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Short Title: Decision-making in advanced Hodgkin Lymphoma

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Abstract
Introduction: In the treatment of advanced Hodgkin Lymphoma (aHL), based on guidelines a multitude of treatment options are available. The availability of PET guided decision-making and new therapeutic agents increase the complexity of the decision-making process.
Methods: Thirteen experts of Swiss university and cantonal hospitals in Switzerland were asked to describe their institutional decision-making practice in aHL. Variables influencing the decision-making process were identified, standardized and converted into decision trees for analysis of consent and discrepancies. The algorithms of all participating experts were analyzed with the objective consensus methodology.
Results: Four decision criteria (age, fertility preservation, fitness, interim PET) and 12 unique treatment regimens were identified. Consensus for the treatment of aHL for young and fit, as well as for older patients without comorbidity was found. Large heterogeneity was identified with use of a variety of different regimens for unfit patients with aHL and for young female patients with a desire of fertility preservation.
Conclusion: Four major decision criteria were identified allowing the representation of expert's approach to first-line treatment of aHL. Among Swiss experts, consensus for a PET guided curative treatment of aHL was identified. The use of a multitude of treatment regimens was observed for older and comorbid (unfit) aHL patients, highlighting the need for clinical trials and recommendations for this group of patients.

Introduction
Hodgkin Lymphoma is a are disease, affecting young adults and in a second peak, patients over the age of 60 years. Among young patients, the cure rate for Hodgkin lymphoma is very high and fertility preservation becomes an important issue. In clinical oncology a multitude of treatment options are available for individual situations [1], and various factors may influence the choice of a specific treatment [2]. In advanced Hodgkin Lymphoma (aHL), first-line treatment is based on several phase 3 studies with adriblastin, bleomycin, vinblastine, dacarbazine

(ABVD) or bleomycin, etoposide, adriblastin, cyclophosphamide, vincristine, procarbazine, prednisone in an escalated dose (BEACOPPesc) as backbone chemotherapy [3, 4]. Treatment algorithms in European countries are reflected in ESMO guidelines [4] and guidelines of the German Hodgkin Study Group (GHSG) (www.ghsg.org). Recommendations for aHL mostly refer to patients without comorbidities and younger than 60 years of age. Due to the toxicity of standard intensive chemotherapy regimens in older patients and long-term side effects in young women, these groups of aHL are mostly not covered in recommendations. Interim PET staging is an accepted standard to escalate or de-escalate treatment regimens for aHL. Although the RATHL study did not meet its primary endpoint (exclude a difference of 5% in terms of PFS at 3 years), for patients with interim PET negativity (Deauville Score 1-3) the omission of bleomycin after 2 cycles ABVD due to expected lung toxicity, is an often used approach [5]. In the HD18 and AHL2011 de-escalation was made possible for interim patients, either by reducing the number of cycles of BEACOPPesc or modifying the treatment by 4 cycles of ABVD [3, 6].
Various palliative treatment options exist for comorbid and frail patients not eligible for intensive first-line chemotherapy regimens or escalation of treatment after interim PET positivity. Furthermore, recommendation of a chemotherapy regimen after reproductive counseling for young women remains complex.
The proximity of Switzerland to France, Italy and Germany influences collaboration within study groups of the mentioned countries and through this influences treatment approaches for aHL. Of the 250 cases of HL diagnosed per year, 20% are treated within trials of the German Hodgkin Study Group (GHSG). Based on trials from the GHSG, BEACOPPesc is the standard of care in aHL for many European countries whereas some others and many non-European countries favour ABVD as their first-line treatment regimen.
We performed a decision-making analysis to understand the clinical management in aHL among lymphoma experts in Switzerland.

