EHA 2017 Annual Congress:
Emerging Targeted Therapies in Relapsed/Refractory Acute Lymphoblastic Leukemia

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Welcome to our summary of certain parts of the European Haematology Association 2017 Annual Meeting. This educational session is entitled Emerging Targeted Therapies in Relapsed/Refractory Acute Lymphoblastic Leukemia.

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Faculty

I am David Marks, Professor and Director of the Bone Marrow Transplant Unit and Head of the ALL programme at Bristol Haematology and Oncology Centre. I am very pleased to be joined today by Dr Hagop Kantarjian, Professor and Department Chair of the Leukemia Department at MD Andersen Cancer Centre in Houston, and his colleague, Dr Elias Jabbour, Associate Professor in the same department at the same institution.

Acute lymphoblastic leukemia: unmet needs

Just to give you some background in ALL and to discuss some unmet needs, the five-year survival of ALL in adults is now approaching 50%, if we look at some more recent data from the US, and some of the bigger groups in Europe. That compares to approximately 90% in children.

The outcome of adult ALL is improving, but it remains unsatisfactory, and the major cause of it being unsatisfactory is relapse.

B-cell acute lymphoblastic leukemia

About 75% of adult ALL is of B-cell origin; it is higher in children, and the major B-cell lineage markers we use include CD19, CD20, and CD22. They vary in their express on B-cell ALL.

How to tackle unmet needs in ALL

We need to divide ways of tackling the unmet needs, and I have divided this up into five main ways. We need to target patients who have persistent MRD post-induction, there is probably room for more aggressive targeting of very high-risk groups. In particular, I mean
MLL rearrangement and hypodiploidy or near-triploidy, and probably also complex cytogenetics.

We need, and we are some way to achieving better and less toxic therapy of relapse, and we need to get those patients more frequently to a transplant, and that transplant itself needs to be less toxic.

It may be worth looking at molecular relapse post-allograph; those patients may be salvageable, and now for the last few years we finally have effective therapy of ALL that is totally refractory.

**Relapsed/refractory ALL**

To move onto the problem of relapsed/refractory ALL, the five-year survival of patients with relapse/refractory ALL is less than 10% and that is well shown in the Fielding paper from 10 years ago in over 600 patients. The reason for this is the complete remission rate is too low and we don’t get enough of the patients to allograft.

**Highlights from EHA 2017**

We have come through a period of what could be termed “Therapeutic stagnation”, and now we have targeted therapies that we are investigating, and these include inotuzumab, ozogamicin, blinatumomab and CAR T-cells. In addition, in Philadelphia-positive ALL, we are beginning to investigate ponatinib, the potent tyrosine kinase inhibitor.

Until this point I think it was standard of care to allograft most patients with Philadelphia-positive ALL, but with new approaches and better results this may change.

What we are going to do in this session is particularly look at the phase 3 studies of blinatumomab and inotuzumab, the updated results, but also, we are going to present expanded data on CAR T-cells in adults and children.

In all, we are going to discuss 10 abstracts. Dr Jabbour will discuss three abstracts on inotuzumab, then I will do one to do with inotuzumab and transplant. Dr Kantarjian three abstracts on blinatumomab, and then I will finally discuss two CAR T-cell abstracts before Elias Jabbour moves onto an abstract on ponatinib. Then I will conclude and briefly sum-up.

I am going to hand over to Dr Jabbour to talk about the abstracts concerning inotuzumab ozogamicin.
Thank you, Professor Marks, for this introduction and for the opportunity.

**Inotuzumab ozogamicin: mechanism of action**

We live in an era of discovery and very exciting drugs with monoclonal antibodies and CAR T-cells. I will cover the part of inotuzumab in ALL, inotuzumab ozogamicin is a humanized monoclonal antibody that binds CD22 with subnanomolar affinity, and upon binding it is rapidly internalized, delivering the conjugated calicheamicin, inside the cell, after the linker is hydrolyzed.

Calicheamicin is a very potent cytotoxic antibiotic, that binds in the minor group of DNA and causes double-strand DNA breaks, leaving to an apoptotic response in cells.

**INO-VATE trial (phase 3)**

The drug was assessed in a randomized trial called the INO-VATE trial, where patients with refractory/R ALL were randomized to either standard care or inotuzumab ozogamicin, given on a weekly schedule for a total dose of 4.8mg/m²/cycle, with dose reduction of a further unit consolidation.

**INO-VATE trial (phase 3)**

The primary endpoints were double response rate, as well as survival. Response rates were significantly improved of 80% compared to 30% in the standard of care arm, and the survival was 7.7 months for inotuzumab compared to 6.6 months in the standard of care arm.

The drug was approved by the FDA last week, as well as in Europe a month ago for the treatment of patients with relapsed/refractory ALL.

