Astinova AI Platform — Drug Combination Design Report

Indication context: KRAS G12C-mutant NSCLC · rational, mechanism-aware combinations

Illustrative sample — synthetic data for format demonstration; not a specific client deliverable.

Objective

Propose rational drug-class combinations to deepen and prolong response to a KRAS G12C inhibitor by pre-empting known adaptive-resistance mechanisms. Each proposal pairs a mechanism-of-action rationale with the expected benefit and the principal liability to monitor. Drug classes shown are illustrative and drawn from publicly established combination biology.

Proposed combinations

#	Backbone + partner (class)	Mechanistic rationale	Expected benefit	Key risk / monitoring
1	**KRAS G12C inhibitor + SHP2 inhibitor**	Vertical blockade of the RAS-MAPK node; SHP2 sits upstream and relays RTK feedback that reactivates RAS after G12C inhibition.	Delays adaptive pathway reactivation; deeper pathway suppression.	Overlapping GI/heme toxicity; schedule/dose optimisation needed.
2	**KRAS G12C inhibitor + EGFR inhibitor**	Blocks EGFR-driven feedback reactivation that is especially strong in colorectal contexts.	Restores sensitivity where EGFR feedback dominates.	Rash/diarrhoea; context-dependent benefit.
3	**KRAS G12C inhibitor + CDK4/6 inhibitor**	Co-targets the cell-cycle machinery downstream of persistent MAPK signalling.	Suppresses residual proliferation of drug-tolerant persisters.	Myelosuppression; overlapping cytopenias.
4	**KRAS G12C inhibitor + anti-PD-1**	G12C inhibition can increase tumour immunogenicity; combining may convert responses into durable immune control.	Potential for durable, immune-mediated benefit.	Immune-related AEs; hepatotoxicity signal to watch.

Prioritisation rationale

Combination 1 (SHP2) is ranked first as a vertical-pathway strategy with the strongest mechanistic coupling to the primary resistance route; combination 4 (immuno-oncology) is the highest-ceiling but highest-variance option. Final selection should weigh overlapping-toxicity windows and available clinical precedent for each pairing.

Proposals are mechanism-based hypotheses for prioritisation and require preclinical combination testing (e.g. synergy matrices) and safety assessment before clinical consideration.