485P Correlation of clinical, genomic and hematological parameters with ATR inhibitor (ATRi) outcomes in phase I/II clinical trials

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Background

- ATR inhibition is an emerging strategy in tumors harboring elevated replicative stress (**Fig 1**).

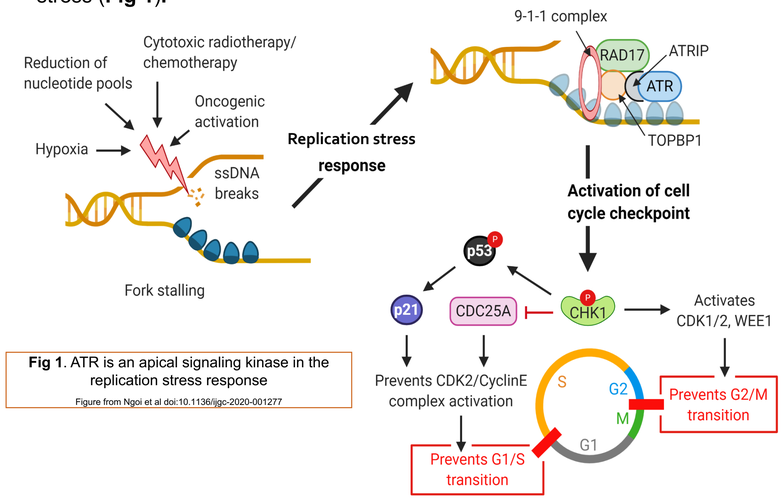


Fig 1. ATR is an apical signaling kinase in the replication stress response

Figure from Ngoi et al doi:10.1136/jgc-2020-001277

- Ongoing trials are exploring ATR inhibitors (ATRi) in genomically selected contexts.
- Anemia is an important toxicity limiting the therapeutic window of this class.
- We sought to identify clinical, genomic and hematological parameters associated with ATRi benefit, and to delineate potential links between ATRi toxicity with efficacy.

Methods

- We retrospectively analyzed clinical records, genomic reports and peripheral blood cell indices retrieved from complete blood count (CBC) reports of patients pre- and during treatment with an oral ATRi.
- Patients received ATRi monotherapy or in combination with a PARP inhibitor (ATRi+PARPi).
- Patients received ATRi in dose-escalation and expansion cohorts, which included ATRi at potentially toxic dose levels.
- Progression-free survival (PFS) was defined as the time from treatment initiation to the time of progression or death, whichever occurred first; Overall survival (OS) was defined as the time of diagnosis to death.

Results

- Between 10/2017 to 1/2022, 119 pts were treated with an ATRi (**Table 1**). 35007 indices were extracted from 1843 CBC reports.
- The median duration of follow-up was 9.6 months.
- Patients treated had a range of genomic alterations (**Fig. 2**) and tumor types (**Fig. 3**).

Fig 2. Distribution of pathogenic genomic alterations of interest amongst included patients

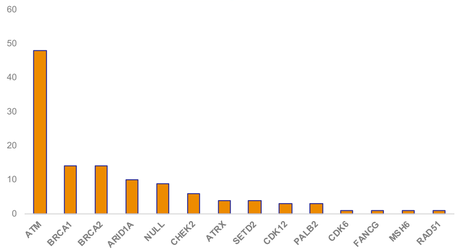
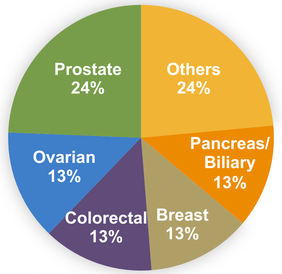


Fig. 3. Distribution of cancer types amongst patients



Clinical Characteristics

Table 1: Patient characteristics

Variable	Median	Range
Age at trial enrolment (years)	59	31-88
Prior treatment lines	4	0-11