**InO plus low-intensity chemotherapy**

We tried to build on this data by using this drug in combination with low-intensity chemotherapy for older patients. We know that, for elderly patients, the outcome is not so great. The median survival is less than a year in these patients; they carry bad prognostic features, and they tolerate poorly intensive chemotherapy. Therefore, combining effective monoclonals with low-intensity chemotherapy may overcome these barriers.
At MD Anderson, we treated around 60 patients with a combination of inotuzumab ozogamicin and low-intensity chemotherapy.

To summarize we used very low dose of chemotherapy. We completely omitted anthracyclins, and we reduced by half the dose of cyclophosphamide and dexamethasone, and methotrexate and cytarabine by 75 and 80% respectively.

**Treatment: InO plus mini-hyper-CVD**

Inotuzumab was given on a monthly infusion. The first six patients with a run-in phase at 1.3 in cycle 1 and moving forward, 0.8mg/m², and once we had stabled safety we escalated the dose to 1.8mg/m² and 1.3mg/m² during subsequent courses from two to four; patients will receive four injections of the drug.

After 34 patients were treated, we reported a rate of VOD of 8%, and therefore, we decided to reduce the dose of inotuzumab from 1.8 to 1.3 during induction and from 1.3 to 1.0 during subsequent courses. Patients will receive maintenance therapy with POMP up to three years. They receive rituximab if they have CD20 expression as well as intrathecal chemotherapy.

**Outcome: InO plus mini-hyper-CVD**

The objective response rate reported was 98%, was mostly CR achieved, and among responders, the rate of MRD negativity at the time of CR achievements was 78% and overall within 12 weeks was 96%. Today, with a median follow-up of three years, with three-year overall survival of 56%. We went back and we compared the outcome into similar patients treated with intensive chemotherapy, where the three-year survival was 32%. When we compared we had a significant improvement in a rate of survival, favoring the combination of low-dose chemotherapy plus inotuzumab ozogamicin.

**Safety: InO plus mini-hyper-CVD**

The study was very positive. The VOD rate was observed, and occurred early on. With those reductions, we were able to reduce the rate of VOD, although not completely. We had one patient who had VOD acquired at a low dose.

**Outlook: InO plus mini-hyper-CVD**

What are we doing moving forward? First of all, we would like to confirm these findings in a randomized trial, where patients who are 60 years and older were randomized to receiving mini-hyper-CVD low-dose chemotherapy plus inotuzumab or mini-hyper-CVD alone, and the primary endpoint being over survival.
Second point; what are we doing to reduce the VOD rate? As we know from the phase 2 studies and the phase 3 studies that the weekly schedule is better, so we are going back to a weekly schedule of inotuzumab, not a multi-schedule, refreshing the dose of inotuzumab, and we further reduce the dose of inotuzumab from 1.8 and 1.3 to 0.9 during cycle one on a 0.6 and 0.3, and to further reduce the dose to 0.3 and 0.3 on a weekly basis. Therefore, we are reducing the dose of inotuzumab, we are giving weekly doses of inotuzumab and, to further improve the outcome, we are adding blinatumomab in a sequential basis, which means they get four cycles of mini-hyper-CVD inotuzumab, followed by four cycles of blinatumomab, and then one year of maintenance. That is for the elderly patients.

**INO-VATE: impact of cytogenetics in adults with R/R ALL treated with InO**

Let’s discuss other aspects related to inotuzumab. One of them was a sub-analysis of the INO-VATE trial, the randomized trial that led to the approval of inotuzumab, essentially assessing the prognostic impact of baseline cytogenetics. What we know today in adult ALL, as well as in pediatric ALL, that hypodiploidy patients with translocation t(4;11), complex karyotype, they do poorly with the chemotherapy, and these patients do require transplants to be done in first remission. The idea was, does inotuzumab ozogamicin overcome the negative prognostic application of these baseline features?

**Frequency of baseline cytogenetic abnormalities in patients treated with InO**

We went back to the INO-VATE trial and we assessed the baseline cytogenetics in the two arms, standard of care, as well as the inotuzumab arm. Half of the patients or 45% had diploid karyotype. We have seen hypodiploidy in about 5%, complex about 17%, and MLL-rearrangement about 5%, and that comes as no surprise because these are relapsing patients.

**Efficacy and safety of InO in cytogenetic subgroups**

Then we correlated the findings with the outcomes with inotuzumab treatment. Essentially, inotuzumab was found to be superior to standard of care across the board. Every patient benefits from inotuzumab. The benefit is seen more among patients with diploid karyotypes, complex karyotypes, and Philadelphia-positive, while patients with hypodiploidy and near triploidy and MLL have a lesser advantage.

