Paper Summary

<!--META_START-->

Title: PIK3R1 W624R Is an Actionable Mutation in High Grade Serous Ovarian Carcinoma

Authors: Concetta D’Ambrosio, Jessica Erriquez, Maddalena Arigoni, Sonia Capellero, Gloria Mittica, Ele

DOI: 10.3390/cells9020442

Year: 2020

Publication Type: Journal Article

Discipline/Domain: Oncology / Cancer Genomics

Subdomain/Topic: Precision oncology; actionable mutations; ovarian cancer; PI3K pathway

Eligibility: Eligible

Overall Relevance Score: 82

Operationalization Score: 90

Contains Definition of Actionability: Yes (explicit and implicit)

Contains Systematic Features/Dimensions: Yes

Contains Explainability: Partial

Contains Interpretability: Yes

Contains Framework/Model: Yes (patient-derived xenograft validation approach)

Operationalization Present: Yes

Primary Methodology: Experimental (patient-derived xenografts, ex vivo/in vivo drug testing)

Study Context: High grade serous epithelial ovarian carcinoma (HGS-EOC)

Geographic/Institutional Context: Italy (Candiolo Cancer Institute, University of Torino) & UK (University o

Target Users/Stakeholders: Cancer researchers, molecular oncologists, clinical trial designers, translation

Primary Contribution Type: Empirical validation of rare actionable mutation in ovarian cancer

CL: Yes

CR: Yes

FE: Yes

TI: No

EX: Partial

GA: Yes

Reason if Not Eligible: n/a

<!--META_END-->

Contextual Background:

The study focuses on identifying and validating rare but actionable genetic mutations in HGS-EOC, partic

General Summary of the Paper

This paper reports the discovery and validation of a rare PIK3R1 W624R mutation in high-grade serous o

Eligibility

Eligible for inclusion: **Yes**

How Actionability is Understood

Actionability is defined as the functional property of a mutation that (1) renders tumour cells dependent (“

> “Mutations have also been defined as ‘actionable’, not only because their functional outcome makes ca

> The study uses PDX models “to validate low frequency mutations as biomarkers for targeted therapy” (

What Makes Something Actionable

- Functional impact on a key signalling pathway relevant to oncogenesis.
- Presence of a targeted drug that inhibits the altered pathway.
- Evidence from functional assays in relevant tumour models (PDX/PDTC).
- Truncal nature of the mutation (present in all tumour cells).

How Actionability is Achieved / Operationalized

- **Framework/Approach Name(s):** PDX–PDTC functional validation pipeline for rare mutations.
- **Methods/Levers:** Whole exome sequencing, pyrosequencing for allele frequency, pathway activation
- **Operational Steps / Workflow:**
  1. Identify candidate mutation via WES and CNA analysis.
  2. Confirm truncal status via allele frequency in tumour and PDX.
  3. Predict functional consequences via in silico analysis and structural modelling.
  4. Test pathway activation via immunohistochemistry (P-S6).
  5. Test drug sensitivity in PDTCs to multiple inhibitors.
  6. Validate in vivo efficacy in PDX tumour growth and biomarker changes.
- **Data & Measures:** Allele frequency, GR metrics in viability assays, IHC quantification of Ki67 and P-
- **Implementation Context:** HGS-EOC PDX biobank.

> “PDX model… invaluable for functional validation, as it allowed overcoming questionable assays in test

> “PIK3R1 W624R carrying cells [were] addicted… to inhibitors of the PI3K/AKT/mTOR pathway.” (Abstra

Dimensions and Attributes of Actionability (Authors’ Perspective)

- **CL (Clarity):** Yes — functional consequences demonstrated through targeted assays and clear drug-
- **CR (Contextual Relevance):** Yes — relevance to ovarian cancer context stressed; rare mutation vali
- **FE (Feasibility):** Yes — presence of clinically available inhibitors; mutation is targetable.

- **TI (Timeliness):** No explicit link.
- **EX (Explainability):** Partial — mechanistic explanation offered but structural modelling inconclusive.
- **GA (Goal Alignment):** Yes — aligns with precision oncology aim of matching mutations to therapies.
- **Other Dimensions Named by Authors:** Truncality, pathway addiction.

Theoretical or Conceptual Foundations

- Precision oncology model of “driver” vs. “passenger” mutations.
- Concept of mutation “addiction” to specific signalling pathways.
- Basket/umbrella trial rationale for cross-cancer therapeutic targeting.

Indicators or Metrics for Actionability

- Mutation truncal status.
- Drug-response curves (GR metrics).
- Biomarker modulation (P-AKT, P-S6) upon inhibitor treatment.
- In vivo tumour growth delay and reduced proliferation index.

Barriers and Enablers to Actionability

- **Barriers:** Low frequency of mutation; inconclusive structural modelling; lack of prior functional charac
- **Enablers:** Availability of relevant inhibitors; PDX/PDTC models mimicking patient tumour biology; hig

Relation to Existing Literature

The authors note that while PIK3R1 mutations are common in other cancers, they are rare in HGS-EOC.

Summary

This study identifies and functionally validates a rare PIK3R1 W624R mutation as actionable in high-grad

Scores

- **Overall Relevance Score:** 82 — Clear conceptualisation of actionability with explicit definition, trunca
- **Operationalization Score:** 90 — Detailed, reproducible pipeline from mutation identification to functio

Supporting Quotes from the Paper

- “Mutations… defined as ‘actionable’, not only because their functional outcome makes carrier cells resp
- “PIK3R1 W624R carrying cells [were] addicted… to inhibitors of the PI3K/AKT/mTOR pathway.” (Abstra
- “PDX model… invaluable for functional validation, as it allowed overcoming questionable assays in test
- “The PIK3R1 W624R #475 PDTCs… were sensitive to… buparlisib… alpelisib… dactolisib… but not…

Actionability References to Other Papers

- COSMIC (CGCv84) database [28]
- DGidb drug–gene interaction database [31]
- References on PI3K/AKT/mTOR inhibitors in clinical development [20, 48–51]

- Prior functional studies on PIK3R1 mutations [32, 38–40]