ELI's 2nd conference on:

“Refractory Hodgkin Lymphoma”

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HL is nowadays a highly curable disease with chemotherapy, with 95%, 85% and 75-80% overall survival (OS) for favorable early-stage disease, unfavorable early-stage disease and advanced stage disease, respectively. Cumulative relative survival has improved through decades with various change in chemotherapy agents, aiming better first complete remission (CR) achievement, but also fewer late toxicity. With first line therapy still being a controverted issue, there is no clear salvage standard for early relapsing or refractory patients.

After an overview of first line chemotherapy, the objective of this meeting was to define refractory HL, to describe the characteristics of these patients and explore therapeutic possibilities, with the goal to elaborate a specific multicenter prospective trial for this specific population.

- **First line chemotherapy**

First-line chemotherapy for HL is still a matter of debate. For early-stage disease, treatment depends on classification of prognostic factors that are not fully consensual between the different cooperative treatment groups. For the GELA-EORTC group, mediastinal bulky mass, age over 50, number of involved nodes (4 or more), erythrocyte sedimentation rate (ESR) and presence of B symptoms are the defined risk factors with favorable group disease having Ann Arbor stage I or II with none of these risk factors. For the GHSG group, bulky mediastinal mass, any extranodal sites, ESR, number of involved nodes (3 or more) and presence of B symptoms are considered risk factors with patients without any and stage I and IIA disease being classified as early favorable patients, and stage IIB with mediastinal bulky mass or extranodal disease being considered as advanced stage patients. Both groups view stage III and stage IV patients as advanced stage disease.

For the GHSG group, since HD10 trial, favorable early-stage disease is treated with 2 cycles of ABVD followed by 20 Gy involved field radiotherapy (5 year freedom from treatment failure and OS 91% and 98%, respectively). With HD14 trial results, early unfavorable patients are now usually treated with 2 cycles of escalated BEACOPP followed by 2 cycles of ABVD an 30 Gy IFRT. For late stage disease, the HD9 trial confirmed improvement of both progression free survival (PFS) and OS through 10 years of follow-up with 8 cycles of escalated BEACOPP compared to 8 cycles of standard BEACOPP and 8 cycles of COPP-ABVD (OS 86% versus 80% versus 75%). Recently published, the HD15 trial has established 6 cycles of escalated BEACOPP instead of 8 cycles as new standard of care with significantly inferior OS with the longer treatment (95.3% versus 91.9%). In addition, patients with residual disease > 2.5 cm and FDG-PET positive all received involved field radiotherapy. Four years PFS estimates for these FDG-PET positive patients was 86.2% compared to 92.6% for PET-negative. Although not randomized data, it shows that even FDG-PET positive patients can have a good outcome with only IFRT, at least for BEACOPP-escalated treated patients. However ABVD is still considered standard of care by other groups with
other trials like the Italian one conducted by Viviani et al not showing OS advantage of BEACOPP over ABVD.\textsuperscript{10}

For the GELA group, early stage disease is treated with 3 to 4 cycles of ABVD according to the presence or not of risk factors, followed by IFRT if required. Most patients with early unfavorable or late stage disease are randomized in the AHL 2011 trial comparing « standard » 6 cycles of escalated BEACOPP with a therapeutic strategy driven by interim PET results with ABVD following two cycles of escalated BEACOPP for PET negative patients.

- **Definition of relapsing /refractory patients**

The group of experts agreed on a definition of relapsing and refractory patients. Primary progressive disease is defined as progression during first-line or less than 3 months after the end of therapy. Early relapse represents progression after 3 months and less than 12 months after the end of therapy. Finally, late relapses occur after 12 months of the end of therapy. According to HD15 trial, 8.4% of patients suffered relapse after a BEACOPP-based first-line regimen. Among them, 3.1% were primary progressive patients, 2.6% early relapsed and 2.8% late relapsed.\textsuperscript{9}For early-stage unfavorable disease, HD14 trial showed that 2 cycles of escalated BEACOPP could improve first relapsed patients rate from 8.4% to 2.5% and refractory patients form 3.8% to 1.3% compared to ABVD alone.\textsuperscript{7}With first line ABVD regimen, failure rate is higher, consistently between 25 to 30%, with half consisting of primary progressive disease.\textsuperscript{10}

