Expanding the therapeutic application of PARP inhibitor: AI evaluation of real-world clinico-genomic data from spontaneous canine tumors

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Introduction

The application of Poly-ADP ribose polymerase (PARP) inhibitors in cancer therapy is undergoing a notable evolution, increasingly emerging as a key treatment strategy across a spectrum of neoplasms, particularly those characterized by BRCA deficiency. While the most substantial therapeutic effects are observed in cancers harboring BRCA1/2 mutations, it is becoming increasingly clear that the benefits of PARP inhibitors extend beyond this specific genetic subgroup. Preclinical data strongly support the exploration of PARP inhibitors in tumors exhibiting "BRCAness" or homologous recombination deficiency (HRD), indicating their potential efficacy as monotherapy or in combination with traditional chemotherapy. Further research and trials are vital to fully understand PARP inhibitors' role in improving treatment outcomes for various cancers.

Methods and Materials

This study employs spontaneous canine tumors as a complementary model for cancer research, aiming to seamlessly bridge the transition from preclinical investigations to clinical application and facilitate a smoother translation from laboratory findings to practical clinical use.

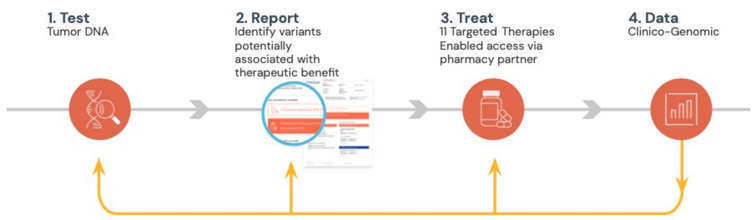

Figure 1. FidoCure® Precision Medicine Platform to identify biomarkers associated with prognosis and treatment prediction.

Results

- Real-world data from 1278 dogs with cancer revealed insights into targeted treatments developed for humans.
- A subset of the data including all dogs with a given mutation was used to model individual treatment responses. Survival rates of patients given each drug were observed within this subset.

$$\begin{aligned} Survival\ from\ Treatment \sim\ & Weight * \beta_1 + Sex * \beta_2 \\ & + Reproductive\ Status * \beta_3 \\ & + Age\ at\ Diagnosis * \beta_4 + Time\ from\ Diagnosis\ to\ Treatment * \beta_5 \\ & + Treatment_1 * \beta_6 + \ldots + Treatment_{10} * \beta_{15} \\ & + Tumor\ Type_1 * \beta_{16} + \ldots + Tumor\ Type_{19} * \beta_{34} \end{aligned}$$

Table 1. Dogs with tumors carrying *BRCA1* and *TP53* mutation have better prognosis when treated with PARP inhibitor olaparib.

Gene	Hazard Ratio 95% CI	p-value	Number of patients		Median survival	
			with olaparib	without olaparib	with olaparib	without olaparib
BRCA1	0.39 (0.20-0.83)	0.0036	76	86	394 days	181 days
TP53	0.34 (0.18-0.75)	0.0009	49	412	inf	144 days

Table 2. Dogs with tumors carrying *RB1 and TP53* mutation have better prognosis when treated with rapamycin.

Gene	Hazard Ratio 95% CI	p-value	Number of patients		Median survival	
			with rapamycin	without rapamycin	with rapamycin	without rapamycin
RB1	0.32 (0.12-0.86)	0.0239	45	58	248 days	169 days
TP53	0.74 (0.56-0.97)	0.0281	209	252	175 days	150 days

Table 3. Dogs with osteosarcoma and soft tissue sarcoma carrying *TP53* mutation have longer survival when treated with olaparib and rapamycin.

Tumor	Hazard Ratio 95% CI	p-value	Number of patients		Median survival	
			with olaparib	without olaparib	with olaparib	without olaparib
OSA	0.11 (0.02-0.54)	0.006	11	42	inf	225 days
STS	0.07 (0.00-0.55)	0.011	11	36	inf	161 days
Tumor	**Hazard Ratio 95% CI**	**p-value**	**with rapamycin**	**without rapamycin**	**with rapamycin**	**without rapamycin**
STS	0.11 (0.02-0.62)	0.0122	18	29	254 days	161 days

OSA: osteosarcoma; STS: soft tissue sarcoma

Discussion and Conclusions

These findings underscore the potential of leveraging **canine tumor models** and **clinico-genomic analyses** to inform targeted treatment strategies, offering valuable insights for advancing precision medicine in both veterinary and human oncology. Further investigation into the association between *TP53* mutation and olaparib response is warranted. The intriguing aspect lies in the role *TP53* mutation has been linked in previous studies to heightened chromosomal instability and elevated HRD scores.

- Real-world evidence and data tools in the FidoCure dataset have identified correlations between gene mutations and survival, especially in response to targeted therapy.
- Canine models, reflecting human diseases with intact immune systems and similar tumor genomic profiles, as confirmed by the FidoCure® database, accelerate clinical studies of novel treatments with scalability challenges.

Contact

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