.3)	2 (8.7)	4 (10.8)
Race			
Asian	0	3 (13.0)	3 (8.1)
Black or African American	0	4 (17.4)	4 (10.8)
White	11 (78.6)	16 (69.6)	27 (73.0)
Other or Unknown	3 (21.4)	0	3 (8.1)
Disease site and histology			
Ovarian carcinoma (ovary, fallopian tube carcinoma, peritoneum)			
High grade serous	2 (14.3)	17 (73.9)	19 (51.4)
Clear cell	4 (28.6)	2 (8.7)	6 (16.2)
Endometrioid	1 (7.1)	2 (8.7)	3 (8.1)
Mullerian origin	0	2 (8.7)	2 (5.4)
Mixed clear cell/endometrioid	1 (7.1)	0	1 (2.7)
Endometrial primary			
Clear cell			
Carcinosarcoma			
High grade serous			
Poorly differentiated carcinoma			
Cervical poorly differentiated squamous			
Eastern Cooperative Oncology Group Per			
0 - Full Active			
1 - Restricted in Physically Strenuous Activity			
Prior # Systemic Cancer Therapies			
Median	4	4	4
Range	1 – 9	1 – 9	1 – 9

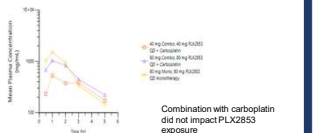
Phase IIa Study of PLX2853 in Gynecologic Cancers With Known ARID1A Mutation and Phase Ib/IIa Study of PLX2853/Carboplatin in Platinum-Resistant Epithelial Ovarian Cancer

Duska et al.
Published online: October 5, 2023
Abstract | Full Text | PDF (738 KB) | Supplemental Material

Treatment Toxicities

Parameter, n (%)	Phase 2a Monotherapy (N=14) n (%)	Phase 1b/2a Combination (N=23) n (%)	Total (N = 37) n (%)
Safety Summary			
Any TEAE	14 (100)	23 (100)	37 (100)
Grade ≥3 TEAE	8 (57.1)	16 (69.6)	24 (64.9)
Any PLX2853-related TEAE	14 (100)	23 (100)	37 (100)
Grade ≥3 PLX2853-related TEAE	7 (50.0)	16 (69.6)	23 (62.2)
Treatment-related SAE	2 (14.3)	2 (8.7)	4 (10.8)
Any PLX2853-related TEAE leading to discontinuation	0	1 (4.3)	1 (4.3)
PLX2853-related TEAE leading to death	0	0	0
Any-grade PLX2853-related TEAE in >10% of patients			
Nausea	9 (64.3)	15 (65.2)	24 (67.7)
Thrombocytopenia and/or platelet count decreased	4 (28.6)	18 (78.3)	22 (59.5)
Fatigue	7 (50.0)	13 (56.5)	20 (54.1)
Vomiting	4 (28.6)	7 (30.4)	11 (29.7)
Anaemia	5 (35.7)	6 (26.1)	11 (29.7)
Diarrhoea	3 (21.4)	7 (30.4)	10 (27.0)
Hyperglycaemia	4 (28.6)	4 (17.4)	8 (21.6)
Decreased appetite	1 (7.1)	6 (26.1)	7 (18.9)
Hyponatraemia	1 (7.1)	5 (21.7)	6 (16.2)
Aspartate aminotransferase increased	2 (14.3)	3 (13.0)	5 (13.5)
Headache	1 (7.1)	4 (17.4)	5 (13.5)
Alanine aminotransferase increased	2 (14.3)	3 (13.0)	5 (13.5)
White blood cell count decreased and/or leukopenia	0	5 (21.7)	5 (13.5)
Dysgeusia	1 (7.1)	3 (13.0)	4 (10.8)
Epistaxis	1 (7.1)	3 (13.0)	4 (10.8)
Dehydration	0	4 (17.4)	4 (10.8)
Constipation	0	4 (17.4)	4 (10.8)
Hyperbilirubinaemia and/or blood bilirubin increased	2 (14.3)	2 (8.7)	4 (10.8)
Lymphocyte count decreased and/or lymphopenia	2 (14.3)	2 (8.7)	4 (10.8)
Dyspnoea	0	3 (13.0)	3 (8.1)
Neutrophil count decreased	0	3 (13.0)	3 (8.1)
Gastroesophageal reflux disease	2 (14.3)	0	2 (5.4)
Grade ≥3 PLX2853-related TEAE that occurred in ≥2 patients			
Thrombocytopenia and/or platelet count decreased	2 (14.3)	11 (47.8)	13 (35.1)
Anemia	3 (21.4)	1 (4.3)	4 (10.8)
Fatigue	2 (14.3)	0	2 (5.4)
White blood cell count decreased	2 (14.3)	2 (8.7)	4 (10.8)

