

Treatments for Ovarian Cancer or Attractive Returns on Investment

Department of Health Promotion, Researcher at Indian Cancer Society, Kollam, Kerala, India

Several clinical and scientific factors have made therapeutic innovation in ovarian cancer challenging. An asymptomatic early-stage presentation makes screening for the disease difficult. As a result, 70% of patients are diagnosed with advanced stage disease. In addition, the heterogeneity of tumour subtypes in ovarian cancer poses considerable scientific challenge to its treatment.

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The unique histopathology, morphology, and genomic alterations of each subtype may require the development of multiple treatments, each involving a distinct mechanism of action. For example, PARP inhibitors have recently been used in addition to chemotherapy to increase treatment effectiveness. However, PARP inhibitors are most effective for women who have the BRCA 1 or BRCA 2 mutations, which make up only 15% of ovarian cancer diagnoses [1]. These technical challenges are compounded by the fact that ovarian cancer receives disproportionately less public funding relative to other diseases. For example, as measured by its National Cancer Institute funding-to-lethality score, ovarian cancer received only \$97,000 of funding per years of life lost per 100 new cases, one-nineteenth of the amount allocated to either prostate or breast cancer. Moreover, private investors are not incentivized to bridge this funding gap because of the substantial costs, long time-horizon, and low success rates associated with these projects [2]. However, by investing in many programs simultaneously, a multiple shots-on-goal approach can reduce the risk of both scientific failure and financial loss. In this paper, we demonstrate that both the dearth of funding and the need for multiple therapies to treat this heterogeneous disease can be addressed by a public-private portfolio approach. Similar to Das analysis of paediatric oncology therapeutics, we simulate the financial performance of a portfolio of ovarian cancer projects, and show that in combination with public funding, this framework can mitigate the downside risk associated with early-stage projects, thus increasing their attractiveness to private capital [3]. Moreover, this approach would enable development programs to be undertaken simultaneously instead of in sequence, ultimately accelerating the rate of therapeutic innovation [4].

Fernandez illustrates the benefits of a portfolio approach applied to biomedical research and development. In their analysis, Monte Carlo simulation is used to assess the financial returns of a hypothetical portfolio of cancer therapeutics. In this article, we extend their analysis to model the returns of an ovarian cancer-specific portfolio. These simulations are calibrated by specifying six key factors, the portfolio constituents, the clinical trial success probabilities and correlations, the trial costs and durations for each phase, and the probability of a successful compound [5]. A portfolio of ovarian cancer therapeutics should cover a variety of research programs in order to maximize the benefits of diversification while maintaining an attractive expected return as shown in (Figure 1). Well-developed and promising avenues of research would be allocated relatively more funding in the portfolio,

while more speculative hypotheses might only include one project until more evidence is proven [6]. For example, research programs involving PARP inhibitors, anti-angiogenesis agents, immunotherapy, or molecular-targeted therapies involving P53 might consist of multiple projects within this portfolio. In practice, these decisions would be made by a team of medical experts and portfolio managers exercising scientific and business judgement developed through years of domain-specific experience [7]. To analyse the performance of an ovarian cancer portfolio, we must estimate the total economic value of a single successful compound. Previous mega fund simulations have estimated the net present value of all estimated future cash flows upon FDA approval. However, in this analysis, we estimate the economic value of a successful compound as a multiple of its projected peak revenues [8].

This technique is commonly used by industry professionals to analyse risky early-stage biotech assets where future cash flows are difficult to forecast precisely. To implement this approach, we analysed the revenues from a set of 86 ovarian cancer-specific compounds in the



Portfolio approach of an ovarian cancer-specific

Thampi V, Department of Health Promotion, Researcher at Indian Cancer Society, Kollam, Kerala, India, Email: vipin_thampi@macc-fm.com