The high-risk patients will not benefit as much from inotuzumab, mainly the MLL-rearrangement, as well as hypodiploidy.

What does that tell us?
Efficacy and safety of InO in cytogenetic subgroups (continued)

Multiple things: if we can introduce inotuzumab in the front-line setting and therefore we can overcome the negative impact of these features. As we have seen with others, mainly blinatumomab, MLL remains hard to treat, and with the small numbers we have, inotuzumab does not seem to overcome these negative features, and CAR T-cells may help in that setting.

Predictive factors for developing VOD in ALL patients treated with InO followed by allo-SCT

My final matter to discuss is as part of the poster by Kebriaei from MD Anderson on the role of transplant and VOD in ALL, and in this study that Kebriaei and colleagues compared transplants and outcomes across different strategies, non-inotuzumab-based regimen and an inotuzumab-based regimen from MD Anderson.

Rate of VOD after allo-SCT

Essentially, she reported a VOD rate of 8% overall and 16% amongst patients receiving inotuzumab ozogamicin. The fatality is similar, 3%, but what she is showing is that patients who receive InO and double alkylators at the conditioning regimen had the highest rate of VODs, compared to patients who did not receive double alkylators and did not receive at all inotuzumab.

We know, for example, from the INO-VATE trial, and Dr Marks will elaborate on that, that we will see more VOD among patients who received inotuzumab; however, practically speaking, patients who receive inotuzumab and had double alkylators did poorly, patients who had a transplant already failed, had inotuzumab and second transplant, they don’t do as well. Therefore, we should be selective. I think the role of transplant in the second or so remission is questionable. We should be more selective and we should avoid using a double-alkylator in the case of conditioning for this patient.

Again, use a lower dose of inotuzumab; we can’t show sequential use may help further reducing the rate of VODs. Interestingly, in the observation of Dr Kebriaei, age did not play a role, nor the donor relation.

With that I pass the microphone to Dr Marks for further discussion.
David Marks

INO-VATE: factors associated with HSCT outcomes in R/R ALL patients treated with InO vs SC

I am just going to talk a bit about Matthias Stelljes’ poster presentation, abstract 525. Within this presentation it is an analysis of the patients who got to allograft in the two arms, and there were 77 in the inotuzumab arm, and 31 had an allograft in the standard of care arm. If you look at their pathways to transplant, it was quite different: 69 of the 77 patients in the inotuzumab arm went directly to transplant. Only eight patients who did not receive a CR after inotuzumab did achieve it with other agents, and then went to transplant.

This was different in the standard of care arm, where 19 patients went directly to transplant after responding to standard of care chemotherapy, but 12 additional patients had a different route to transplant; they did not achieve a remission and they received other agents, including agents such as blinatumomab.

Toxicities after HSCT: InO vs SC

Overall, it was quite clear that the patients receiving inotuzumab, when they went to transplant were more likely to be MRD-negative, and that is something that we know correlates with a lower relapse rate and better outcome. However, there were toxicities of inotuzumab. When there was a comparison of non-relapse mortality at one year, there was a somewhat higher rate in the inotuzumab arm, 36% vs 20%, although the difference was not significant at two years.

This, as Dr Jabbour has said, was associated with the use of dual-alkylating agents.

There was a suggestion of a lower relapse rate in the inotuzumab arm of 33% vs 46% at two years. We obviously need larger numbers to confirm that difference.

OS after HSCT: InO vs SC

Finally, in terms of the survival, there was similar survival in the two arms, and I think the main thing that we draw from this is we have to do transplants differently after inotuzumab; we have to do them in a less toxic way and a more smart way, because there were five cases of fatal VOD.

Discussion points: managing VOD risk

That is the inotuzumab data, and Elias, I would like to come back ask and perhaps hone down on a few things. In your inotuzumab hyper-CVD study, you had veno-occlusive disease in 8% of patients, can you tell me a bit about the severity of that VOD? Where there any severe cases? Any fatal cases?
Elias Jabbour: Yes, David, we had five patients who had VOD. Only in one of them was severe enough; the patient had two cycles of chemotherapy then we stopped; we dropped the chemotherapy. He had multiple organ failure and passed away. The other four patients, one of them had VOD post-transplantation and it resolved completely, and the three others we were able to manage them – with ursodiol, as well as defibrotide in one. Interestingly, we are using nowadays L-carnitine to prevent and to help the VOD resolution.

In all four or five, the VOD was mild and resolved, and people were able to pursue their treatment obviously without inotuzumab.

What we are doing today to reduce further the VOD rate, we are being more selective, we are doing what we call an ultrasound, called elastography, to look for the flexibility of the liver tissue and to be able to select patients in whom inotuzumab may not be too good, or high risk of VOD.

