GENERAL DISCUSSION

This thesis examines the pharmacoeconomic value of targeted cancer therapies (TCTs) applied in the Serbian context. Additionally, the differing Dutch setting served to compare the main inferences drawn for Serbia regarding its economic and clinical aspects. Firstly, burden of disease and drug utilization analyses to identify the scale of cancer burden and availability of TCTs in Serbia was undertaken (Part I). Subsequently, the focus was shifted to estimating costs and effectiveness of TCTs. Illustrative examples of metastatic renal cell cancer (mRCC) TCTs concerned the evaluations of two consecutive therapeutic lines within the Serbian and the Dutch context. Through survival analyses and one network meta-analysis, main methodological issues in modelling of TCTs effectiveness were addressed (Part II). Finally, cost minimisation models comparing the same TCTs with different administration routes were used to illustrate costing structures in Serbian and Dutch oncologic health care (Part III).

Part I: Epidemiology of cancer and access to TCTs in Serbia

To my knowledge, the collection of long-term nation-wide estimates of age-standardised incidence and mortality for Serbia reflects the first publication in this specific area (Chapter 2). Steady increase in overall cancer incidence and mortality through time was revealed in the observed period (1999-2009) for overall cancer and for the 4 most frequent and most fatal cancer sites. Although incidence of overall cancer was comparable to that of the European average, standardised mortality rate for overall cancer in Serbia was notably higher within the European ranking. Alarmingly high mortality rates were found for 4 cancer types: breast and cervical cancer in women and lung and colorectal cancer in men. Notably, trends reflect the strong aging of the Serbian population, one of the most important risk factors, caused by negative natural increase and negative net migration.

Relatively high mortality to incidence ratio observed in Serbia may indicate poorer cancer survival than in other European countries. This could be attributed to the prevalence of risk factors, lack of successful organised screening programmes or delayed adoption of novel cancer therapeutics. Obviously, the nature of specific cancer in combination with potential availability of TCTs that bring survival gains determine which healthcare interventions have most potentials to improve current epidemiological situation. Breast cancer is a typical example in which survival was prolonged by successive administration of TCTs [1], while the effect of mammography screening on survival remains controversial [2-4]. Cervical cancer, however, shows how early detection through simple PAP screening can be a highly effective strategy in cancer prevention [5].

Notwithstanding the need for further research in identification of risk factors and selection of appropriate interventions, presented epidemiological data confirmed earlier more scattered findings that the cancer burden is substantial for Serbia [6]. As the proportion of elderly in Serbia is one of the highest in Europe, and it will continue to rise as an independent risk factor for cancer incidence and mortality, absolute numbers of cancer cases and deaths are even more unfavourable than age standardised rates shown in Chapter 3 and will continue to increase [7,8]. Obviously, in such a situation potentials of any TCT to improve cancer survival should be carefully considered and reflect crucial opportunities to enhance healthy aging.

Every TCT with market authorisation issued by the European Medical Agency (EMA) [9] was inspected for the reimbursement status and pharmacoeconomic assessment in
Serbia, the Netherlands and Scotland (Chapter 3). In total, 41 TCTs were reviewed that were licensed for use in 70 indications. The most of TCT indications (60) were accepted for reimbursement in the Netherlands and considerably less numbers with positive evaluations were identified for Scotland (26) and Serbia (20). Observed differences were based on distinctive approaches in drugs’ assessments and a crucial part of it appeared to be related to cost effectiveness analysis.

While in Scotland a requirement for full cost effectiveness analysis exists for all treatments regardless of their novelty [10], in the Netherlands two special policies may either grant conditional reimbursement to expensive hospital drugs inclusive TCTs or even exempt them from cost effectiveness analysis at initial submission [11]. Notably, in the Netherlands cost effectiveness analysis is required combined with real world data collection from the practice only 4 years after initial approval. A threshold for acceptable cost effectiveness is clearly defined in Scotland, but not in the Netherlands. Unlike the Netherlands or Scotland, Serbian health care authorities did not publish any details on reimbursement decisions or rationales around cost effectiveness evaluations. Only basic descriptions on what cost utility and budget impact analysis should be comprised of was provided in official documents [12].