- **Prognostic factors of relapsed and refractory hodgkin lymphoma**

**International Prognostic Score**

Nowadays, at diagnosis we still rely on the IPS (International Prognostic score) and its 7 clinical risk factors\textsuperscript{11} to stratify advanced stage HL. Still useful in identifying a group of patient’s prognosis, it does not help clinicians to make therapeutic decisions on an individual basis. In fact, it is a poor discriminative prognostic index compared to interim FDG-PET performed after 2 cycles of first line therapy, with high and low scores patients having similar outcomes depending on PET positivity.\textsuperscript{12}

**Biological factors**

If several biological and pathological factors have been shown predictive of outcome, there are very few published data on true phenotype of HL at relapse. Almost all medical knowledge is based on analysis of initial diagnosis biopsies. In addition, very few studies used paired specimens, at diagnosis and at relapse. Every expert agreed that a biopsy is mandatory at relapse, early or late, with the possible exception of primary progressive disease. With international collaboration, we could expect to collect large number of samples in order to evaluate biomarkers at the time of relapse. The few existing data on tumor cell lines show that relapsing tumors tend to be more aggressive, with increased genetic instability through time. A burning question was if there is a specific phenotype for refractory HL and if it should be looked for on the few tumor cells (Hodgkin Red Sternberg cells, HRS) or on the majority of microenvironment cells or on both. Indeed, interaction between these two components is essential.\textsuperscript{13}

Recently, more prognostic biological factors identified by immunochemistry, cytogenetic and molecular studies have been correlated with relapse or more aggressive disease. Far from being exhaustive, we are presenting the most discussed biomarkers during the meeting. Among those, BCL2 expression,\textsuperscript{14} cytotoxic molecules positivity (TIA-1, granzyme B),\textsuperscript{15,16}
diminution of MHC II expression, amplification of multi-drug resistant gene ABCC1 and positivity of CSF1R in the HRS cells were shown to have adverse prognostic value. As well, in the microenvironment many biological factors have been studied. Tumor-associated macrophages (corresponding to IHC CD68+, CD163+ cells) are consistently shown in multiple trials to be a strong bad prognostic factor.\textsuperscript{17,18,16} For example, in a retrospective French study, Deau et\textsuperscript{19} showed that the expression of c-kit, TIA-1 and CD68 (IHC) were independently associated with refractory disease. Recently, Steidl et al performed gene expression profiling for microdissected HRS cells and found that in-situ hybridization for mRNA CSF1Rand CD68 expression in IHC predicted survival, underlying the interaction between HRS and the microenvironment.\textsuperscript{17} A combined score relying on these two factors was strongly correlated with PFS and OS. In addition, CD68 expression was shown to be predictive of survival after ASCT with failure post-ASCT varying between 12.5\% and 62.5\% depending of the percentage of tumor infiltration by macrophages.\textsuperscript{20} However, a few studies did not find any correlation between CD68 and CD163 microenvironment cells expression and prognosis.\textsuperscript{21,22,23} If every panel expert was enthusiastic concerning the prognostic value of CD68 expression, not everyone agreed on its possible use in clinical practice, due to issues with robustness and reproducibility of the techniques. Concerning CD20 expression, some studies have showed a bad prognostic value on DFS.\textsuperscript{15} (Greaves et al, JCO 2012 in press) In the latter study, FOXP3 was also correlated with a worse outcome, outlining the role of microenvironment Treg lymphocytes. Once again, the impact of this biomarker is controversial at this point.\textsuperscript{16} Cytogeneticand molecular biology are now increasingly used to stratify prognostic groups. With HRS cell laser microdissection analysis, recurrent imbalances were correlated to treatment outcome, mainly 16p gain (found in 83\% of primary refractory patients), probably linked to primary drug resistance gene and ABCC1 locus.\textsuperscript{17} Randy Gasgoyne reported a soon to be published (Scott et al, JCO) study using Nanostring technology on whole biopsy specimen with 23 genes analyzed and permitting stratification of bad prognosis HL treated with ABVD. According to Randy Gasgoyne, this prognostic tool is more reproducible and robust than CD68 IHC and could have a future clinical implication. The next issue would be to know if intensified regimen as BEACOPP or targeted therapy could overcome this inherent biological worse prognosis.

