

## Supplementary file 1

doi:10.34172/bi.33219

https://bi.tbzmed.ac.ir/

# Checkpoint inhibition and beyond: Precision immune engineering for the immune-privileged landscape of ocular malignancies

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**Table S1.** Emerging innovation domains integrating radiotherapy, epigenetics, AI, and adaptive ethics in ocular immuno-oncology.

Innovation Domain	Mechanistic Principle	Current Evidence & New Data	Barriers to Implementation	Next-Generation Trajectories	References
<b>Radio-Immunotherapy Synergy</b>	RT exposes antigens; ICIs amplify systemic antitumor immunity	2025 mUM study: ORR 39.1%, CR 8.7%, PFS 11.6 mo, OS 27.6 mo	Toxicity, response heterogeneity	Precision biomarker-guided RT+ICI regimens; stereotactic dose tailoring	(233)
<b>Targeted Agents + ICIs</b>	MAPK-mutated CM sensitizes to immunotherapy via improved antigenicity	Early synergy in conjunctival melanoma preclinical models	Adaptive resistance, scarcely studied in ocular contexts	Mutation-stratified trials; integrative biomarkers to guide sequencing of BRAF/MEK + ICI	(6)
<b>Epigenetic Reprogramming</b>	HDAC/DNMT inhibitors restore antigen presentation in	Preclinical synergy in non-ocular tumors	Off-target effects, no UM-specific trials	UM-adapted epigenetic-ICI trials; combinatorial epigenome finesse for immune sensitization	(6)

	ICI-resistant tumors				
<b>Microbiome-Immune Modulation</b>	Microbes influence immune checkpoints and epigenetics	Intratumoral bacteria found in UM cases; gut link to ICI response in melanoma	Unmapped ocular microbiome diversity; variable dysbiosis	Engineered ocular probiotics; microbiome transplantation; 3D organoid platforms to explore microbial immunomodulation	(265)(266)
<b>AI-Enabled Immune Adaptation</b>	AI integrates multi-omic and imaging data for dynamic therapy	AI predicts ICI response; EYE-CAN-AID multimodal AI resource	Data scarcity, privacy, and real-time validation challenges	Closed-loop AI-therapeutic controllers; ensemble models (e.g., ELF) for ocular digital pathology	(267)
<b>Ethics &amp; Adaptive Design</b>	Trial designs tailored to ultra-rare ocular tumors	Bayesian/adaptive designs and international registries supporting rare cancer trials	Patient scarcity, consent complexity, and global data governance	N-of-1 precision trials; tele-recruitment and decentralized consent; harmonized global registries	(10)