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VALUATION OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT PROJECT METHODS INCORPORATING RISKS AND UNCERTAINTIES (REAL OPTIONS ANALYSIS AND MONTE CARLO SIMULATION)

Vrednovanje farmaceutskog istraživačko-razvojnog projekta metodima koji uključuju rizike i neizvesnosti (Analiza realnih opcija i Monte Karlo simulacija)

Abstract

The paper provides an overview of the modern possibilities of evaluating research and development projects through a concrete example of a drug candidate from the Gilead company called Magrolimab. The analysis pointed out the specifics of pharmaceutical research and development projects in the business and financial sense: the long duration of the project and its phases, the main factors of uncertainty related to the project, related economic and regulatory aspects and the potential opportunities of management to influence the project during its course. An overview of various managerial flexibilities as well as valuation approaches using real options analysis methods and Monte Carlo simulation is given. The current status of the Magrolimab project from a macro- and micro-perspective, the risks and uncertainties related to it, as well as the possibilities of managerial flexibilities related to this project, were particularly pointed out. Valuation results using methods that include risks and uncertainties are given, individually and comparatively in relation to the net present value method. In the end, the potential advantages and synergy of different approaches were pointed out based on the concrete example of the candidate Magrolimab.

Keywords: *Valuation, Research and Development Project, Pharmaceuticals, Real Options Analysis, Monte Carlo Simulation, Expected Net Present Value*

Sažetak

Rad pruža pregled savremenih mogućnosti vrednovanja istraživačko-razvojnih projekata kroz konkretan primer kandidata za lek firme Gilead zvani Magrolimab. U analizi je ukazano na specifičnosti farmaceutskih istraživačko-razvojnih projekata u poslovnom i finansijskom smislu: dugo trajanje projekta i njegove faze, glavne faktore neizvesnosti vezane za projekat, povezane ekonomske i regulatorne aspekte i potencijalne mogućnosti rukovodstva da utiče na projekat tokom njegovog toka. Dat je pregled različitih menadžerskih fleksibilnosti kao i pristupa vrednovanja metodima analize realnih opcija i Monte Karlo simulacijom. Posebno je ukazano na postojeći status projekta Magrolimab iz makro- i mikro- perspektive, rizike i neizvesnosti u vezi njega kao i mogućnosti menadžerskih fleksibilnosti vezanih za ovaj projekat. Dati su rezultati vrednovanja metodima koji uključuju rizike i neizvesnosti, pojedinačno i komparativno u odnosu na metod neto sadašnje vrednosti. Na kraju je ukazano na potencijalne prednosti i sinergiju različitih pristupa a na osnovu konkretnog primera kandidata Magrolimab.

Ključne reči: *vrednovanje, istraživačko-razvojni projekat, farmaceutika, Analiza realnih opcija, Monte Carlo simulacija, Očekivana neto sadašnja vrednost*

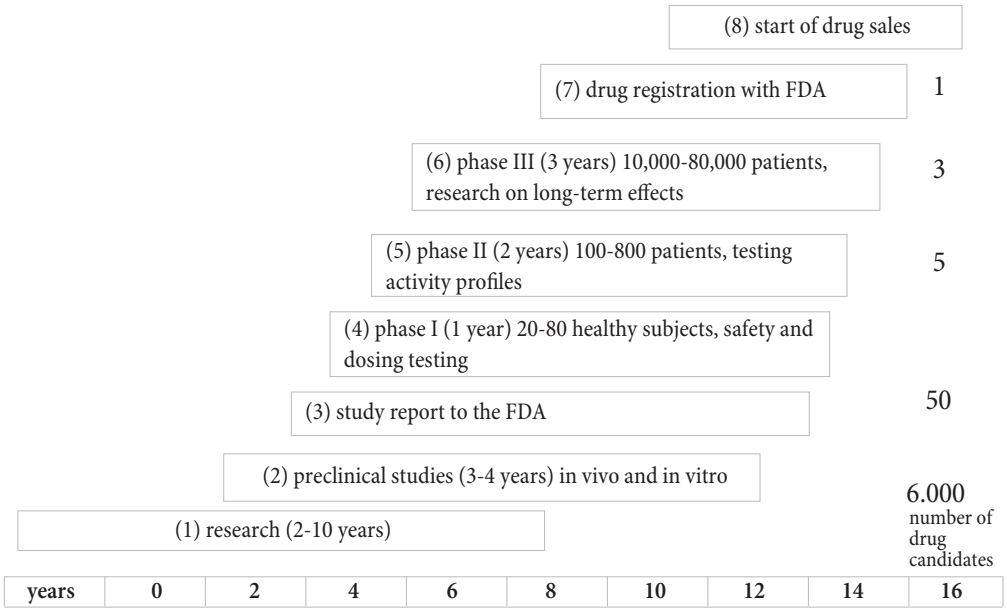
Introduction

Modern pharmaceutical companies operate with an orientation towards research and development projects that will provide the company with future sources of additional income despite global competition. Company management is interested in increasing the level of income from investments in pharmaceutical projects that should enable this. At the same time, Big Pharma exist in global economy where „Most important defect is ignorance of technological change. In case of technology-driven competition, market forces exist in vacuum" [17, p.5]. One of the possible ways to increase efficiency is to take into account the risks that arise in pharmaceutical projects, the likelihood of their realization in terms of the level of capital investments and cash flow from future drug sales, e.g. taking into account the uncertainty of the future. In this sense, the paper indicates the main types of risk analysis as a vital part of the process of evaluating pharmaceutical projects. Approaches to risk analysis will be indicated and a conclusion will be given on the possibility of including methods in the process of evaluating pharmaceutical projects. Then, the features of modern methods for valuing a pharmaceutical research and development project (abbr. PDP) will be presented on a specific example as a case study, taking into account the regulatory, market, and financial aspects. It allows the inclusion of relevant specificities of PDP from the fields of microeconomics, organization, finance, marketing, and management. Taking into account that without additions that would identify the impact of risk, uncertainty, and managerial flexibility in project management, the net present value (NPV) valuation method fails to adequately recognize and adequately include their impact in the calculation of the value of PDP. For this purpose, Monte Carlo simulation and Real Options methods were used. The example of the PDP Magrolimab from Gilead was used, including existing software solutions. Finally, a conclusion will be given on the usefulness of choosing the previously mentioned methods in the process of valuing pharmaceutical projects.

