Targeting ATR Pathway in Solid Tumors: Evidence of Improving Therapeutic Outcomes

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ABSTRACT

The DNA damage response (DDR) system is a complicated network of signaling pathways that detects and repairs DNA damage or induces apoptosis. Critical regulators of the DDR network include the DNA damage kinases ataxia telangiectasia mutated Rad3-related kinase (ATR) and ataxia-telangiectasia mutated (ATM).

The ATR pathway coordinates processes such as replication stress response, stabilization of replication forks, cell cycle arrest, and DNA repair. ATR inhibition disrupts these functions, causing a reduction of DNA repair, accumulation of DNA damage, replication fork collapse, inappropriate mitotic entry, and mitotic catastrophe. Recent data have shown that the inhibition of ATR can lead to synthetic lethality in ATM-deficient malignancies.

In addition, ATR inhibition plays a significant role in the activation of the immune system by increasing the tumor mutational burden and neoantigen load as well as by triggering the accumulation of cytosolic DNA and subsequently inducing the cGAS-STING pathway and the type I-IFN response.

Taken together, we review stimulating data showing that ATR kinase inhibition can alter the DDR network, the immune system, and their interplay and, therefore, potentially provide a novel strategy to improve the efficacy of antitumor therapy, using ATR inhibitors as monotherapy or in combination with genotoxic drugs and/or immunomodulators.

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INTRODUCTION

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METHODS AND MATERIALS

A review was conducted of the PubMed and Google Scholar databases for retrospective studies at the preclinical and clinical levels.

The objective was to demonstrate the utility of ATR inhibitors in patients with solid tumors, both as monotherapy and in combination with other drugs.

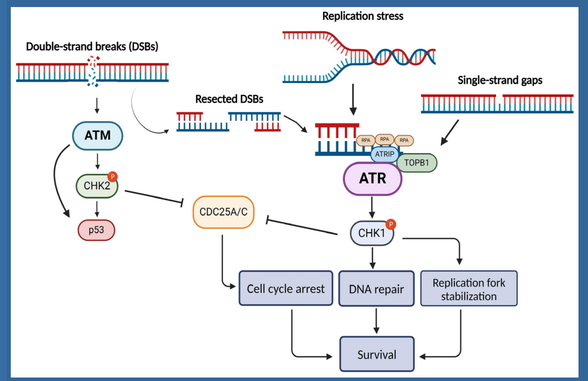

Fig 1: Schematic overview of the ATR/ATM pathways

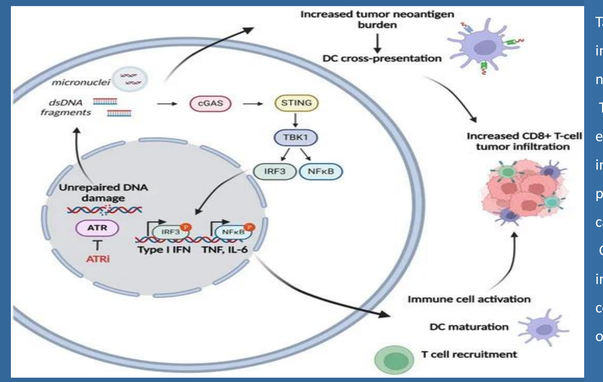

Fig 2: ATR pathway implication in the anti tumor immunity

Table 1: Clinical trials of Ceralasertib (AZD6738) in patients with solid tumors.

NCT04564027	Active, not recruiting	Advanced Solid Tumors	Ceralasertib	ORR	2	54	February 2024
NCT05514132	Active, not recruiting	Advanced Solid Tumors	Ceralasertib + Olaparib	DLT	1	14	April 2025
NCT05469919	Active, not recruiting	Advanced Solid Tumors	Ceralasertib	DLT	1	12	December 2024
NCT03878095	Suspended	IDH1/2 mut Advanced Solid Tumors	Ceralasertib + Olaparib	ORR	2	50	March 2024
NCT03330847	Active, not recruiting	mTNBC	Ceralasertib + Olaparib	PFS	2	273	September 2024
NCT03801369	Recruiting	mTNBC	Ceralasertib + Olaparib	ORR	2	132	December 2027
NCT03740893	Recruiting	Operable TNBC	Ceralasertib	Biomarker	2	81	December 2025
NCT03182634	Completed	mBC	Ceralasertib + Olaparib	ORR	2	70	November 2023
NCT04090567	Recruiting	HER2−, BRCA+ mBC	Ceralasertib + Olaparib	ORR	2	60	March 2025
NCT05582538	Recruiting	mTNBC	Ceralasertib followed by Durvalumab/nab-Paclitaxel	PFS	2	37	November 2025
NCT05450692	Recruiting	mNSCLC	Ceralasertib + Durvalumab	OS	3	580	May 2025
NCT03334617	Active, not recruiting	mNSCLC	Ceralasertib, Ceralasertib + Durvalumab	12-week ORR	2	531	September 2024

CONCLUSIONS

Taken together, data present in this report demonstrate that the inhibition of the ATR kinase can modify the DNA damage response network and the immune system.

These results potentially offer a new approach to improving the effectiveness of anticancer therapy using combinations of an ATR inhibitor with genotoxic drugs and/or immunomodulators, with promising early signals of efficacy in lung cancer, melanoma, and gastric cancer.

Given the limited responses seen with single-agent use of ATR inhibitors, future clinical trials should focus on further evaluation of combination strategies and on discovering novel predictive biomarkers of response.

REFERENCES

1. Cadet, J.; Wagner, J.R. DNA Base Damage by Reactive Oxygen Species, Oxidizing Agents, and UV Radiation. Cold Spring Harb Perspect. Biol. 2013, 5, a012559
2. Chatterjee, N.; Walker, G.C. Mechanisms of DNA Damage, Repair, and Mutagenesis. Environ. Mol. Mutagen. 2017, 58, 235–263
3. Ganai, R.A.; Johansson, E. DNA Replication—A Matter of Fidelity. Mol. Cell 2016, 62, 745–755
4. Tubbs, A.; Nussenzweig, A. Endogenous DNA Damage as a Source of Genomic Instability in Cancer. Cell 2017, 168, 644–656
5. Van Houten, B.; Santa-Gonzalez, G.A.; Camargo, M. DNA Repair after Oxidative Stress: Current Challenges. Curr. Opin. Toxicol. 2018, 7, 9–16
6. Jackson, S.P.; Bartek, J. The DNA-Damage Response in Human Biology and Disease. Nature 2009, 461, 1071–1078