We are using a weekly use of inotuzumab instead of the monthly dose of inotuzumab, lower dose of 0.3 per dose, and then we are trying to space the transplant, if we have to do transplantation, with L-carnitine as well as ursodiol giving prophylactic measures.

Discussion points: role of InO in ALL

Dr Kantarjian: Dr Marks, if I may make several comments on the data of inotuzumab? The first one is the outcome of transplant post-inotuzumab. Even though we are getting more patients to the allogeneic stem cell transplant following inotuzumab than following chemotherapy, the results post-transplant remain very poor. Therefore, we are using two expensive strategies with modest benefits, and I think in the future should be to incorporate something in addition to the inotuzumab before the stem cell transplant, to increase the efficacy of that approach and potentially to reduce the rate of veno-occlusive disease by spacing the time between the transplant and the inotuzumab.

This we can potentially achieve by incorporating the second monoclonal antibody, blinatumomab, in-between the inotuzumab courses and the allogenic stem cell transplant.

The second point that is important is, even though inotuzumab is highly effective, where the marrow CR rate of 80%, yet the survival remains modest, and I think the future should not be with either monoclonal antibody alone, or with chemotherapy which is inferior to the monoclonal antibody and to the antibody constructs, but we should start looking at combined modality approaches that approve the survival significantly so that we can make the treatment value of this expensive approach effective.
The third thing I want to allude to is the rate of veno-occlusive disease, because the publications with inotuzumab just came about; people are aware of the problem of the VOD, but the only way post-inotuzumab today is with allogeneic transplant, and if you compound those two procedures you get a high rate of VOD, in the range of 10–15%, despite our best efforts.

A point of importance is inotuzumab alone and the lymphoma studies did not lead to VOD. Inotuzumab followed by allogeneic transplant causes VOD. Inotuzumab with chemotherapy in the elderly ALL without transplant is starting to show VOD, so the incidence of VOD could be higher among older patients who start with, perhaps, a damaged liver. It is very important now that inotuzumab may become widely available, for the community of oncologists and the leukemia experts to be very aware of this problem, and to look at dose adjustments, dose schedules, as well as preventive strategies for veno-occlusive disease, including avoiding double alkylator preparative regimens for the stem cell transplant.

I think the latter point, regarding the issue of VOD with inotuzumab, should have rapid penetration into the leukemia practice, otherwise we may start seeing veno-occlusive disease that is preventable, and by avoiding VOD we could improve the potential cure rate of these patients with refractory ALL.

**David Marks:** Thank you very much.

The only other thing I wish to add to that and the issue with VOD is that I think it would be valid to explore different conditioning regimens after inotuzumab. I am sure Dr Kebriaei is doing that. Within the UK we are planning our next trial – we will be looking at two reduced-intensity conditioning regimens. Two-thirds of our patients are likely to have had inotuzumab, and what we will try and find out in our next trial is whether we can safely do reduced-intensity transplants in the hope that people who are MRD-negative that that will be sufficient therapy.

**Discussion points: patients with MLL rearrangements**

Dr Jabbour, if I can just return to one point? Do you think we have enough data in the patients with MLL rearrangement to say that inotuzumab is definitely less effective in this subset of ALL?

**Elias Jabbour:** David, from the INO-VATE trial the numbers are small, but we feel that consistently with inotuzumab, even though the single agent in the end in MLL did not do well so far, so small numbers, but in definite trials the outcome has not been so good with these new monoclonal antibodies. Why is that happening? It is hypothetical. What
do we do for the future? I think maybe CAR T-cells should be offered to these patients earlier if they are high-risk patients, because they don’t go into MRD-negativity early on, and maybe in the frontline CAR T-cells will be able to overcome the negative impact of translocation t(4;11).

David Marks: I would like to hand over to Dr Hagop Kantarjian to talk about three blinatumomab abstracts.

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Blinatumomab: mechanism of action

I am going to discuss blinatumomab, which is a bi-specific monoclonal antibody construct that enables the CD3+ T cells to recognize and eliminate the CD19+ cells, which are the acute lymphocytic leukemia cells.

This drug was approved for use in patients with relapsed/refractory pre-B ALL in the setting of salvage therapy and this was on the basis of single group trials that showed that the drug is effective and has manageable side effects. That initial approval was December 2015.

Blinatumomab vs standard chemotherapy in R/R ALL (TOWER trial)

Based on the results of the single arm studies, we developed the multi-institutional phase 3 trials comparing blinatumomab to standard of care chemotherapy. In this trial, the patients were randomly assigned on a 2:1 ratio to either receive blinatumomab or standard of care chemotherapy, and the primary endpoint of the study was the overall survival.

This trial accrued a total of 405 patients, who were randomly assigned to receive blinatumomab, and this was the case in 271 patients, or chemotherapy in 134 patients.