PDP and approaches to incorporating risk in the valuation process

Pharmaceutical development relies on R&D activities and the intangible assets (patents and trademarks) that arise from these activities, which at the same time contribute to global public health. Like other projects, PDPs are characterized by various risks: technological and market risks and risks related to the implementation of the project (cost budget, staffing, deadlines, and sufficient funding [59, p. 310]. The main aspects of PDP that are analyzed during the preclinical phase are toxicity and aspects of

Figure 1. Drug development process [47, p. 69]



efficacy: drug delivery systems (DDS), pharmacokinetics (PK), pharmacodynamics (PD). Amount of investment in a single agent is low during the research phase, and increases during the preclinical development phase due to the need to conduct a larger number of analysis that will verify the aforementioned aspects of toxicity, DDS, PK and PD in the laboratory and then in different animals. The issue of defining manufacturing process of the future drug also arises. PDP risks are widely distributed in terms of area and impact on the success of the project. The key moment is the completion of clinical studies through the publication of their results, since the sale of the drug is conditional on the approval of the drug by the Medicines Agency, which in turn is conditional on the positive results of clinical studies. The following diagram shows the PDP phases in terms of duration parameters, the number of candidates on which the next phase is conducted, and the number of subjects during the clinical trial phases.

The probability of a drug being approved in the period 1980-2005 was 22%, and now it has fallen to around 12%, similar to the probability before 1980 [16]. The composition of the aforementioned 12% by clinical trial phase is as follows: 59.52% success from phase I to phase II, 35.52% success from phase II to phase III, 61.95% success in phase III, and 90.35% success in the approval phase of the new drug [15]. At the end of the 20th century, the reasons for failure were mostly related to pharmacokinetics, while at the present time, failure is mostly due to the efficacy and safety of the drug [34, p. 98]. In terms of pricing the future product, the specificity lies in the small number of large buyers on the market (state health funds, large insurance companies). Mapping the value that a particular feature of a drug has for a specific buyer based on knowledge and application of the aforementioned buyer preferences [49, p. 210] significantly determines the pricing of the future drug.

PDPs carry following risks: the high value of the investment in clinical studies, the duration of the project, and the low probability of project success. According to Koller, the two main parameters of risk are the probability of an event occurring and the consequences of the event occurring [33, p. 19]. Damodaran states that"...although risk can have very negative consequences for those exposed to it, risk is also a reason for higher returns for those who use it to their advantage" [13, p. 125]. The Project Management Institute (PMI) in its"A Guide to the Project Management Body of Knowledge, PMBOK) defines project risks as"an uncertain event or condition that, if it occurs, could have a positive or negative impact on one or more projects objectives, such as scope, schedule, cost, and quality" [42, p. 309]. PDP risks can be decomposed into a hierarchical risk structure. Harpum and Danson cite the following factors as the main sources of uncertainty in PDP:

- business environment (competition, customers, partners, changes in technology, policy, etc.);
- strategy (business model, therapeutic areas, patient population);
- commercial aspects (competitive advantage, interest rates, currencies, cash flow, intellectual property, contracts);
- regulatory aspects (risk-benefit ratio, future changes in the regulatory framework);
- pharmaceutical research phase (drug mechanism of action, model predictability);
- project operational activities (patient population, safety, efficacy, cost-effectiveness, pharmacokinetics, drug formulation, process development);
- information (data loss, data integrity and access, data availability);
- human resources (reorganizations, leadership, employee turnover, fraud, lack of ethics, intellectual property theft, crime, strikes);
- operational activities of production and logistics (factory qualification, safety, natural disasters, supplier problems, licenses, product returns, product contamination) [24, p. 140].

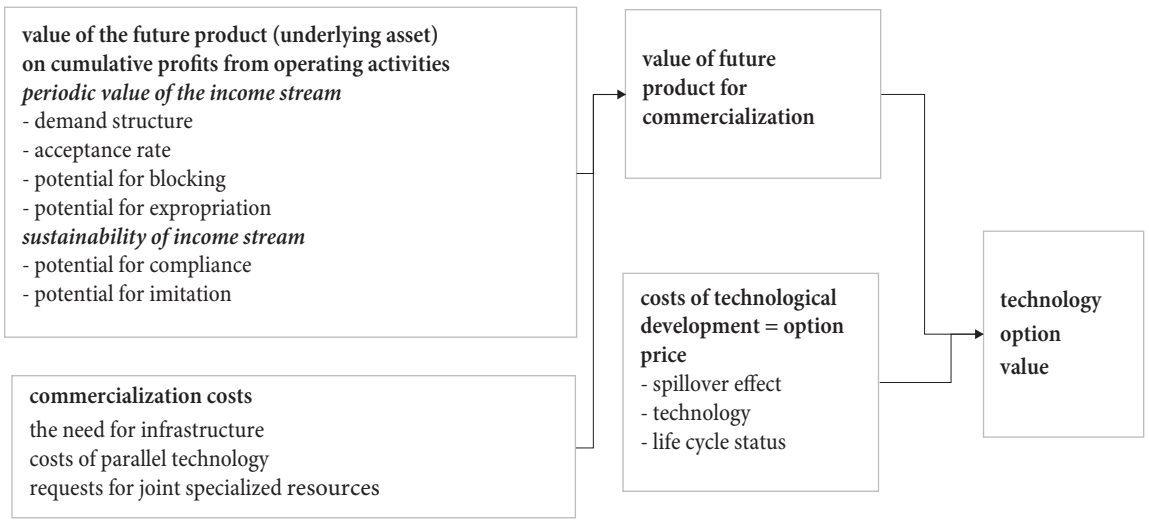
The evaluation of PDP should be based on the risk management strategy, through"testing the main features of the product as early as possible, collecting information that reduces future uncertainty, insisting on early identification of failures, minimizing the damage from negative outcomes (ie, including a backup strategy) and maximizing the benefits from positive outcomes (ie, ensuring that the capacities are in place to provide the full benefit from them)". „As part of uncertainty quantification, it is necessary to include the interdependence between the most important inputs" [41, p. 280]. The literature indicates

the following approaches used for valuation purposes: sensitivity analysis, scenario method, simulation, decision tree analysis, Monte Carlo Simulation (MCS), and Real Options Analysis (ROA). The following presentation will focus on two methods, MCS and ROA, in which a smaller part related to decision tree analysis will be presented due to their connection in application.