Serbia can draw on the experiences of Scotland and the Netherlands to choose the approach that combines the advantageous sides of both. Clearly defining pharmacoeconomic criteria and publishing reasoning for each of the decisions should become standard procedure in Serbian submissions, including those for TCTs. Additionally, if there is a need for an exemption based on epidemiologic or clinical arguments, fast access policies with postponed submission of cost effectiveness evidence can be considered. However and obviously, Serbia differs markedly in many economic and clinical parameters when compared to Scotland and the Netherlands and this should be taken into account. Given the economic background of Serbia, a major part of sustainability of the drugs' reimbursement may be related to the availability of generic alternatives (biosimilars) for brand drugs. Obviously, biosimilars are yet lacking for most of the drugs within the new class of TCTs. Furthermore, the gross domestic product per capita (GDP/c) which in the end finances the health care system and thus TCTs reimbursement is 7 to 9 times smaller in Serbia than in Scotland or the Netherlands. One way to incorporate this core economic parameter is by inclusion of this GDP/c in the threshold for cost effectiveness, thus keeping the health care system sustainable. Notably, the World Health Organisation (WHO) advices to consider thresholds in the range of 1 to 3 times GDP/c [13].

Part II: Cost effectiveness of TCTs

In Chapter 4, cost effectiveness was estimated through standard area-under-the-curve Markov modelling for everolimus, second line treatment of mRCC in comparison to the best supportive care. Relying on survival data from everolimus’ pivotal randomised clinical trial (RCT) [14] and estimating costs for the Serbian setting, it was found that everolimus cannot be cost effective under common thresholds of cost effectiveness suggested by WHO (3 GDP/c equalling approximately €13,500/QALY [13]). Yet, due to only a small incidence of mRCC the total budgetary impact of everolimus seems acceptable.

Huge uncertainty exists on the potential survival gains of everolimus. Estimates of overall survival (OS) from the clinical trial were affected by the allowance of cross-over for the patients in the control arm once they had progressed [14]. Statistical adjustment for cross-over is possible with the use of patient-level data only [15]. Since these data were
not available, the only source for OS estimates remained the public submission file to the National Institute for Health and Care Excellence (NICE), in which the hazard multiplier for everolimus’ OS was calculated based on individuals’ data [16]. This hazard multiplier came with a wide confidence interval however, and impacts the final estimate of cost effectiveness more than any other parameter.

On the costs side of the incremental cost effectiveness ratio (ICER) the most dominant input is the cost of the drug. Therefore, under significantly different economic conditions, and comparable price of everolimus the mean ICER estimate at approximately €90,000/QALY is not expected to change dramatically. Indeed, this was confirmed in one specific conference proceedings when a similar Markov model was used to estimate everolimus’ ICER in the Netherlands (€92,000/QALY) [17] and within the NICE submission for the UK perspective (£76,000/QALY) [16].

As discussed above, the analysis of everolimus was confronted with certain shortcomings deriving from data unavailability for some key parameters (Chapter 4). The proportional hazards’ (PH) assumption, so commonly present in survival analyses within health economics assessments [18,19], was necessitated by the structure of available data in everolimus case. To show the impact of this assumption and test an alternative approach of fractional polynomials (FP), progression free survival (PFS) and OS of all clinically effective TCTs in first line mRCC were simultaneously estimated through a network meta-analysis (Chapter 5).