Of the 405 patients, 376 received at least one dose of the treatment. As expected, some of the patients randomized to the standard of care elected to exit the study.

Blinatumomab significantly prolonged OS compared with standard chemotherapy

Once the results were finalized, it was shown that blinatumomab was superior to the standard of care chemotherapy, so when we looked at the overall survival, it was
significantly longer with blinatumomab compared to the chemotherapy group. The median overall survival was 7.7 months with blinatumomab and 4 months with chemotherapy. The hazard ratio for mortality was 0.71, favoring blinatumomab. The p value was 0.01.

**Remission rate and quality of remission was improved with blinatumomab vs chemotherapy**

Also, when we looked at the overall and marrow complete remission rates, they were significantly higher with blinatumomab, so the overall response rate was 44% with blinatumomab and 25% with chemotherapy. The complete response rate was 34% with blinatumomab vs 16% with chemotherapy.

Also, when we looked at the molecular response rate, it was significantly better with blinatumomab, indicating that not only the rate of response was higher, but the quality of the responses was also higher.

**TOWER: response and survival in patients treated with blinatumomab according to salvage status**

In the EHA meeting there were two analyzes which are relevant to blinatumomab. The first one was the comparison of blinatumomab vs standard of care chemotherapy by the salvage status. When we looked at the patients by the salvage status, it was still evident that blinatumomab was superior to intensive chemotherapy in both salvage one and subsequent salvages, but, as expected, when we looked at the complete response rate with blinatumomab it was higher in salvage one, so this tells us that if we want to use this monoclonal antibody therapy, we should use it earlier rather than later.

**Blinatumomab improved remission rates vs SOC independently of the number of prior salvage regimens**

When we looked at the results in salvage one, blinatumomab produced an overall response rate of 51% vs 36% with standard chemotherapy, and the rate of minimal residual disease was also significantly higher among responders among responders, 49% vs 39%. Finally, the best response rate was higher with blinatumomab: 44% vs 28% with chemotherapy.

When we look at Salvage 2, blinatumomab was still superior, the complete response rate with blinatumomab was 39% vs 14% and the MRD negativity rate was 48% vs 10%.

**Blinatumomab improved OS vs SOC independently of the number of prior salvage regimens**

Now, when we look at survival, it was also evident that blinatumomab was associated with a significantly superior survival compared to standard of care chemotherapy in both Salvage 1 and Salvage 2. In Salvage 1 the median survival with blinatumomab was 11.1
months vs 5.5 months with chemotherapy, so almost twice as long, and in Salvage 2 the median survival was 5.1 vs 3 months. So, it is obvious that blinatumomab today in the setting of salvage therapy in adult ALL is superior to standard of care chemotherapy, the question is, 'Should we still use it only as a single agent or in combination with chemotherapy?'

**RIALTO: Blinatumomab in children and adolescents with R/R B-precursor ALL**

The next question that was addressed during the EHA is the use of blinatumomab in pediatric and adolescents with refractory/relapsed pre-B ALL, and this was an important study because there was very little data in patients younger than 18 years old. So, in this study, the same sequence of blinatumomab was used, a 4 week, continuous infusion, followed by 2 weeks of a break, and patients could receive up to five cycles, two inductions, and three consolidations, and when the patients achieved the complete remission they were offered allogeneic stem cell transplantation.

**Blinatumomab in children and adolescents with R/R ALL**

So, when we look at the totality of the data there were a total of 40 patients that were accrued on the study, so these were all young patients under the age of 18 years who had refractory/relapsed ALL and the results were quite promising, because the overall complete response rate after two cycles of therapy was 63%, and the rate of complete response was independent of the % of the blasts, which is a bit different than in the adult ALL study, where patients that had a higher incidence of peripheral blasts had a lower response rate.

As with the adult ALL, the rate of complete molecular response or MRD-negativity among patients who achieved the complete remission was very high, 76%, and it was high regardless of the pre-treatment % of blasts.

Finally, among the patients who received the treatment, of the 25 patients who achieved the complete remission, 10 were able to access allogeneic transplant and complete remission for a rate of 40%, vs only three out of 14 who did not achieve a complete remission for a rate of 21%. So, this shows that the drug is not only highly effective in children and adolescents with acute lymphoblastic leukemia, but it also offers twice the rate of accessing allogeneic stem cell transplantation, particularly in complete remission, which should improve the results of the allogeneic transplant.

In addition, it is important that the cytokine release syndrome in those patients was 25%, which is a similar incidence to what we have seen in the adult ALL [studies].
**TOWER: exposure-adjusted AEs in adults with R/R ALL treated with blinatumomab or SOC**

Now, the third study which was important from the EHA meeting is the exposure-adjusted adverse events when patients are treated with blinatumomab vs standard of care chemotherapy. And this is important because patients on blinatumomab achieve higher rates of complete remission and therefore stay longer on the treatment, as opposed to chemotherapy, so it may appear that there is a higher rate of adverse events simply because the patients are receiving blinatumomab for a longer period.