MCS is based on a stochastic approach by applying a large number of random numbers to previously estimated probabilities of events, and through a large number of random numbers, a probability distribution of the dependent variable is obtained. It is implemented using a computer. Prof. Radenković believes that the MCS finds its meaning in three groups of problems: deterministic problems that are difficult or expensive to solve, complex phenomena that are not sufficiently known, and statistical problems that do not have an analytical solution [43, p. 28]. In accordance with the nature of PDP, we can conclude that the MCS has its place in the evaluation of PDP. Starting from a large number of random numbers, the values of the net cash flow for each of the attempts are added up and different outcome values are obtained, and thus the distribution of the values of the net cash flow. This distribution can be used to calculate the value of PDP. MCS is not a stand-alone method and is combined with other techniques and has the following stages: creating a financial model of the project (input, calculation and output variables); defining probabilities (discrete values, discontinuous or continuous distribution); simulating balance sheet and income statement items based on capital budgeting data, and based on this, the result in the form of a project value through NPV. Apps mostly used are Crystal Ball from Hearne Software and @RISK from Palisade Corporation. They use the so-called triangular risk distribution, with a lower limit, an upper limit and the most probable value for values such as the weighted sales revenue growth rate (CAGR). There is the possibility of using different statistical distributions. Briley and Myers report a particularly high level of use of MCS by pharmaceutical companies for the purposes of PDP valuation. As the main areas of use, they list the following specific PDP problems:"Will the agent be usable as a drug?" Will it have side effects? Will it receive FDA approval; market success. FDA approval does not guarantee sales of the drug. There may be a competitor with a similar (or better) drug. The pharmaceutical company may or may not be able to sell the drug on the world market. The selling price and marketing costs are unknown" [6, p. 268].

ROA is often cited in the literature as an alternative to traditional valuation methods. Chance divided the value of a firm into the present value of existing assets and the present value of future growth opportunities [8, p. 491]. Drawing on the analogy with financial options, real options would be the equivalent of a call option, where unlike financial options that provide the right to financial instruments, real options give the same rights (discretionary investment options) to a company that has future development opportunities [54, p. 5]. The

Figure 2. Factors affecting the option value of technological positioning [50, p. 30]



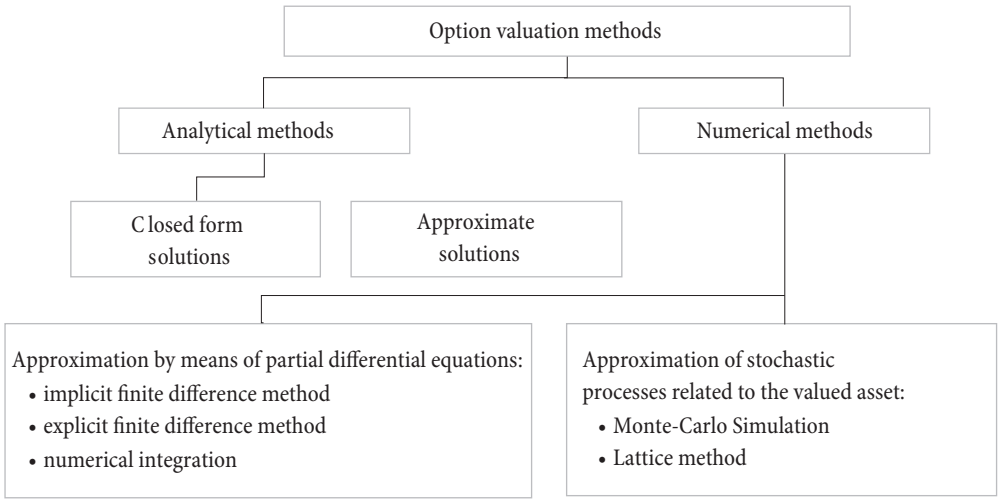
aforementioned investment options are also known as managerial flexibilities."The value of flexibility represents the difference between the value of active project management (ie taking into account managerial flexibilities) and passive project management, which implies that decision makers would not have the option to influence the project during its duration [46, p. 269]. The ability of pharmaceutical company management to influence its PDP portfolio is an example of the managerial flexibilities of the company. According to Broyles, the uncertainty associated with capital projects is what makes the value of real options [7, p. 138]. The strategic options available to management depend on the level of innovation of the research results and the market situation facing the product – the result of development [2, p. 26]. Considering the value of real options, entrepreneurship is expressed through managerial flexibilities in the research and development phase, and during the commercialization phase.

There is general agreement on the taxonomy of managerial flexibilities in the literature. In his division of real options, Damodaran starts from the taxonomy of financial options and then applies them as such by analogy to real options. With him, the focus is on the options of postponement, growth and giving up [12, p. 29-44]. In addition, Broyles sees as managerial flexibility the possibility to supplement or change the purpose of the project, by using it for a purpose different from the initial one:"investing in features that allow the asset to have alternative uses that are more profitable" [7, p. 136]. With PDP, these possibilities would for example be investing in additional therapeutic areas for a drug that is initially intended for only one therapeutic area.

Hommel classified the existing methods based on mathematical models that result in the exact or approximate value of real options. Due to the complexity of real situations, there is an attempt to calculate"correct" values through solutions in a closed form, and generalization is difficult to apply. As an alternative approach, the method was used otherwise intended for financial options.

Two ROA approaches are dynamic programming and contingent claims. Dynamic programming provides possible values of the valued asset through extrapolation during the option's life, and calculating backwards the values of the optimal future value reduces to the present moment [45, p. 93]. It implies the discount rate as an exogenous variable. The contingent claims method is based on the idea of Black, Scholes and Merton that the valuation of securities depends on the value of the company as a whole. In the valuation of financial assets/securities, the equivalent attempt is to replicate the value of the new asset through a portfolio of pre-existing exchange-traded securities. [40, p. 13]. In the literature, the methods used to value financial options are used the Black-Scholes - Merton model (BSM) model and the binomial (Cox, Ross & Rubinstein, CRS) model. In addition to the value of the option, the BSM model also provides a sensitivity analysis, using the terminology of the model: dividing the PDP value by the value of the real option change is the Delta

Figure 3. Classification of real option valuation methods [27, p.27]



parameter; by comparison with yield variability, Vega; the time until the end of the project duration (Theta) is the sensitivity of the PDP value in time. Due to the duration of the project and the high investment, the Delta varies depending on the phase in which the PDP is positioned. Vega indicates the competitive situation of the product, Teta, a change in the competitive situation, i.e. the possibility of accelerating PDP.