In the network meta-analysis, 8 RCTs were included involving around 4,700 patients on 7 treatment alternatives (interferon alpha [IFN], sunitinib, bevacizumab combined with IFN, pazopanib, placebo, temsirolimus combined with bevacizumab and cediranib). The assumption of hazards’ proportionality between all treatments coming from various RCTs was strongly rejected. Although theoretical grounds for PH modelling do not exist, this was the only approach used in network meta-analyses for mRCC assessment cited in the literature so far [20-26]. Comparison of FP and PH models illustrated the extent of their respective impact on survival estimates.

Advantages of FP modelling concerned multi-dimensional effect estimates, more flexible survival curves through time and allowance for treatments’ hazards to intersect. Applications of PH models, however, prevented intersections of treatments, relied on hazard rate as the only estimate of treatment effect and indirectly assumed constant effect through time, regardless the terminal nature of mRCC. For PFS estimates, this resulted in serious overestimates of survival without progression or death in the PH model. The most effective treatment on PFS seems to be sunitinib, followed by pazopanib and bevacizumab combined with IFN in both FP and PH model. The OS data were again affected by cross-over, yet this time there were no direct or indirect estimates to adjust the effect change. Using intention-to-treat data without cross-over adjustments, the FP and PH models differed less and their estimates were more coherent. There was no clear advantage for any of the treatments on OS and this is consisted with the original trials’ estimates [27-37].

When effectiveness estimates were put in the economic backgrounds of Serbia and the Netherlands, FP and PH model demonstrated huge variations in outcomes (Chapter 5). The combined estimates of effectiveness expressed in QALYs varied to up to 6.3 times (pazopanib) between FP and PH models and they were always lower with the former. Differences of estimated ICERs between countries generally correlated with the price differences of drugs and were frequently smaller than differences in ICERs estimated by
different models. If informal willingness to pay thresholds were set to 3 times GDP/c [13], none of the first line mRCC treatments would appear cost effective in Serbia (€91,000-386,000/QALY), while only the most cost effective treatment options (pazopanib and sunitinib) would have some likelihood of falling below cost effectiveness threshold in the Netherlands (€95,000-462,000/QALY).

**Part III: Cost minimisation analyses of TCTs**

Recently, some TCTs became available in more than one pharmaceutical formulation. Generally, new formulations are expected to lower the cost of drugs’ administration and maintain the effectiveness of older formulations. In the examples of trastuzumab in Serbia and rituximab in the Netherlands, older intravenous (IV) formulations were compared with newer subcutaneous (SC) formulations (Chapters 6 and 7). Since new SC formulations have shown non-inferior efficacy in comparison to the standard IV drugs [38-41], cost minimisation models were considered sufficient for the economic evaluation of proposed TCT formulations. Within the cost minimisation framework it was also possible to analyse differences in disease management and resource use costs between Serbia and the Netherlands.

Cost minimisation models were differently designed in the Serbian and the Dutch study. Notably, the Dutch study followed the clinical trial design and collected measurements of time and costs spent in practice for administration of IV and SC rituximab in diffuse large B-cell lymphoma (DLBCL) during the trial. The Serbian study was based on the estimates of time and costs provided by clinicians per each of the steps in the administration algorithm, for IV and SC trastuzumab in early and metastatic breast cancer (BC). Both studies confirmed that new SC formulations could be cost saving strategies which when transferred to the whole DLBCL and BC bring reasonable savings (Chapters 6 and 7).

Important parts of the savings came from differences in drug costs (SC versus IV) due to the different dosing regimens of two formulations in both health care systems. Yet, substantial discrepancy exists in the scale of the savings other than drug costs. Considerable differences between Serbia and the Netherlands were noted. While savings in time spent in facilities were impossible to be expressed monetary in Serbia, these savings contribute the most to the total costs’ difference observed in the Netherlands (Chapters 6 and 7). Additionally and in the absence of cost price estimates, labour wages of a nurse or an oncologist could not be expressed dependently on the number of offered services in Serbia, and therefore these expenses were neglected in the presented cost minimisation study (Chapter 6). Although underestimated in this way, savings in time of medical staff and facilities established through CMA in Serbia can have huge impact on BC clinical practice. This illustrates an urgent need for better costing data in Serbia, potential along the lines of the specified Dutch Framework for Costing [42].