Methods

We contacted 13 Swiss oncological centers and their representatives to participate in this decision-making analysis. Lymphoma experts representing various cantonal and university hospitals across Switzerland with a regular oncology-hematology tumor board agreed to participate. The experts were asked to openly respond in any format they preferred (phone call, sketch, text or presentation slides) to the following question “Please describe which treatments you use for first-line treatment of advanced Hodgkin Lymphoma outside of clinical trials. “Please describe criteria relevant to your treatment choice”. Nodular lymphocyte-predominant Hodgkin Lymphoma were excluded from analysis. Radiotherapy options or participation within a trial were not considered or analyzed in the algorithm.
The initial responses were collected and standardized decision-criteria determined based on the objective consensus methodology [7, 8]. Insular decision-making factors not used by at least 2 centers were excluded from further analysis [9], but are addressed in the discussion.
The resulting decision criteria included age (with cut-off values at 50, 60 and 70 years), fitness (categorized as fit, unfit and frail), desire for fertility preservation (FP) (classified as yes or no) and a PET response after 2 cycles if applicable (classified as positive or negative PET). A total of 12 different treatment regimens or single agents were recorded, see Table 1.
The initial input was converted into draft decision trees, which were then iteratively corrected to represent the center’s management strategy [7, 8]. The final decision trees were approved by the experts in May 2022 and were analyzed for consensus and discrepancies as performed in other settings [10-13]. A consensus was defined when a majority (at least 50%) would recommend a single specific treatment for any given parameter combination.

Results

A total of 13 lymphoma experts provided 12 unique treatment proposals with 21 variants of administration based on the implementation of up to four decision criteria (age, fertility preservation, fitness, interim PET). The individual regimens are listed in Table 1. An example of a single-center decision tree is provided in Figure 1. Figure 2 shows the decision-making tree based on all responses. There was consensus for fit patients who were under 60 years of age irrespective of the wish of FP to perform the intensive BEACOPPesc regimen with an interim PET/CT adapted response with two or four further cycles (62-100%). In the setting of patients over the age of 50 or 60 years respectively, agreement for fit patients with a negative PET after 2 cycles of ABVD followed by four more cycles of AVD, were observed (consensus of 54%).
No consensus was achieved for unfit or frail patients of any age. Figure 3 provides an example of the heterogeneity encountered. For unfit, patients under the age of 50 years old with a positive PET (if applicable),

nine different treatments were recommended by 13 experts. In all other cases (unfit, older than 50/60 years and negative PET or frail of any age) no single most common treatment could be identified.

Discussion

The present study documents areas of consensus and variability in the approach to first-line treatment of aHL among lymphoma experts in Switzerland. Most institutions categorized aHL within three patient defined key criteria: age, fertility preservation and fitness. A fourth, treatment related criteria based on the prognostic importance of the interim PET on survival [14], was applied. Age and comorbidity could be further identified as important variables in decision-making as treatment-related toxicity affects the outcome in this group of patients [15]. Fertility preservation was a considered variable although its implementation in decision-making varied among the Swiss centers.

The curative intent of BEACOPPesc with de-escalation of chemotherapy cycles for interim PET negative patients was the most commonly recommended regimen [3]. The alternative first-line regimen with ABVD, although with a higher rate of fertility preservation, was clearly perceived as an inferior treatment [16, 17]. The survival benefit of 10% at 5 years in a meta-analysis of BEACOPPesc when compared to ABVD, justifies the preference of this option after a reproductive counseling for young women [18]. This algorithm of Swiss oncology lymphoma experts is in contrast to a UK cross-sectional online survey where infertility was more important to physician's treatment decision than progression-free survival when considering young women with unknown fertility preferences [19]. De-escalation from BEACOPPesc to ABVD was proposed by some experts [6] as fertility after two cycles of BEACOPPesc may be preserved [17]. In addition, many Swiss centers are familiar with the intensive BEACOPPesc regimen due to a long tradition of cooperation with the GHSG making this regimen the standard of care for aHL in many institutions.

Bleomycin, a lung toxic chemotherapy has a treatment-related mortality of 9% in patients older than 60 years of age and yields lung alterations in 43% of patients [20]. The omission of bleomycin after two cycles of ABVD based on PET negativity is better tolerated with preserved efficacy [21, 22, 5]. Based on this result some experts alternatively treated this age group of older and fit patients with the antibody-drug conjugate brentuximab vedotin (BrV) combined with AVD for a total of six cycles [23]. In contrast to other phase 3 trials for aHL no age limit was defined in this study as bleomycin was replaced by BrV omitting the drug with a potential toxic effect on the lungs.

BrECADD is a second alternative regimen chosen by some experts to reduce the acute and long-term toxicity of the bleomycin containing BEACOPPesc. The phase 2 study confirms the efficacy with comparable response rates of this BEACOPP variant [24, 25].