CRS maps moments in time to moments of decision-making, and determines the sequential scheme of managerial flexibilities on the time axis according to their occurrence. PDP value does not change until the next decision node is reached, and after that it does not change again until the next decision [5, p. 52]. The value of the option at the decision point is the expected present value of the cash flow discounted at the risk-free rate. The procedure involves two scenarios (optimistic, pessimistic) as a way of limiting the uncertainty associated with the decisions made. The calculation procedure is recursive. The result is conditioned by managerial flexibilities, that is, by making decisions by predicting their effects in a positive and negative sense. The current value of the asset in a risk-free context would be $V = \frac{pV^{+} + (1-p)V^{-}}{1+r}$ and the risk-free upside probability is $p \equiv \frac{(1+r)V - V^{-}}{V^{+} - V^{-}}$ where $V+$ and $V-$ are the optimistic / pessimistic value after making the decision, r is the risk-free discount rate and p is the probability of event ie. the results of a specific decision [9, p. 178]. PDP implies phase investing equivalent to sequential decision-making and the formation of a binomial tree composed of individual phases of R&D. Starting from the Cash Flow data, the value is adjusted stepwise for each stage according to the probabilities of optimistic and pessimistic outcomes. An alternative is to use a decision tree, with the following procedure: describing the application; input parameters; option parameters; creating a binomial tree and calculating the asset value at each node of the tree; calculating the value of the option at each tree node via recursive induction; results analysis [32, p. 98]. Kellogg and Charnes have used the decision tree approach and the binomial tree with growth option for the purposes of valuing a Biotech company. The probabilities of success of individual stages of PDP and portfolio products according to different market success were taken from historical data available until then [30, p. 584]. Burr and Kimball suggest linking the results of corporate planning (primarily capital budgeting) to the use of ROA, by"..using optimistic and pessimistic forecasts. But the second part can be essential, recognizing the value

Table 1. examples of PDP Real Options

Operational flexibility	**Example with PDP**
Postponement	Postponement of investments in the development of gene therapy and monoclonal antibodies. Minimal research into new types of drugs/therapies. Postponement of capital investment in the development of nanoparticles as a method of drug administration. Postponement of clinical study phases until disputes with competitors regarding contested patents are resolved.
Withdrawing	Selling the right to manufacture and sell a drug whose patent has expired, or granting an exclusive license to sell the drug. Selling a patent for a new drug candidate, before starting or during clinical studies.
Phased investment	PDPs are multi-phased (research – preclinical development – phased clinical development, registration, post-marketing studies).
Resizing (enlarge/reduce)	Buying someone else's (selling your own) research project or its segment. Purchase (sale) of a department specialized in the research of a certain therapeutic area, mechanism of drug action or type of drug. Determining the optimal breadth of patent definition for a new drug candidate. Signing a market access agreement (Market access agreement) which determines the financial terms of sales to the health fund or is based on the results of therapy [55]
Temporary change of status (stop / restart)	Investing in new medical technologies (selling own research). Legal fight to preserve the patent with generic companies in the period before the patent expires.
Change option (input/output)	Human, plant or artificial input. Another or additional way applications medicine. Optimization of the portfolio of production plants, including the sale of existing plants.
Strategic flexibility	**Example with PDP**
Growth Option (Scope/Scope)	Capital investment in biotechnology. Gene therapy
Strategic insurance	Investing in new development technologies (human genome, immunotherapy)

Source: Author

of managerial flexibility. There are chances to modify the plan during its life of the project" [31, p. 146] or initiate an abandonment project, through"closing factories, stopping the production of a specific product, withdrawing from a market, stopping a process, etc. [36]. D'amico and Villani complement the inclusion of technological risk in phased investment projects by including Markov chains. where those risks are seen through the probability of success of one PDP phase that is not independent of other phases, where"decision-making is in fact random variables dependent on the status of the Markov chain to which they belong" [11]. The table below gives examples and perspective pharmaceutical company of operational and strategic flexibility.

PDPs characteristically have a Real Option of phased investment and sequential decision-making: at the end of each phase of R&D, the question arises as to whether it is worthwhile to enter the next phase. The decision on this can be based on the decision tree, where the profitability of commercialization will be determined recursively, based on the facts known at that time about the market conditions, i.e. the existence of current PDP competition (including the time schedule between the moment of commercialization of own PDP and PDP of competing firms), up-to-date information on the safety and effectiveness of own agent and other relevant parameters (status of existing or new relevant diagnostic tools, level of innovativeness of the agent, etc.). Then we go back to the previous stages. According to Hess, Real Option of giving up the PDP in the late phase of the project, i.e. its non-implementation (basically, continuing with the implementation of the PDP which has a small chance of success) has a material impact on the decline in the value of the shares of the pharmaceutical company, as the capital market recognizes the effects of the use or non-use of real options giving up [26].

Magrolimab project status: pharmaceutical, market, economic and macro parameters

PDP valuation will be carried out on the case of the candidate Magrolimab (hereinafter referred to as MLB) owned by the US company Gilead Sciences (hereinafter referred to as Gilead). This drug candidate is a product of biotechnological development, and is in clinical studies in 2024. Details about the disease it is intended to treat, the agent itself, the market and the competition will be presented. In order to identify the cash flows of MLB, the characteristics of MLB, the competitive situation, as well as risks and managerial flexibility will be considered from the perspective of Gilead itself.

"MLB is a potential first-in-class anti-CD67 immunotherapy. The basic mechanism of action of MLB is the blocking of inhibition CD67 signal regulatory protein (SIRPα) interaction.." [19]. CD67 belongs to the group of carcinoembryonic antigens, and is also known under the code CEACAM8 [58], with targeted indications: NHL/PTCL, solid tumors, AML, RR MM and two types of pediatric cancer.

The first indication is the type of lymphoma. The incidence of NHL is 15 newly diagnosed patients per 100,000 inhabitants. 10,000 new cases are diagnosed each year in the UK [39, p. 275]. NHL accounts for 5% of all malignancies, with a 3-5% annual increase in incidence [52, p. 230]. Current options for relapsed PTCL are: Crizotinib (Xalkori), Belinostat (Beleodaq), Pralatrexalate (Folotyn), Brentuximab vedotin (Adcentris), and Romidepsin (Istodax) (Lymphoma.Org, Peripheral T-Cell Lymphoma Fact Sheet, 2023). The 2nd indication for MLB is solid tumors, in patients with BRCA1 or BRCA 2 gene mutations. 85% of cancers whose cause is a hereditary factor are due to BRCA1 or BRCA 2 gene mutations, while the general prevalence in the population for BRCA1 mutation is 1 in 300 people, and for BRCA 2 in 800 people [1, p. 154]. The 3rd MLB indication is acute myeloid leukemia (AML)."The incidence of AML is currently estimated at 5 to 7 per million US residents. The current cure rate for AML has risen to approximately 45% to 65% with the advent of more intensive conventional chemotherapy and bone marrow transplantation" [14, p. 1500]. The 4th indication is relapsed or refractory multiple myeloma (Relapsed/Refractory Multiple Myeloma, RR MM) plasma cell in the bone marrow. The incidence in the US is about 4 to 5 cases per 100,000 population per year [1, p. 343]. The 5th indication is from the field of pediatric oncology, recurrent or poorly responding neuroblastoma (nerve cancer) and osteosarcoma (bone cancer) [51]. The

mechanism of action of MLB (inhibition of CD67) is innovative and MLB currently has no direct parallel in development. Competing therapies therefore represent those already approved for use, and those agents that lead to comparable results for MLB.