**Exposure-adjusted AE rates in blinatumomab vs SOC in adults with R/R ALL**

Therefore, the study looked at exposure-adjusted adverse events, accounting for the longer duration on blinatumomab, and it showed that, in fact, the exposure-adjusted adverse event rates were, in general, lower with blinatumomab than with standard of care chemotherapy, which is what would be expected. The most frequent adverse events were fever, nausea and anemia in both arms, and we did see a higher rate of cytokine release syndrome with blinatumomab at a rate of 63 vs no events/100 patient-years, which is what would be expected with blinatumomab.

Regardless of those, the data is that when we adjust for the duration of exposure, blinatumomab is less toxic than standard of care chemotherapy, except for the cytokine release syndrome, which is easily manageable with the use of steroids.

**Blinatumomab: regulatory status**

As a result of the TOWER trial, the FDA, on 11 July 2017, granted full approval of blinatumomab therapy in ALL salvage and expanded the indication to include Philadelphia-positive acute lymphoblastic leukemia.

**Discussion points: blinatumomab in pediatric patients with ALL**

**Marks:** Okay, thank you very much.

Perhaps I can just pick up on a couple of points, so the pediatric data is particularly fascinating. Do you expect the data of using blinatumomab in children to be different? Do you think we expect different efficacy or different toxicity?

**Kantarjian:** So, this was not known at the time of the analysis, but, in general, when you look at previous studies of chemotherapy or, say, CAR T-cells in children, what we find is that children usually tolerate such treatments better than adults, and, in general, they appear to have a more sensitive disease, achieving higher response rates.
This, I think, was the case in this small group of 40 patients, where the overall response rate was 63% and many of those patients were able to access transplants.

One of the issues was the rate of cytokine release syndrome. Again, if one had to predict one would say that the rate of cytokine release syndrome and the severity will be better tolerated in children than in adults, because of the experience in CAR T-cells, where the cytokine release syndrome is more severe in adult ALL with CAR T-cells than in children with acute lymphoblastic leukemia, and I think this was seen in the pilot experience, where the cytokine release syndrome was not a big issue in those children receiving blinatumomab therapy.

**Discussion points: chemotherapy for R/R ALL in the era of targeted therapies**

**Marks:** There are still some patients throughout the world with relapsed/refractory ALL who are just receiving conventional chemotherapy, not with any targeted therapy. Do you think that is still justifiable?

**Kantarjian:** So, based on the single monoclonal antibody therapies compared with chemotherapy, we find that single agent monoclonal antibodies are superior, in terms of achievement of the complete marrow response rate, overall response rate, MRD negativity, access to transplant, and survival. However, the issue is the cost of those single agent monoclonal antibodies, and I think we are at the first step. It is true that today if we look at the patients with refractory/relapsed acute lymphoblastic leukemia, those antibodies, including blinatumomab and inotuzumab, offer superior outcomes compared with standard of care chemotherapy. But I think the next step is to move to combine modality approaches of those antibodies with chemotherapy, as well as combinations of the cocktails of the antibodies, including blinatumomab and inotuzumab. Only then, when we start showing that the median survival is not less than a year, but in excess of two years in the salvage setting, that we can get more patients to allogeneic transplant and that we can actually cure these patients with this sequence of combined modality therapies followed by allogeneic transplant in a safe manner, only then can we discuss a good treatment value for these antibody combinations with chemotherapy and I think that is how the data is evolving.

One of the studies that Dr Jabbour did not show is our results with mini-hyper-CVD with inotuzumab in the setting of ALL salvage, where we show that for the first time the overall response rate in this refractory/relapsed setting is close to 80% and where the median survival is almost double that achieved with single agent monoclonal antibody therapies.
CAR T-cell therapy: data presented at EHA 2017

Okay, so now I am going to talk about two CAR T-cell abstracts, the ELIANA trial, which is in pediatric and young adult patients with relapsed refractory ALL, and also a major analysis of safety data from two single arm multicentre studies.

ELIANA: CTL019 in pediatric and young adults with R/R ALL

ELIANA was a particularly interesting study because it was a global registration study, and it sought to see if the very impressive results that come from using the CAR T-cell that was used at the University of Pennsylvania could be demonstrated across the world.

So, this was a big study, 88 patients were initially enrolled, I think it is good to focus on these numbers, and within those 88 patients there were seven manufacturing failures, so a bit less than 10% and I think that is what we have got to expect, it isn’t going to be used for everybody.