Variable treatment options were reported for unfit and frail patients for first-line treatment reflecting a missing standard of care for this population. Comorbid patients are excluded in most trials and represent therefore a group of aHL patients where an individual approach is addressed. For patients not suitable for lung and/or cardiotoxic based regimens a palliative treatment approach with alternative single agent or chemotherapy combinations, radiotherapy only or new drugs as well as best supportive care can be considered.

Not yet established as first-line regimens are the anti-PD-1-based treatment approaches.

Two randomized phase 2 trials in early stage unfavorable HL with nivolumab concomitant with AVD (N-AVD) or sequential with 4 doses of nivolumab, 2 cycles of N-AVD, and 2 cycles of AVD, followed by 30 Gy involved-site-radiotherapy (GHSG) resulted in an excellent remission rate of 90 and 94% CR respectively. [26]. Based on CheckMate 205 with 4 doses of nivolumab, followed by 12 doses N-AVD promising efficacy was observed for aHL [27].

Experts in the current decision-making analysis proposed prednisone, vinblastine, adriblastin, gemcitabine (PVAG) [28] or cyclophosphamide, adriblastin, vincristine, prednisone (CHOP) [29] for those not suitable for bleomycin and chlorambucil, vinblastine, procarbazine and prednisolone (ChlVPP) [30] for patients with severe comorbidities. New drugs, such as the antibody-drug conjugate BrV have a low toxicity profile and were evaluated individually although their efficacy is suboptimal as monotherapy [31]. PD-1 blockade via pembrolizumab [32] or nivolumab [33] are well tolerated with a low toxicity profile and effective in relapsed aHL and were therefore used as palliative treatment regimens in comorbid patients.

Similar results of the multitude of regimens were documented in a population-based, retrospective analysis including 269 patients with HL older than 60 years conducted in 15 referral centers in Switzerland. 10 different types of first-line systemic regimens were reported, with only 5% of patients included in clinical trials [34]. Forty percent of patients with HL are older than 50 years at diagnosis and have a significantly worse outcome than

younger patients [35]. There is a clear need to include older patients not suitable for bleomycin-containing regimens in clinical trials with new drugs.

A limitation of our study is that we are not able to evaluate outcome data for the individual approaches; this is due to a large heterogeneity of the patient population and limited availability of suitable databases. Additionally, it cannot be excluded that individual experts would deviate from their described decision strategy in individual cases, for example in young women. While the number of participants could be higher or lower, we would not expect a different number of experts significantly affecting areas of high consensus or areas of high variability.

To the best of our knowledge, this is the first decision-making analysis in the approach to first-line treatment of aHL of this kind among lymphoma experts. The decision-making criteria identified reflect in part the available guidelines for a curative approach and outcome data for older and comorbid patients. Additionally, the specific recommendations are probably influenced by geographical location and even by shared languages with neighboring countries, characterized by their specific study protocols and guidelines. Furthermore the findings represent the large variability of treatment choices for patients not being typical candidates for clinical trials (older or unfit patients). Based on this knowledge the need to define recommendations for an increasing group of older patients with aHL is urgently warranted.

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Statement of Ethics 'Ethical approval and consent were not required as this study was based on publicly available data

Conflicts of Interest
Paul M. Putora has received a grant to the institute from Takeda related to this project, and grants to the institute from Bayer and AstraZeneca unrelated to this project.
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Author Contributions
Felicitas Hitz made substantial contributions to the conception, the acquisition, analysis and interpretation of data; drafted the work; finalizded the approval of the version to be published; agreed to be accountable for all aspects of the work
Noémie Lang interpretation of data; revised it critically; finalized the approval of the version to be published; aggreed to be accountable for all aspects of the work
Ulrich Mey interpretation of data; revised it critically; finalized the approval of the version to be published; aggreed to be accountable for all aspects of the work
Alden Moccia interpretation of data; revised it critically; finalized the approval of the version to be published; aggreed to be accountable for all aspects of the work
Walter Mingrone interpretation of data; revised it critically; finalized the approval of the version to be published; aggreed to be accountable for all aspects of the work