For NHL / PTCL, a small market share is expected because rare diseases"do not support multiple approvals for the same type of disease [16, p. 4], 30% incidence of AML as Unfit AML." As MLB comes last to the RR MM field, some 5-10% market share can be expeced. For solid tumors and AML there is no competition that could threaten the success of MLB in the short term. The probability of a successful transition from phase III clinical studies to the registration phase for a biological oncology drug from the therapeutic area of multiple myeloma (RR MM) is 68% [3, p. 14], transition from phase II to phase III 24.6%, from phase III to the registration phase 54%, and 82.4% for approval registration (New Drug Application, NDA) [BIO, p. 9-14]. The success of moving to the registration stage is given as 40%. In February 2024.

In order to prepare data on the expected amount of sales for the base scenario of the MLB valuation (without the influence of managerial flexibilities, i.e. the effects of uncertainty), assumptions used are based on the available information. As Mrdja stated for management purposes, the same logic was used when preparing the data for the valuation: „..we need numbers as accurate and „realistic" as possible" [37, p. 236]. To plan MLB sales volumes, the world population is divided into key countries (USA, European Union, Japan), other developed countries, developing countries, and the rest of the world. Potential patients of solid tumors are women, i.e. 50% of the total population. Data on incidence were taken from available sources, as well as the coefficient of actually recognized cases: key countries and other developed countries (0.8), developing countries (0.3), rest of the world (0.1). Expected market share growth over time: 50% solid tumors, 7.5% RR MM, 10% NHL/PTCL. The FDA halted MLB studies related to AML [21] and solid tumors [20].

Gilead owns facilities for the production of drugs for the needs of clinical studies, cell therapy and facilities for the production of final products. The active substance for other drugs is purchased from third parties, and there does not seem to be any greater tendency to increase production capacity, i.e. to expand its own network of production facilities [22]. Gilead is financially stable but with a visible decrease of financial performance during the period 2015-2022. due to acquisitions (Imunomedics and Forty Seven) in 2020, and the expiration of patents and a decline in turnover was not followed by the appearance of new PDPs that would increase revenues: Imunomedics' drug Trodelvi is successful, while MLB firms Forty-seven is still not generating revenue.

Macroeconomically, the Global Economic Prospects report expects global economic growth of 2.4% in 2024 and 3.0% in 2025. [60, p. 5]. There are no signs of significant changes in the financing of public health systems in the USA, Europe, Japan and BRIC. Firm Fitch expects a neutral rating of pharmaceutical companies, a focus on research and development and a further exit from the generic and parapharmaceutical segment, with a further focus on chronic diseases treated by specialist doctors [18]. As relevant sources for the development of national health systems, relevant sources are Euro Health Consumer Index (EHCI), Global Competitiveness Index (GCI), Bloomberg, IMS Report, Globocan Report and IPSOS Report [35, p. 158].

The MLB patent expires in 2031 in the US and the European Union. The probability that the registration of an oncology drug with someone other than the FDA and the EMEA will be stricter, i.e. with greater limitations (later line of treatment, etc.) is 28% [28, p. 3]. Approval of

Table 2. An overview of MLB competition by indication and MLB project status

Indication	NHL / PTCL	Solid tumors	AML	RR MM
Existing competition	4 modern therapies and therapies used for decades	1 modern therapy	1 modern therapy	8 modern therapies
Incoming competition	15 agents	-	-	2 agents
MLB status	it is not a basic but an additional method of treatment	The only existing candidate	Studies suspended as a whole	One of three candidates

Source: Author

reimbursement by funds and insurance occurs simultaneously with registration, with 2-4 months of negotiation.

MLB Valuation Parameters for Capital Expenditure and Cash Flow Planning

MLB belongs to the group of monoclonal antibodies and according to information from 2013, within the cost structure of monoclonal antibodies, the purification stage includes the protein A chromatography process at a cost of $241 per gram, and the final filling and control stage accounts for over 50% of the total production costs, $238 and $185 per gram respectively [56, p. 29]. The cost of producing monoclonal antibodies ranges from $95-$200 per gram [57, p. 1]. The purchase value of MLB per patient is $16k in the first year ($21.3 in 2028, due to inflation) of therapy and $8k in the second year with a reduction in the further period due to the improvement of the technology. In terms of the geographic distribution of sales revenue, MLB will largely follow the historical sales distribution by geographic segment of Gilead's current products. The annual cost of monoclonal antibody therapy for some types of cancer is $100k higher than the average cost across all therapeutic areas, while the average cost of monoclonal antibody therapy is $96k [25]. Taking into account these data and the further increase in therapy prices to date, it will start from $508k for the annual therapy of a patient in the USA. For capital expenditures, balance sheet and operating expenses, three cash flows will be included, from year 2024. The 1st is related to investment in clinical studies, regulatory activities, medical department and commercial activities. For clinical studies, the cost per patient was $75k for phase III and $120k for phase II, with the number of patients data taken from the [10]. For the purposes of planning the balance sheet, the data from Gilead's available financial statements will be used: accounts receivable (17% of revenue), inventory (6% of revenue), liabilities (minor), etc. Gilead's average rate of financing (WACC) will be used as a discount rate: 4.9% [23] and Gilead's effective tax rate of 29.6%, average effective rate in the period 2014-2023 (Q3), data from published financial statements.

Risks, uncertainties and managerial flexibility of the Magrolimab project

PDPs are characterized by various risks and uncertainties: global, political and macroeconomic aspects, changes in global demand, the state of distribution chains. Then, regulatory factors: tax support, accelerated implementation of clinical studies and registration. Also market risks: changes in the pharmaceutical market of manufacturers, distributors, insurance companies as customers, M&A activities. The following financial risks were identified: financing and company financial stability. Regarding media aspects and the influence of social networks, they should be taken into account in the light of the recent Covid pandemic and vaccination as a newly established political issue. The mentioned risks and uncertainties do not have the characteristics of clear significant changes in tendencies, nor specific distinctive uncertainties for this PDP. Operational risks are related to the success of PDP itself. The following uncertainty parameters (for the purposes of NPV calculation) or stochastic variables (in terms of MCS) were chosen:

In the overview below, identified MLB Real Options are provided. For the purposes of evaluating MLB, a Real Option of acceleration or expansion, through investment in the area of solid tumors, was chosen.