**Policy recommendations**

The final goal of this thesis was to draw inferences on potential TCTs’ cost effectiveness in Serbia and provide recommendations for conduct of rational reimbursement policy towards this group of drugs relying on the Western European/Dutch experiences. From the presented cost effectiveness estimates of selected mRCC TCTs, it can be concluded that none of the examined drugs appears cost effective under the common threshold. Furthermore, it could be implied that most of the TCTs’ ICERs will not significantly differ
between the countries and once the effectiveness is properly estimated, the main driver of cost effectiveness likely remains the cost of the drugs. Based on the existing price parities among countries for most of TCTs, relatively good transferability of the estimated ICERs can be assumed. Under this assumption most of the TCTs’ ICERs reviewed in this thesis for the Netherlands or Scotland will not be found cost effective in Serbia. Main discrepancy appears in a low economic capacity of Serbia to finance the drugs estimated at the upper limits of cost effectiveness thresholds in some of the most developed countries.

More broadly, under present TCTs’ pricing any mid-income country (€1,000 – €11,000 of GDP/c [43]) would be faced with similar dilemma on their reimbursement. Although it is clear that most TCTs will hardly comply with the standard cost effectiveness merits, sensitive question arises on whether they should actually be put in these standard merits [44,45]. Some of the most influential institutions renowned for rigorous health economic assessment such as the British NICE, or the Scottish SMC apply specific end-of-life treatment guidelines or decision modifiers in case of TCTs [46,47]. These allow reimbursement of a TCT despite exceeding regularly determined cost effectiveness thresholds if a TCT: (i) does not have therapeutic alternative; (ii) prolongs life for at least 3 months; (iii) constitutes relatively small budgetary impact. Furthermore, presented policies in the Netherlands (Chapter 3) are created to enable fast access for clinically proven expensive hospital drugs. Economic evaluation in such situations is necessitated 4 years after initial approval and it should include collected real world data on treatment’s effectiveness [48].

It was out of the scope of this thesis to determine and define the most appropriate policy on TCTs reimbursement. It, however, identified Serbia as a country with substantial and rising burden of cancer, which emphasised importance for proper and, perhaps, specific TCT evaluation. Neither of TCT policy models described here (Dutch or Scottish) did exclude pharmacoeconomic assessment from the reimbursement process. Moreover, it is the economic evaluation that proved crucial for the reimbursement of TCTs. Serbia should, therefore, clearly specify reimbursement criteria and within them elucidate details of the TCTs pharmacoeconomic assessment.

Modelling the effectiveness of TCTs is a demanding task. This thesis emphasises the importance of accounting for all underlying assumptions in TCTs’ survival analysis. With the yet rarely practiced approach of FP, it proves feasible and advantageous to model networks of evidence on survival analysis. Within the field of novel TCTs which triggers debates on proper use of cost effectiveness, methodological issues should be tackled with caution and with help of specific guidelines. This can be particularly important for countries that recently implemented cost effectiveness policy, such as Serbia and experiences from the Western European countries – such as the Netherlands – can help here [49].

Future perspectives

Results of this thesis opened the perspectives for further research. Although fundamental epidemiologic and pharmacoepidemiologic data for Serbia were collected in the field of cancer and TCTs to facilitate presented analyses, some basic data for future pharmacoeconomic assessments are still missing. These include country specific utilities per each of the cancers and per the disease phases and establishment of willingness-to-pay thresholds and would require nation-wide surveys. From the clinical perspective it
would be interesting to confront findings of this thesis on TCTs cost effectiveness and potential outcomes on preventive strategies’ cost effectiveness in Serbian setting. Only balanced utilisation of curative and preventive methods relying on rational cost utility assessment can lead to sustainable reduction of cancer burden in Serbia.

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