Christian Taverna interpretation of data; revised it critically; finalized the approval of the version to be published; aggreed to be accountable for all aspects of the work
Urban Novak interpretation of data; revised it critically; finalized the approval of the version to be published; aggreed to be accountable for all aspects of the work
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Adrian Schmidt interpretation of data; revised it critically; finalized the approval of the version to be published; aggreed to be accountable for all aspects of the work
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Natalie Fischer interpretation of data; revised it critically; finalized the approval of the version to be published; aggreed to be accountable for all aspects of the work
Paul Martin Putora made substantial contributions to the conception, the analysis and interpretation of data; drafted the work; finalizded the approval of the version to be published; agreed to be accountable for all aspects of the work

Data Availability Statement
All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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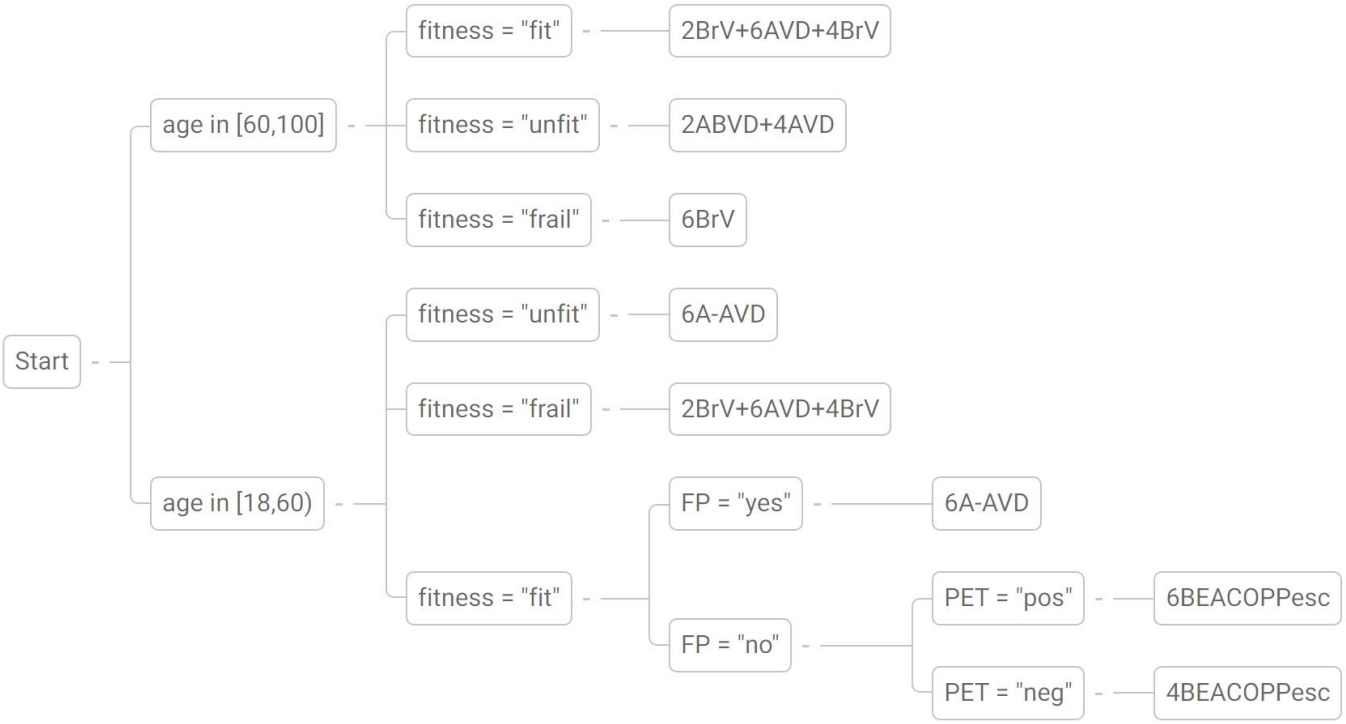
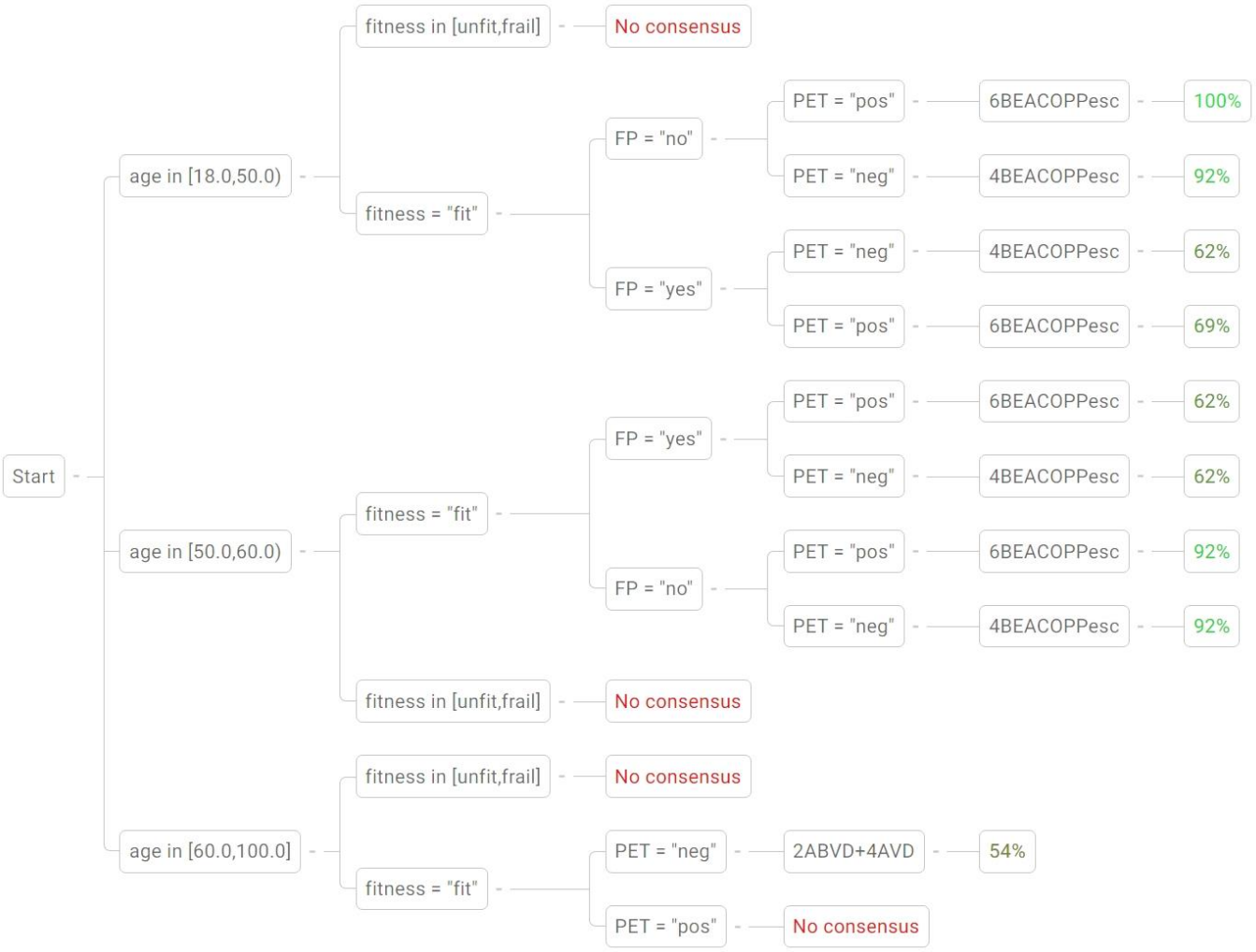
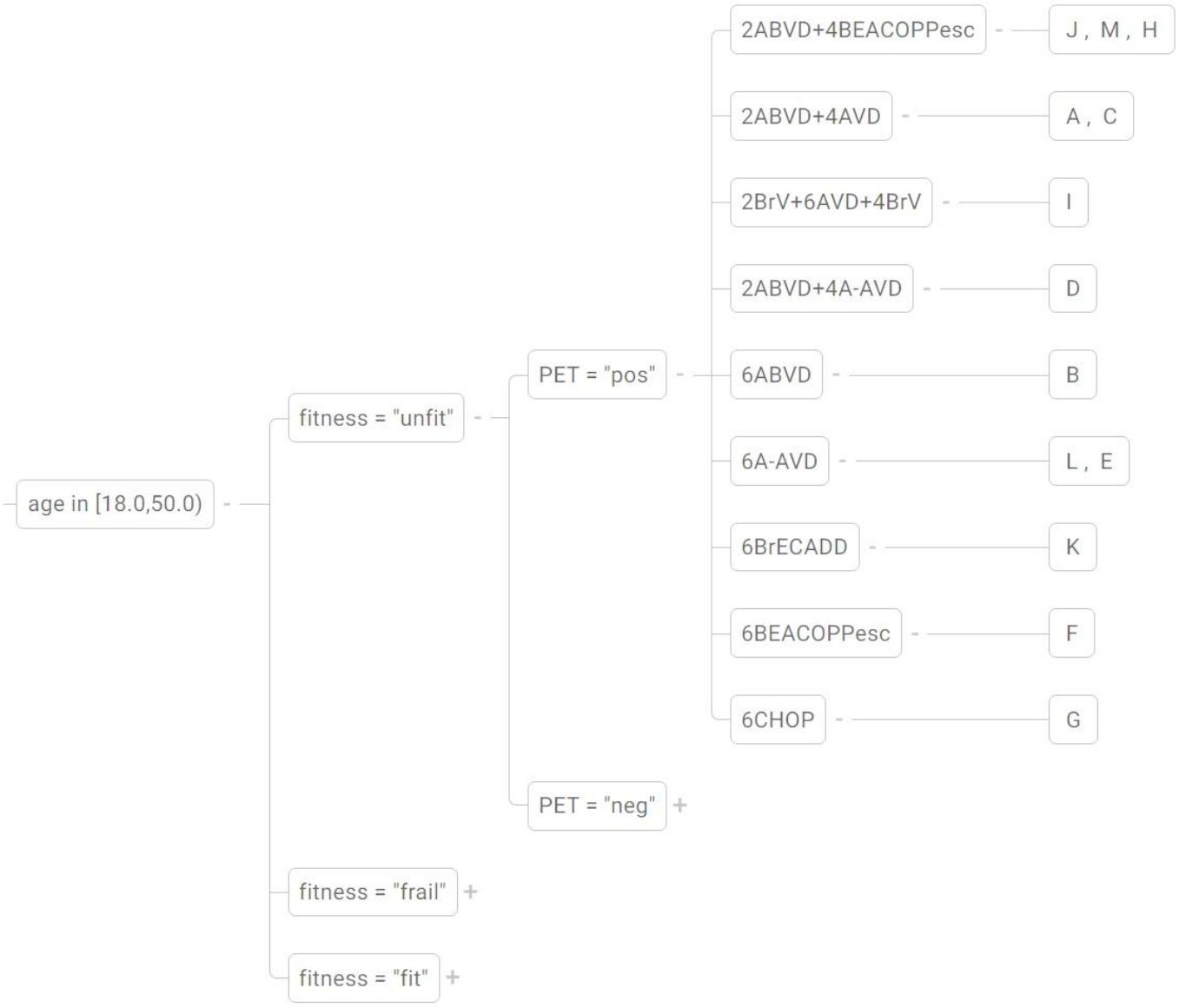
Figures:







BEACOPPesc*	Bleomycin, etoposide, adriblastin, cyclophosphamide, vincristine, prednisone
ABVD*	adriblastin, bleomycin, vinblastine, dacarbazine
AVD	adriblastin, vinblastine, dacarbazine
A-AVD	brentuximab vedotin, adriblastin, vinblastine, dacarbaczine
BrECADD*	brentuximab vedotin, etoposide, cyclophosphamide, adriblastin, procarbazine, prednisone
BrV+AVD+BrV	brentuixmab vedotin sequentially combined with adriblastin, vinblastine, dacarbazine
ChlVPP	chlorambucil, vinblastine, procarbazine and prednisolone
PVAG	prednisone, vinblastine, adriblastin, gemcitabine
CHOP	cyclophosphamide, adriblastin, vincristine, prednisone
BrV+Pembro	brentuximab vedotin plus pembrolizumab
BrV	brentuximab vedotin
Pembro	pembrolizumab

Table 1 Type of used chemotherapy, immuno-chemotherapy regimens or single agents
*PET guided de-escalation or escalation regimens