Table 3. Stochastic risk and uncertainty parameters for valuation (RR MM, NHL/PTCL)

Parameter	Initial value	Probability distribution
Probability of transition from phase II clinical studies to phase III	23%/24.6%	PERT distribution (minimum and maximum value 10% smaller/ larger than the initial one
Probability of transition from phase III clinical studies to the registration phase	68%	PERT distribution (minimum and maximum value 10% smaller/ larger than the initial one
Probability of success in registering a drug in the USA	86.4%	PERT distribution (minimum and maximum value 3% smaller/ larger than the initial one
The value of the purchase value of realized goods per patient, annual therapy	21,279 usd	Normal (0.68 standard deviation)

Source: Author

CSR model allows moments in time to be mapped to decision-making moments, i.e. determines the sequential scheme of managerial flexibilities on the time axis according to their occurrence. The model implies that the value of the asset (in our case, MLB project status) does not change until the next decision node is reached, and after that it does not change again until the next decision [5, p.52]. It includes an optimistic and a pessimistic scenario as a way of limiting uncertainty. The approach for the baseline scenario is NPV, including the calculation of expected NPV (E-NPV). MCS will be an approach that includes risks, with sensitivity analysis, and the ROA will be implemented through CSR model used by Jensen, through the real option of phased investment [29, p. 73], and by Sereno, for valuation of pharmaceutical patents [48, p. 17].

Valuation of the Magrolimab pharmaceutical project

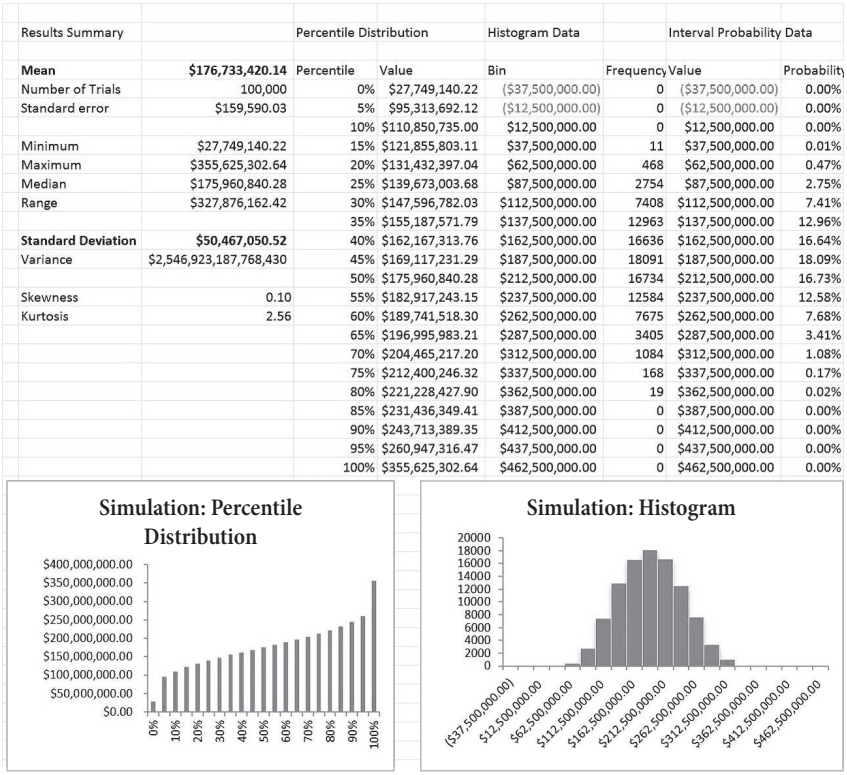
For the purposes of valuation using the NPV method, the previously mentioned parameters related to the income statement and the balance sheet were used. Projection

Table 4. MLB Real Options

scenario	option	year	phases	parameters
1	1	2025	acceleration of phase 2 studies, expansion of phase 3 studies for both indications	40% higher research and development costs in the 1st 3 years (2025-2028). Revenues and investments in promotion happen one year earlier. Failure: Sales do not start a year earlier
	2	2026	initiating own production of final products	investments in fixed assets 13.7 m usd 2025-2031, reduction of purchase value by 60%. Failure: 10% less sales
2	3	2027	initial focus exclusively on the RR MM indication	lower R&D costs by 40% for the NHL/PTCL indication with 20% lower income for that indication in the 1st year. Failure: 50% less sales per NHL/PTCL indication
	4	2028	adjustment - signing of franchises for the rest of the world	cancellation of investments outside the main markets (USA, EU, Japan), introduction of gross margin sharing with the franchise owner (15% for the franchisor). Failure: failed negotiations reduce the amount of sales in the rest of the world by 30%
	5	2029	MLB project sale negotiations	NPV of the real scenario. Failure: pessimistic scenario

Source: Author

Figure 4. Evaluation of Magrolimab using Monte Carlo simulation with 4 random variables



Results Summary		Percentile Distribution		Histogram Data		Interval Probability Data	
Mean	**$176,733,420.14**	Percentile	Value	Bin	Frequency	Value	Probability
Number of Trials	100,000	0%	$27,749,140.22	($37,500,000.00)	0	($37,500,000.00)	0.00%
Standard error	$159,590.03	5%	$95,313,692.12	($12,500,000.00)	0	($12,500,000.00)	0.00%
		10%	$110,850,735.00	$12,500,000.00	0	$12,500,000.00	0.00%
Minimum	$27,749,140.22	15%	$121,855,803.11	$37,500,000.00	11	$37,500,000.00	0.01%
Maximum	$355,625,302.64	20%	$131,432,397.04	$62,500,000.00	468	$62,500,000.00	0.47%
Median	$175,960,840.28	25%	$139,673,003.68	$87,500,000.00	2754	$87,500,000.00	2.75%
Range	$327,876,162.42	30%	$147,596,782.03	$112,500,000.00	7408	$112,500,000.00	7.41%
		35%	$155,187,571.79	$137,500,000.00	12963	$137,500,000.00	12.96%
Standard Deviation	**$50,467,050.52**	40%	$162,167,313.76	$162,500,000.00	16636	$162,500,000.00	16.64%
Variance	$2,546,923,187,768,430	45%	$169,117,231.29	$187,500,000.00	18091	$187,500,000.00	18.09%
		50%	$175,960,840.28	$212,500,000.00	16734	$212,500,000.00	16.73%
Skewness	0.10	55%	$182,917,243.15	$237,500,000.00	12584	$237,500,000.00	12.58%
Kurtosis	2.56	60%	$189,741,518.30	$262,500,000.00	7675	$262,500,000.00	7.68%
		65%	$196,995,983.21	$287,500,000.00	3405	$287,500,000.00	3.41%
		70%	$204,465,217.20	$312,500,000.00	1084	$312,500,000.00	1.08%
		75%	$212,400,246.32	$337,500,000.00	168	$337,500,000.00	0.17%
		80%	$221,228,427.90	$362,500,000.00	19	$362,500,000.00	0.02%
		85%	$231,436,349.41	$387,500,000.00	0	$387,500,000.00	0.00%
		90%	$243,713,389.35	$412,500,000.00	0	$412,500,000.00	0.00%
		95%	$260,947,316.47	$437,500,000.00	0	$437,500,000.00	0.00%
		100%	$355,625,302.64	$462,500,000.00	0	$462,500,000.00	0.00%