For routine use at diagnosis, a French team from the LYSA group studied circulating cytokines and proteome to identify refractory HL. They constructed a cytokine signature score based onIL6, IL1RA and sCD30 expression that could predict outcome of patients treated with ABVD and identified about half of the patients with refractory disease.\textsuperscript{24} However, it cannot penetrate clinical practice due to difficulties in standardization of technical analysis. The same group is now using proteomics analysis of plasma and ionization mass spectrometry to identify the profile of long-term responding compared to early relapsed patients.

**PET SCAN**

It is now well accepted that FDG-PET improves the accuracy of HL staging at diagnosis. If 10 to 25\% of patients are upstaged and few downstaged,\textsuperscript{25,26} however treatment strategy is only modified in 6 to 9\%. Moreover, SUV max at baseline did not show any relationship with treatment outcome and initial FDG-PET is not helpful in identifying refractory patients.\textsuperscript{12,22} On the other hand, interim FDG-PET has proven its prognostic value to identify refractory or relapsing patients after first-line chemotherapy.\textsuperscript{12} Multiple trials are now evaluating interim FDG-PET adapting strategies to see if a change in therapy can improve late outcome. Recently, FDG-PET has also prove to be predictive of outcome at time of relapse or progression. First, in a small study with 24 patients, FDG-PET performed after 2 cycles (PET-2) of salvage IGEV (ifosfamide, Gemcitabine, Vinorelbine) and before autologous steam cell transplantation (ASCT), 13/14 patients with negative PET-2 maintained CR after ASCT while 9/10 with positive PET-2 relapsed.\textsuperscript{28} Recently, Moskovitz et al. published a combined analysis including 153 relapsing patients responding to a ICE-based (Ifosfamide,
Carboplatin, Etoposide) salvage therapy. In this study, metabolic imaging performed just before ASCT result was the only factor significantly associated with outcome (5 years EFS 31% versus 75% for FDG-PET positive versus FDG-PET negative patients: p<0.0001).39 Other studies and a metaanalysis showed similar results with longer PFS and OS with pre-transplant negative FDG-PET.30,31

FDG-PET for follow-up has also been evaluated and based on the lack of cost-effective benefit, the ACR guidelines do not recommend it as a tool to detect relapses. If in any situation, FDG-PET at follow-up should be limited to high risk patients (defined as positive interim FDG-PET?).

In conclusion, the panel strongly agreed on the prognostic value of FDG–PET before ASCT at relapse. However, how to modify treatment according to results is still a matter of debate. Should these partially responding FDG-PET positive patients receive a third line of chemotherapy to aim negativity before ASCT, go directly to single ASCT as usual, proceed to tandem ASCT oralloSCT?

- Treatment of refractory and relapsing HL

ASCT is currently the standard of care for chemosensitive relapse, with 2 major trials showing improvement in PFS without statistically significant change in OS.34,35 Consistently through different trials, primary progressive disease has shown inferior results to salvage treatment, as in the HDR2 phase-II pilot study with 2 years OS 24% for primary progressive disease compared to 58% for early and late relapses.36 In a retrospective study with 3807 patients, 206 primary progressive patients were identified. Their freedom from second failure (FF2F) was 17% and their 5 years OS was 26%. For patients treated with salvage ASCT (34%), OS and FF2F were 43% and 31%, respectively.37 These poor results confirm the importance to find new therapeutic options for these patients.

Approaches according to different European groups

**LYmphoma Study Association (LYSA) (figure 1)**

According to LYSA, patients are stratified in 3 prognostic groups. The poor risk group is defined by primary refractory or high risk relapse (early relapse AND stage III-IV disease at relapse). The intermediate group is composed of either one of the two risk factors (early relapse OR stage III-IV disease). The standard risk comprises relapsed patients with none of the risk factors (relapsed after 12 months and stage I-II disease).