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Cortellis database [9]. Using a 4-fold increase in value-to-peak sales, a ratio suggested by industry experts as a conservative valuation, we obtained an average valuation estimate of \$2.1 billion. As expected, the top-performing portfolio occurs when the underlying projects are mutually uncorrelated and the value-to-peak sales multiplier is 6. In this best-case scenario, the fund yields a positive expected annualized return of 19.4% per annum and PoL of 6.6%. Such a fund achieves an attractive rate of return, but the result requires the unrealistic assumption of uncorrelated outcomes between any two projects in the portfolio and an optimistic valuation. This extreme scenario must be compared against the performance achieved under higher correlations and lower valuations [10]. For example, in the most realistic case, using qualitatively calibrated correlations based on expert opinion and a value-to-peak sales multiplier of 4, the portfolio yields an expected annualized return of 8.5% per annum, PoL of 31.4%, and ES 25% of -80.3%. This large tail risk suggests that an ovarian cancer fund financed using only private capital is unlikely to be attractive to investors. Even when the multiplier is increased to 6, the expected cumulative return on the portfolio in the worst 25% of cases is -70.5%. One key factor that contributes to the unattractive risk-reward profile of this private sector fund is the fact that the portfolio consists only of early-stage phase 1 assets. Since the cumulative probability of an ovarian cancer therapy's approval from pre-phase 1 status is only 12.6%, it is not surprising that that this fund has substantial downside risk.

To mitigate this risk, we consider mixed-phase portfolios in which later-stage assets are included in the portfolio. These later-stage assets increase the probability of developing multiple successful candidates, and therefore increase expected returns and decrease risk. The most common form of funding from non-profit organizations comes in the form of philanthropic grants [11]. Many of these grants are designed to accelerate innovation in a particular therapeutic area by funding basic scientific or early-stage translational research. In our simulations, we model the effect of a \$10 million grant for each project in early-stage phase 1 development. We find that, on their own, the effects of these grants on portfolio performance are marginal, and would do little to increase the attractiveness of these projects to private investors [12]. For example, compared to the mixed-phase private sector portfolio, philanthropic grants increased the expected annualized return from 9.4% to 10.2% per annum, but only decreased the ES 25% from 65.8% to -64.0%. In response, many philanthropic organizations have begun to explore different funding models in order to leverage their return on investment, a return which may be measured in terms of social, medical, and, in some cases, financial metrics. One such model, venture philanthropy, applies the principles of venture capital to invest directly in projects that promote the social good [13]. Like venture capital, venture philanthropy is characterized by high degree of investor engagement. In addition to providing capital, venture philanthropists also offer operational and managerial advice. In contrast to venture capital, where success is measured by financial return, the success of venture philanthropy is measured by its social impact. However, the financial returns of such an investment may be sufficient to allow a philanthropic organization to further its mission without needing additional donor contributions. Another possible public-private partnership that can be used to reduce the risk of early-stage research is the use of government-backed guarantees [14]. Various forms of guarantee structures such as development impact bonds have been used effectively to attract private capital to previously neglected initiatives as shown in (Figure 2). In the structure we consider, a government agency or non-profit organization promises to absorb the initial losses on the portfolio



Development impact bonds

to a predetermined amount, shielding private sector investors from substantial negative returns. Although the public sector is involved, the selection and management of the portfolio would remain led by the private sector. In our simulation, in the event of a negative portfolio return, the government agrees to cover the first \$1 billion of losses, reducing the downside risk experienced by private-sector investors [15]. Relative to the purely private sector fund, the government-backed guarantee significantly improves the previously unattractive investment returns. This result demonstrates that the guarantee structure has the potential to transform a financially unattractive portfolio of ovarian cancer therapeutic candidates with substantial tail risk into one that could realistically attract private sector capital. This structure could then be further reinforced with other revenue boosting mechanisms such as advance market commitments and priority review vouchers. Ovarian cancer differs from many other oncological conditions. Its asymptomatic onset makes early detection difficult, while its heterogeneous nature may require members of its broad patient population to need treatments that use multiple mechanisms of action. These scientific challenges are a significant impediment to developing the medical innovation required to cure a disease that affects hundreds of thousands of patients each year, as is the dearth of available funding for research and development. Moreover, these factors, along with the limited number of potential projects, help to explain why the financial returns of a purely private sector fund in this area are not as attractive as those of a general oncology mega fund. The strategic use of a public-private portfolio structure would be able to address some of these issues by leveraging multiple sources of funding, diversifying risk, and fostering critical partnerships between the public and private sectors.

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In order to make this proposition attractive to investors, however, a collaborative investment framework is required. Philanthropic funding and government guarantees are able to act to support private investment by mitigating the downside risk at a relatively low expected cost to taxpayers. In particular, financial guarantees that shield investors from the substantial downside risk of the worst-case scenario can significantly improve the risk-reward profile of these portfolios. Finally, a mixed-phase portfolio seems to be more attractive than an entirely phase 1 ready early-stage fund because the expected number of successful projects is increased.

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None

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None

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