Source: Author

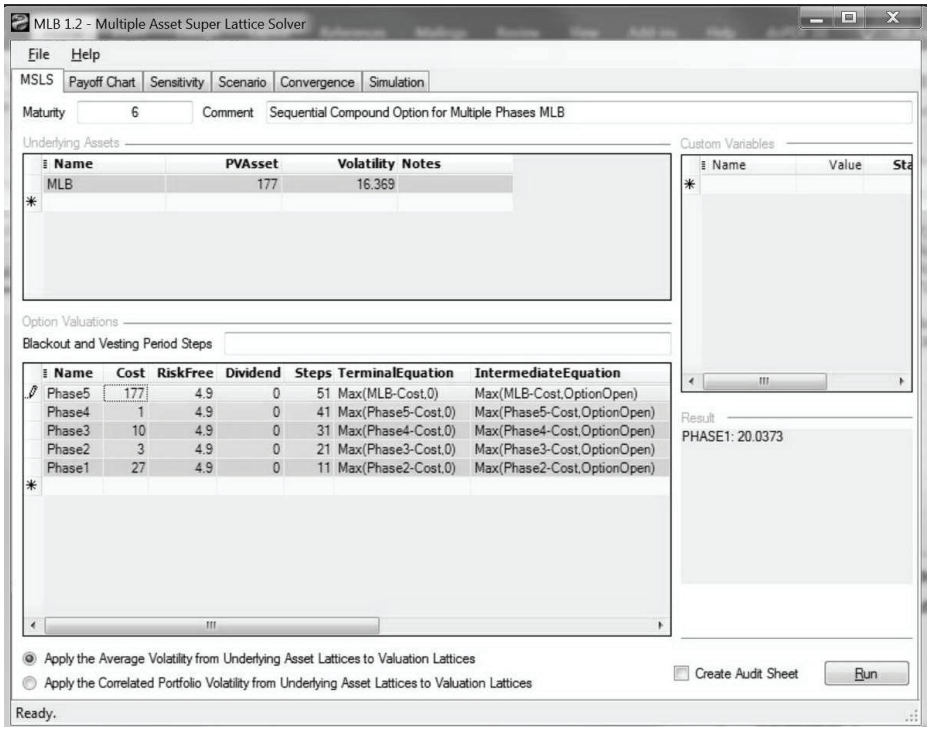
period calculations (2039-2050) were prepared, thus eliminating influence potentially incorrect valuations due to inadequate calculated terminal (residual) values [4, p. 8]. Three variants of NPV calculation have been prepared. The optimistic scenario implies the success of clinical studies and success in drug registration and the expected level of market success and gives MLB a value of $1.317M. A realistic scenario involves using a Probability of technical and regulatory success (PTRS) approach where revenues are weighted by the risk of success in clinical studies and drug registration, a 65-80% reduction in clinical studies cost. In this scenario MLB is valued at $177M. The 3rd is the pessimistic scenario, in which the PDP for MLB will not result in regulatory approval for any therapeutic area and result in a loss of $100M as MLB value. MS Excel NPV function was used to calculate all three scenarios. Pharmaceutical companies also use the so-called expected net present value (abbr. E-NPV), by weighting the probability of scenario realization and its value. The weights are 38%, 42% and 20% respectively, and the E-NPV is $ 555M. Valuation that takes risk and uncertainty was conducted through two steps. In the first step all values from realistic NPV scenario are taken, while taking into account the probability of success of registration of new therapies as deterministic. The probability distributions of the parameters and calculation using the MCS are included, where the parameters of risk and uncertainty are taken as a distribution of variables: the purchase value of the realized goods is determined as a normal distribution with a mean of 0.68 and a standard deviation from 0.68. The data were then entered into the RiskAmp application [44] with 100,000 iterations, randomly choosing the values of 4 stochastic variables. Results of MCS are mean value

Table 5. Effects of applying real options, in millions of dollars

option	year	NPV amount (success)	difference vs real scenario	NPV amount (failure)	difference vs real scenario
1	2025	204	27	147	(30)
2	2026	180	3	168	(9)
3	2027	187	10	83	(94)
4	2028	178	1	173	(4)
5	2029	177	0	(100)	(277)

Source: Author

Figure 5. Calculation of the value of MLB project real options



Source: Author

of $ 177M, median $176M, and standard deviation of $50M.

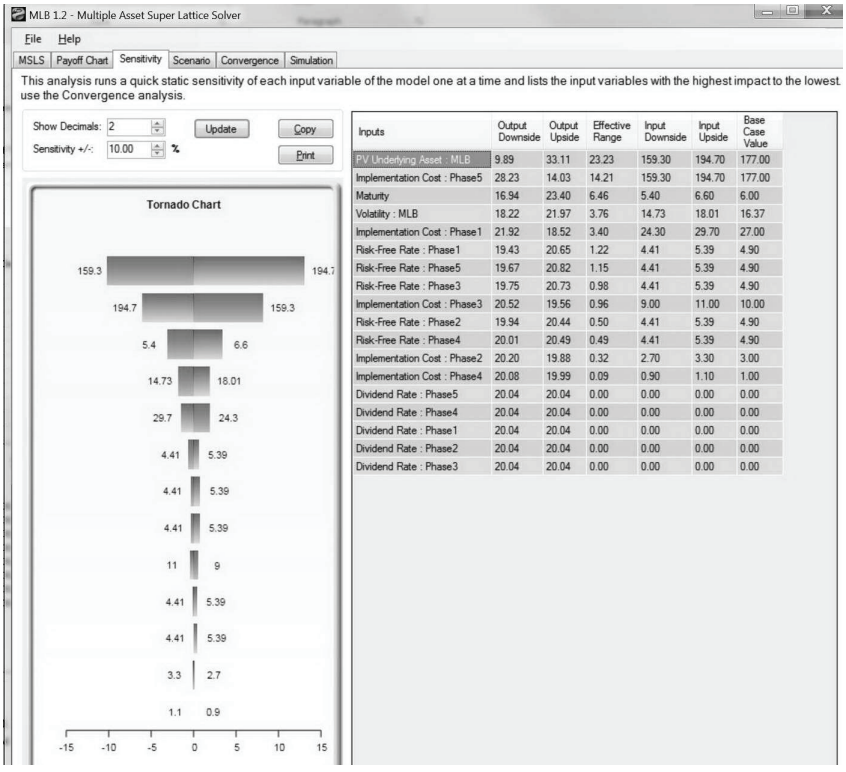
ROA calculation (sequential) used the CSR model by Mun [38, p. 185-187] and the following data: risk-free discount rate 4.9%; (WACC) of Gilead; realistic scenario NPV of $177 M, level of uncertainty about expected cash flow, weighted uncertainties of phase II clinical studies success, phase III clinical studies success, and the risk of the successful drug registration process of 16.369%; dividends are not paid; investments in period 2025-2028 are Real Options 1-4 (amounts to real option values of $27M, $3M, $10M, and $1M, and for 2029, a real option of opt-out.