In the end, 68 patients were infused and this, again, is telling us that some patients drop out between enrolment in the study and infusion of CAR T-cells.

The median age of patients in this study was 12 years.

So, first of all, some big scale, pan-global data, 83% of patients achieved complete remission and all of those patients were MRD-negative. And what is particularly interesting is they give us longer-term follow-up, so the overall survival at 12 months in these patients was 79%, and it is of interest to see that at six months it was 89%, so there was a drop-off between 6 and 12 months, so you can’t just show 6-month data and assume that all those patients will remain okay.

There were 11 deaths, that is out of 68 patients infused, but seven of those were due to disease progression.

Overall, within that study, there was 78% cytokine release syndrome, 21% grade 3, 27% grade 4.

So, those data were very interesting, and what I am going to move onto now is a major safety analysis of two multicenter trials, these, again, are in children and young adults.
Safety data from 2 multicenter trials of CTL019 in children and young adults with R/R ALL

So, in these two studies 97 patients had a single infusion of CAR T-cells, and I think this study better than any other in this age group describes the toxicity of CAR T-cells. There were 82% of grade 3 and 4 adverse events and 73% of patients had severe adverse events, and this number comes up again and again, 44% of patients had grade 3 to 4 cytokine release syndrome.

So, just to look at the impact of the toxicity on overall survival, of the 97 patients 21 of the 97 died after receiving the infusion, but of those 21 patients 16 died due to disease progression, so that is far and away the major cause of death.

So, the investigators then honed down on the cytokine release syndrome, it was described in over 80% of patients, as I stated, and 34% needed anti-IL-6 therapy with tocilizumab. But it was really very impressive in this global, multicenter setting that there were no deaths due to cytokine release syndrome, and many of these patients had more than 50% blasts, and we know that is associated with more cytokine release syndrome.

Just other things they described that had not been previously described, with cytokine release syndrome the more severe forms you get a coagulopathy, they saw that in 10% of patients, and it was also interesting that 3% of patients had documented tumor lysis syndrome that required therapy.

The only caveat they talk about, in terms of safety, is that the longer-term effects of B-cell aplasia are yet to be evaluated, obviously, the people who have prolonged B-cell aplasia have CAR T-cell persistence and they are more likely to be survivors.

Discussion points: selecting an appropriate therapy for patients with R/R ALL

Kantarjian: Dr Marks, if I may make a couple of comments on the CAR T-cells.

Today, we get a lot of questions and emails about patients with refractory/relapsed ALL, and the patients and the treating physicians are asking “Well, if we have the two options of monoclonal antibody-based therapy or CAR T-cells, which one should we consider?”. And even though I would say, first, that those two options are not mutually exclusive, because you have to get a spot on the CAR T-cells. The other point to mention is that it is, perhaps, that the results of monoclonal antibody therapies or antibody therapies with chemotherapy may be as good, if not better and less toxic, than the CAR T-cells. So,
we have to consider the option of the antibody combination results, which as I said in our hands are giving a CR rate of 80% and doubling the median survival, vs the outcome with the CAR T-cells.

The second point relates to the cytokine release syndrome, so even though this multi-institutional study in pediatric and adolescents is showing that it is reasonably safe, we are starting to gather the experience in adults with acute lymphoblastic leukemia. And what we find is over half of the patients are having to go to the intensive care unit as a result of the cytokine release syndrome complications and potential multiorgan failure, so even though CAR T-cells are a breakthrough in the treatment of adult ALL and perhaps other hematologic malignancies, such as lymphomas and others. What we have to do is consider that they could be today as allogeneic transplant was in the early days in the 1980s. We are still learning our way, we need to know whether the best outcome is in the setting of salvage active disease or whether we can move it to a frontline approach in minimal residual disease, and we have to continue comparing the results of the CAR T-cells in adult ALL vs what we get with the combined modality approaches, with antibodies in combination with chemotherapy.

**Discussion points: selecting an appropriate therapy for patients with R/R ALL (continued)**

Another question that we get is, “Well, if I have a patient who is eligible for CAR T-cells, these are CD19 CAR T-cells, is that a contraindication to using blinatumomab before this, because the blinatumomab could select a clone of CD19 T cells and this would preclude the value of CAR T-cell therapy in these patients?”

So, we did an analysis that combined the patients from MD Anderson and Germany and we found that, in fact, patients who received blinatumomab relapsed with a CD19 rate of less than 10%. So, in fact, CAR T-cells would not preclude the use of blinatumomab beforehand to induce the patients in a complete remission.