![LYmphoma Study Association (LYSA) diagram](https://example.com/lysa_diagram.png)
Other factors should be considered for treatment decisions such as bulky disease, anemia, ECOG, B symptoms and relapse in irradiated field. Salvage is based on DHAP, DHAOX or ICE regimen for 2 to 3 cycles, with IGEV (ifosfamide, gemcitabine, vinorelbine) and GVD (gemcitabine, liposomal doxorubicin and vinorelbine) as third option if needed. This is followed by stem cell collection after first cycle and ASCT for chemosensitive disease. Radiotherapy is typically used if not previously done, in sub-diaphragmatic localisation if partial response or FDG-PET positivity before ASCT. IFRT is given, preferably after ASCT, at a dose of 30 Gy (boost 6-10 Gy). Responses to treatment are evaluated with CT Scan after 2 or 3 cycles of salvage and patients in CR are said to be chemosensitive with no other imaging tests performed before ASCT. However, patients with persistent tumour on CT SCAN are scheduled for FDG-PET read using the 5 points scale Deauville criteria^38-40. Patients with score 1-3 are considered chemosensitive and directed to proceed to ASCT and patients with score 4 or 5 are directed to third line salvage treatment to improve response. They recall that a treatment strategy based on FDG-PET/CT evaluation is not yet prospectively validated.

Treatment strategies according to each prognostic group are the following: poor risk patients with chemosensitive disease all go to a first ASCT and then can either be consolidated with a second ASCT or a alloSCT (with fludarabine and busulfan conditioning). Patients going to alloSCT are observed in a prospective study (HR 2009). Intermediate risk patients are usually treated with single ASCT and are generally not directed to alloSCT. Patients relapsing without risk factors with chemosensitive disease do not receive any type of consolidation after reinduction, except for radiotherapy if needed. Moreover, patients with chemosensitive disease with alternative bad prognostic factor (relapse in an irradiated field and/or bulky disease at relapse) also receive ASCT. Finally, non-chemosensitive patients are treated the same whatever their initial risk group: after a third line chemotherapy, they can either go to fourth line (now including Brentuximab Vetodin (BV), SGN-35) or be included in phase I-II trial. Waiting the results of on-going studies, maintenance treatment after high dose therapy is not yet recommended.
In order to evaluate the role of risk-adapted treatment with single or tandem ASCT for first relapse/refractory HL, the GELA realized a phase III prospective multicenter H96 trial. Long-term results of this trial were presented at the EBMT 2010 meeting. Patients with poor-risk group went to tandem ASCT while intermediate-risk had single ASCT. Importantly, among the 150 patients included in the poor risk group, 137 patients (91%) went to first ASCT, but only 105 (70%) could receive the second one, mostly for progressive disease. After median follow-up of 6.5 years, 5 year FF2F for poor risk patients was 47% with OS of 58%, which compared favorably with historical data. For patients having received the tandem procedure, FF2F was 65%. This trial showed that 1/3 of patients could not receive tandem ASCT because of rapid progressive disease, underlying how unsuccessful we are with current treatment strategies in these poor prognosis patients.

Waiting for prospective trails results, Dr P. Brice finally recommended, on the name of LYSA, tandem ASCT for primary progressive or poor risk patients and PET-2 negative, third line regimen with tandem ASCT for PET-2 positive patients, and single ASCT for standard risk patients.

British Group

![Diagram of British Lymphoma group recommendation.](image)

John Radford, from University of Manchester, presented the British Group actual treatment strategy. They proceed to salvage chemotherapy with ESHAP (etoposide, cisplatin, cytarabine and methylprednisolone), DHAP or IVE (Ifosfamide, epirubicin, etoposide) for 2 cycles and then perform FDG-PET to evaluate response. Patients with FDG-PET negative (CR) are directed to ASCT, as in other countries. Patients with FDG-PET-positive, but non-progressive disease may be directed to alloSCT. For patients with a stable or progressive disease, salvage chemotherapy or BV based regimen is recommended. In this situation, they repeat FDG-PET after 2 to 4 cycles of third line in order to proceed toSCT (alloSCT or ASCT, with a preference for alloSCT whenever possible for Dr Radford) in case

![Diagram of ASCT and AlloSCT in relapse HL patients.](image)
of response. If still non-responding, they either choose another salvage line chemotherapy (gemcitabine, bendamustine…) or direct patients to phase I or II trials if available.