The calculation was carried out in Real Options Valuation Super Lattice Software v.2017. Jonathan Mann's" Multiple Asset Super Lattice Solver" module with phased investment real options. The result is $20M. The value represents the sum of NPV and Real Options values, i.e. $197M. Below is a presentation of data and results from the software, where the real options are called phases (phase 1 – phase 5). The results of the sensitivity analysis are given below, with 10% as the sensitivity level.

Results analysis

E-NPV is based on data on the expected values of variables, useful for comparison with other valuation results. The MCS value is equal to the NPV real scenario value. Probability distributions (PERT and normal distribution) assign small probabilities to the extremes,

Figure 6. Tornado plot of sensitivity analysis of the MLB project real options



Inputs	Output Downside	Output Upside	Effective Range	Input Downside	Input Upside	Base Case Value
PV Underlying Asset : MLB	9.89	33.11	23.23	159.30	194.70	177.00
Implementation Cost : Phase5	28.23	14.03	14.21	159.30	194.70	177.00
Maturity	16.94	23.40	6.46	5.40	6.60	6.00
Volatility : MLB	18.22	21.97	3.76	14.73	18.01	16.37
Implementation Cost : Phase1	21.92	18.52	3.40	24.30	29.70	27.00
Risk-Free Rate : Phase1	19.43	20.65	1.22	4.41	5.39	4.90
Risk-Free Rate : Phase5	19.67	20.82	1.15	4.41	5.39	4.90
Risk-Free Rate : Phase3	19.75	20.73	0.98	4.41	5.39	4.90
Implementation Cost : Phase3	20.52	19.56	0.96	9.00	11.00	10.00
Risk-Free Rate : Phase2	19.94	20.44	0.50	4.41	5.39	4.90
Risk-Free Rate : Phase4	20.01	20.49	0.49	4.41	5.39	4.90
Implementation Cost : Phase2	20.20	19.88	0.32	2.70	3.30	3.00
Implementation Cost : Phase4	20.08	19.99	0.09	0.90	1.10	1.00
Dividend Rate : Phase5	20.04	20.04	0.00	0.00	0.00	0.00
Dividend Rate : Phase4	20.04	20.04	0.00	0.00	0.00	0.00
Dividend Rate : Phase1	20.04	20.04	0.00	0.00	0.00	0.00
Dividend Rate : Phase2	20.04	20.04	0.00	0.00	0.00	0.00
Dividend Rate : Phase3	20.04	20.04	0.00	0.00	0.00	0.00

Source: Author

Table 6. Summary of MLB PDP valuation results

Valuation method	Result obtained
NPV - optimistic scenario	$1,317M
NPV - realistic scenario	$177M
E-NPV	$555M
NPV - pessimistic scenario	$(100)M
MCS	mean: $177M; median $176M; standard deviation: $50M.
ROA	$197M

Source: Author

so as long as the two values of the distributions are symmetrical, the value of the simulations gives a central value similar to NPV. The median is $1M less than the mean value obtained by MCS. A standard deviation of $50M is not large compared to the differences between the NPV scenario values. This may indicate that the fundamental risks do not change the value of the overall project, while they converge towards the expected values and the existing level of available information does not change over time.

The results of the sensitivity analysis indicate that the NPV of the project (pv underlying asset), real option 5 (sale of the project), maturity date, level of uncertainty and real option 1 (expansion) have the greatest impact on the value of real options, in order of influence level. Comparing the NPV obtained by ROA and the optimistic NPV scenario, for MLB the level of uncertainty that is inherent (the success of phase 3 and registration, essentially) significantly affects the value of the project, than what the management can contribute by their decisions, that is, the partof uncertainty that is beyond the control of the management prevails. The E-NPV of $555M, where the result of real options gives a lower value than through E-NPV, is contrary to the result of Tang, who for PDP in the preclinical phase for the result of value through NPV as a result received a negative value, and through valuation through real options, a positive value [53, p. 385]. The values obtained by the analysis of real options E-NPV are comparable, but the value through ROA gave a higher result.

Conclusion

The approaches to the inclusion of risk in the evaluation of PDP, the specifics in terms of scope and limitations in application are discussed in this paper. Specifics of PDP are stated, including regulatory aspects, cash flows, risks and uncertainties and that early detection of certain project risks is imperative. Monte Carlo simulation gives the value of PDP in the form of a distribution of values. The usefulness of the Real Options approach is conditioned by the existence of managerial flexibilities and provides their value. Using the example of the Magrolimab candidate, the application of modern evaluation methods was provided. The data used were taken from available public sources. The main risks to the success of the project, as well as potential managerial flexibility were identified. In the case of MLB, the low probability of success relativizes the contribution of MCS. Sensitivity analysis provides a risk structure. There is a distinction between an optimistic scenario on the one hand and a realistic or pessimistic scenario on the other. The result of this approach shows that where the project depends on technical-technological success with little certainty of a positive outcome, ROA do not provide a qualitative contribution to the value of the project. For the purposes of PDP valuation, the optimal procedure involves a combination of NPV, MCS (in terms of risk), ROA (in terms of managerial flexibility), while additional procedures include sensitivity analysis and Expected net present value. Further research could go in the direction of quantifying the uncertainty of PDP by therapeutic areas, the distribution of probabilities for them, and updating the prediction of the success rate of the project passing from phase to phase of clinical studies.

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