Plasma concentration-time profile following 40 to 80 mg/day PLX2853 QD in combination with carboplatin or 80 mg/day PLX2853 QD monotherapy



Combination with carboplatin did not impact PLX2853 exposure

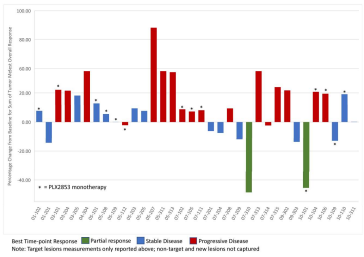
Driver Mutations Present

	Phase 2a Monotherapy (N=14) n (%)	Phase 1b/2a Combination (N=23) n (%)	Total (N=37) n (%)
		12 (52.2)	12 (32.4)
	100)	4 (17.4)	18 (48.6)
		7 (30.4)	7 (18.9)
BRCA1			
Wildtype	8 (57.1)	9 (39.1)	17 (45.9)
Pathogenic Variant	2 (14.3)	2 (8.7)	4 (10.8)
Unknown	4 (28.6)	12 (52.2)	16 (43.2)
BRCA2			
Wildtype	8 (57.1)	12 (52.2)	20 (54.1)
Unknown	6 (42.9)	11 (47.8)	17 (45.9)
TP53			
Wildtype	10 (71.4)	10 (43.5)	20 (54.1)
Pathogenic variant	4 (28.6)	13 (56.6)	17 (45.9)
ATM Pathogenic Variant	1 (7.1)	1 (4.3)	2 (5.4)
PIK3CA Pathogenic Variant	6 (28.6)	1 (4.3)	7 (18.9)

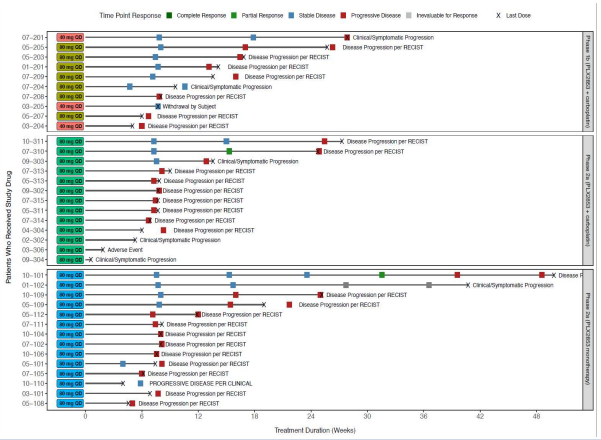
Best Response in Evaluable Subjects

	Total Evaluable	PR	SD	PD
PLX2853 monotherapy	14	1 (7.1%)	5 (35.7%)	8 (57.1%)
PLX2853 + carboplatin	20	1 (5.0%)	9 (45%)	10 (50%)

Waterfall Plot of Evaluable Subjects



Swimmer Lane Plot of all Evaluable Patients



Conclusions

- Results did not meet the pre-specified response criteria for evidence of clinical activity
- This larger cohort of gynecologic cancer patients confirmed the safety profile of the agent and demonstrated the feasibility of combination with carboplatin at full monotherapy dosing of PLX2853 (80mg daily)
- These data provide rationale for further exploration of BET inhibitors in patients with ARID1A-mutated gynecologic malignancies, possibly in combination with agents targeting potential feedback mechanisms such as the PI3K pathway