This therapeutic strategy has been studied in a single centre series with 61 relapsed patients, presented at the ASH 2011 meeting (Figure 3). In this trial, 28 (46%) patients were in metabolic CR and directed to BEAM ASCT, 25 patients with PR FDG-PET positive disease (41%) were consolidated with alloSCT with a BEAM-Camptothecin conditioning regimen. Finally, patients with stable or progressive disease were salvaged with third line chemotherapy and then directed to alloSCT in case of response. According to this small prospective study, 4 years PFS and OS were respectively 85% and 92% for patients who went to ASCT. AlloSCT-treated patients had 4 years PFS and OS of 71% and 88% respectively despite higher risk disease. The British group is now including patients in the PAIReD trial, with the goal to test this risk-adapted strategy in a larger cohort, where patients with less than metabolic CR and non-progressive disease all go to alloSCT. (Figure 4)

Figure 4. Design of the British Lymphoma group future study (PAIReD).

GHSG

We must take into account that nowadays relapsed German patients with HL were treated with escalated BEACOPP in first-line with radiotherapy consolidation for end of treatment FDG-PET positive disease. If they represent a smaller population than those relapsing after ABVD, once relapsed, their prognosis may be worse. As for other groups, the primary goal is to destine patients to ASCT. The "Cologne High dose regimen", consisting in more intensive chemotherapy before BEAM ASCT, has been tested in a large European randomized trial. The results showed that it was not more effective than two cycles of DHAP alone but more toxic. 42

FIL

On the name of FIL, Dr Luminari presented a large retrospective study with patients prospectively included in clinical trials. In a 2012 update, 130 (9%) of 1499 HL patients were considered to be refractory or relapsing. These patients were treated in their physician’s discretion, either with chemotherapy alone, ASCT or palliative care. Overall, patients treated with ASCT had superior 5 years OS (65% vs 38%) than patients treated with chemotherapy alone. For now, FIL have on-going trials evaluating changes of therapies. Some of them focus on first-line interim FDG-PET adapted therapy and even propose ASCT as immediate
salvage after interim FDG-PET positivity. HD0802 protocol with IGEV salvage for first line interim FDG-PET positive patients was also presented. After salvage a FDG-PET is performed and negative patients receive single BEAM ASCT while FDG-PET positive patients are conducted to high dose Melphalan conditioning ASCT, followed either by RIC alloSCT if sibling donor available or BEAM conditioning second ASCT. 

In summary, all experts agreed that SCT, whether autologous or allogeneic, should be used as consolidation for the majority of relapsed HL patients after a BEACOPP or ABVD first-line treatment. In addition, FDG-PET seems useful to stratify patients into prognostic groups, with pre-ASCT FDG-PET positive patient’s risk of relapse after SCT being consistently higher. However, the treatment of this latter poorer risk group is not consensual. AlloSCT in HL has been studied in multiple series, with variable conditioning regimens, mostly RIC recently. High rates of non-relapse mortality (NRM) associated with myeloablative conditioning have been problematic in the first trials. With RIC, 1 year NRM and 3 years PFS are consistently around 20% and 30%, respectively, with more relapses but less TRM than with myeloablative conditioning. Although still considered as poor results by some haematologists, we must take into consideration that a lot of these series included multi-treated patients, often post-ASCT, with variable ECOG-PS and status of disease remission at the moment of transplantation. On the basis of promising PFS and OS results in a unicentric British trial, it seems appealing to study the role of alloSCT for poor risk relapsed patients in first line salvage where TRM would be less of an issue. Moreover, the place of tandem ASCT and BV maintenance will also have to be further investigated.