Variable	Category	N(%)
Gender	Female	60 (50.4)
	Male	59 (49.6)
Ethnicity	White	89 (74.8)
	Asian	14 (11.8)
	Black	8 (6.7)
	Others	8 (6.7)
Eastern cooperative oncology group (ECOG) performance status (PS)	0	22 (18.5)
	1	97 (81.5)
Prior PARPi therapy	Yes	37 (31.1)
	No	82 (68.9)
ATRi therapy received	ATRi monotherapy	110 (92.4)
	ATRi + PARPi	9 (7.6)
Schedule of ATRi dosing	Intermittent	102 (85.7)
	Continuous	17 (14.3)

Table 2: High grade hematological toxicity on ATRi

Variable	N (%)
Required red blood cell transfusion	61 (51.3)
Grade ≥ 3 anemia	56 (47.1)
• **Grade ≥ 3 anemia within 6 months of ATRi initiation**	• 55 (46.2)
Grade ≥ 3 ANC	38 (31.9)
• **ANC < 0.75**	• 21 (17.7)
• **Grade ≥ 3 ANC within 6 months of ATRi initiation**	• 37 (31.1)
Grade ≥ 3 thrombocytopenia	15 (12.6)
• **Grade ≥ 3 thrombocytopenia within 6 months of ATRi initiation**	

Factors associated with objective response to ATRi

- Amongst 111 evaluable patients, the objective response rate (ORR) was 7.2%.

Table 3: Significant associations of clinical, genomic and baseline CBC indices with best objective response

Parameter	Best response	n	Mean	Std	SE	Median	P-value
(Log) Baseline Reticulocyte Count	CR/PR	8	0.28	0.60	0.21	0.38	0.033
	SD/PD	95	0.75	0.52	0.05	0.68	

Legend: CR: complete response; PR: partial response; SD: stable disease; PD: disease progression; n: number; std: standard deviation; SE: standard error

Factors associated with improved PFS

- The median PFS was 2.96 months (95% confidence interval (CI): 2.2, 3.3).

Table 4: Significant associations of clinical, genomic and baseline CBC indices with improved PFS on multivariate analysis

Parameter		Estimate	SE	ChiSq	Pr > ChiSq	HR	95% CI		P-value
-(Log) Baseline IRF	Per fold decrease	-0.48	0.18	7.00	0.0082	0.62	0.44	0.88	0.0082
Grade ≥ 3 anemia within 6 months of ATRi initiation	Yes vs No	-0.58	0.24	5.71	0.017	0.56	0.35	0.90	0.017

Legend: ChiSq: Chi-squared; Pr: probability; HR: hazard ratio; IRF: immature reticulocyte fraction

Factors associated with worse OS

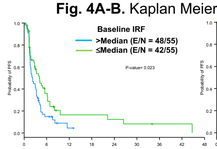
- The median OS was 15.1 months (95% CI): 11.4, 19.8).

Table 5: Significant associations of clinical, genomic and baseline CBC indices with worse OS on multivariate analysis

Parameter		Estimate	SE	ChiSq	Pr > ChiSq	HR	95% CI		P-value
ECOG PS	1 vs 0	1.00	0.44	5.14	0.023	2.73	1.15	6.49	0.023
(Log) Baseline NLR	Per fold increase	0.44	0.14	9.50	0.0021	1.55	1.17	2.06	0.0021

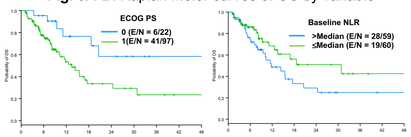
Legend: NLR: neutrophil: lymphocyte ratio

Fig. 4A-B. Kaplan Meier curves of PFS by variable



(4A) (4B)

Fig. 5A-B. Kaplan Meier curves of OS by variable



(5A) (5B)

Conclusions & Future Directions

- Anemia is an on-target toxicity of ATRi. High-grade anemia occurred in 47.1% of patients treated with oral ATRi (+/- PARPi).
- The development of grade 3 anemia within first 6 months of ATRi was associated with improved PFS. Lower baseline IRF and reticulocyte count, were associated with improved PFS and objective response, respectively. Higher baseline NLR was associated with worse OS. These deserve further evaluation as biomarkers of ATRi therapy.

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