New therapeutic option, targeted therapy

BV has emerged as a very promising new therapeutic option since its FDA authorization. In a pivotal phase II trial, 102 patients with post-ASCT relapsed and refractory HL were included. Overall response rate (ORR) was 75% with 34% CR. Median duration of response was 6.7 months with an interesting 20 months for CR patients. Of note, BV as a single agent showed similar ORR with more CR than the only chemotherapy regimen (GVD: Gemcitabine, liposomal doxorubicin, vinorelbine) studied in a phase III trial post-ASCT setting. In addition, interesting results are pending for first line treatment where BV was combined to ABVD or AVD. Pulmonary toxicity was a concern when used in association with bleomycin. Cycle 2 FDG-PET results were reported for 37 patients and 36 of them (97%) had negative interim FDG-PET. At the moment we are writing this review, BV is soon to be approved by European authorities. However, it is still unclear when it should be included in the treatment strategies algorithm: at relapse as a bridge to auto or alloSCT, in preASCT FDG-PET positive patients as a third line agent to achieve CR or only as it has been studied in post-ASCT relapse? How many cycles should we administrate to patients who achieve CR? Moreover, the role of maintenance is not defined yet.

In addition, there are multiple ways to target the BCR signalling or neoplastic B cell proliferation. HDAC inhibitors, PI3k/AKT/mTOR inhibitors and JAK/STAT inhibitors are now currently tested in different phase I and II trials. HDAC inhibitors, when used as single agents (panobinostat, mocetinostat and vorinostat) did not permit achievement of sufficient ORR to be get FDA authorization (27%, 27% and 4% respectively). Combination studies with hypomethylating agents, mTOR inhibitors and standard chemotherapy are in progress. Each of the specific components of the PI3k/AKT/mTOR pathway has their specific inhibitors being studied. Cal-101 (PI3kgamma and delta inhibitor), IPI-145 (PI3k and delta inhibitor) and Mk-2206 (AKT inhibitor) have shown interesting preliminary results. When used as single agents, for the moment, Jak1/2 inhibitors (SB1518) have not yield to promising results in phase I trials, but combination studies may represent an investigation field.
In summary, if all these experimental agents are not effective enough on their own, there is a strong scientific rationale for combination therapy with or without chemotherapy, immunomodulatory (lenalidomide) agents or BV to aim synergic effect on the different signalling pathways.

- Conclusion and perspective

In conclusion, relapsed and refractory patients are stratified into three prognostic groups for which definition is uniform in all countries. It seems clear that primary progressive diseases suffer the poorest outcome. In addition, patients relapsing after first-line escalated BEACOPP or first-line ABVD probably do not share the same clinico-biological characteristics, which makes more complex the interpretation of different studies. There is obvious lack of data concerning biology at relapse and a definite need to obtain relapse biopsies to identify biomarkers associated with outcome. FDG-PET after 2 cycles of salvage chemotherapy seems strongly associated with progression after ASCT. It would seem logical to aim FDG-PET negativity, as shown by Moskowitz trial. However, this should be evaluated in a prospective multicenter study. Due to different population of patients in all the trials reviewed here, it is impossible to clearly define the place of tandem ASCT, alloSCT or BV maintenance post-ASCT.

A phase I/II feasibility trial (BraVE) is about to begin in the Netherlands combining BV with escalating dosage second-line chemotherapy (DHAP) in refractory or relapsing HL patients eligible to high dose treatment followed by ASCT (Figure 5). BraVE could be a good platform for a future international prospective controlled phase III trial randomizing between DHAP alone and BV-DHAP, considering that toxicity in phase I/II trial is not prohibitive. Primary end point could be the evaluation of metabolic response after 2 cycles of salvage. Moreover, subgroup analysis would permit a better definition of the different risk groups. Therapeutic attitude for FDG-PET positive patients post-salvage would be in the investigator discretion according to its group recommendation. In a second time, the different approaches results (standard or RIC alloSCT, tandem autoSCT, single autoSCT) could be prospectively studied.

![Figure 5. Design of the BraVE study.](image)

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BIBLIOGRAPHY