**Discussion points: role of CAR T-cell therapy in ALL**

**Marks:** Thank you very much, so that raises lots of points. I certainly, absolutely agree adults, all the data we have and it is much more limited data in adults, with shorter follow-up, suggests that this is a more toxic therapy in adults, and I think currently in adults this is not a ward-based therapy, it is a therapy that in a good percentage of patients ends up in intensive care, so at the moment it is not generalizable to large numbers of patients.
Finally, I think that there is no competition really, for me, between the targeted antibody therapies and CAR T-cells, and I think one of the [issues/points] is if we can use the blinatumomab and inotuzumab to make people have a lower disease burden, that is the point that CAR T-cells may be able to be used more effectively but also more safely, and I only have an experience of several patients having CAR T-cells, but part of the art of CAR T-cell therapy is actually getting the patient to the therapy in good shape, and I think now with inotuzumab and blinatumomab we do have a new way of doing this.

Elias, do you have any comments about CAR T-cells that you wanted to make?

**Jabbour:** David, my question is, moving forward, where to do you see the CAR T-cells being used? Shall we move it to the frontline and where in the frontline or MRD setting?

**Marks:** So, I think that there are some very bad players, I think you alluded to that before, patients with MLL rearrangement who remain high-level MRD positive, those patients are unlikely to be cured by a transplant, and I think CAR T-cells need to be investigated in those patients. I think, similarly, it may be that patients with hypodiploidy or near triploidy are in such a bad prognostic group that it may be justified to use them up front, once they are maximally cyto reduced.

I think where they have an established role now is for post-allograft relapse, and my strategy at the moment is to use blinatumomab or inotuzumab, get them to a minimal disease state and then refer them for CAR T-cells, because I think that there really isn’t a lot of data about second transplants being effective or safe and I think CAR T-cells do now have some real data in that setting.

So, carry on, please, Elias.

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**Ponatinib plus hyper-CVAD in adults with Ph-positive R/R ALL**
One of the extraordinary ALL therapies besides monoclonals are the tyrosine kinase inhibitors, starting with imatinib, followed by dasatinib and ponatinib, where really for these patients it was Ph-positive ALL, the outcome has improved in a major way from survival of ...% at one year to approaching 80% today at three years.

One of the most potent TKIs we address is ponatinib. So, ponatinib is a third-generation tyrosine kinase inhibitor. It does overcome most of the mutations, mainly the 359 mutation, a gatekeeper mutation that causes resistance to all TKIs. We know this mutation is more commonly seen in ALL and it emerged as a reason for resistance for both dasatinib and imatinib, and that was one of the rationales to use ponatinib in these patients.

The second rationale to use ponatinib in ALL was essentially the achievement of CMR or complete molecular response. We know that ponatinib is superior to other TKIs and therefore we have hypothesized that the use of ponatinib can induce a higher rate of CMR.

Based on these rationales we developed a study where we were using hyper-CVAD in combination with ponatinib for frontline therapy for patients with Ph-positive ALL.

**Response: ponatinib plus hyper-CVAD in adults with Ph-positive R/R ALL**

We have treated so far 66 patients, the results are very positive, where everybody responded but most importantly the CMR rate was 77%, undetectable disease with this treatment, and that comes at the price of a good safety profile – I will come back to that.

**Survival: ponatinib plus hyper-CVAD in adults with Ph-positive R/R ALL**

Today, we have 3.5 years of median follow-up. The three-year survival is 77% as well.

In our study, 11 patients received a transplant in remission and a transplant was only offered for patients who did not achieve a CMR, and by performing a landmark analysis we did not show any difference in outcomes, and therefore it is highly effective in hyper-CVAD – ponatinib is highly effective.

**Discussion points: ponatinib plus hyper-CVAD in adults with Ph-positive R/R ALL**

The question that we have, we face today is, “Do you also need a transplant at your first remission?”, and the second question, “Do we need intensive chemotherapy? Can we move it to less intensive regimens and combine low-intensive chemotherapy, steroids, or maybe blinatumomab plus ponatinib?”.

Dr Kantarjian discussed blinatumomab and there was data presented by Dr Martinelli and published in J Clin Oncol, where blinatumomab was shown to be effective in these
patients with refractory/relapsed Ph-positive ALL, with a 36% response rate. So, therefore the idea moving forward is to combine blinatumomab and ponatinib in a frontline setting, in relapsed/refractory as well, with the aim to eventually cure these patients without the need for an intensive approach.

A second question is, “What is the role of transplant? Can we consider transplants?” We know that CMR is really important for the long-term outcome, not CMR alone, it does not suit everybody, amongst CMR patients we do see patients relapsing, therefore the future is to be able to identify patients at low risk of relapse in order that transplant can be spared and the patients can be cured with chemotherapy and TKI or Blina and TKI, and this work is in progress.

**Marks:** So, there were some patients who achieved a complete molecular response and then came out of that response, were those patients salvageable?

**Jabbour:** Yes, patients who relapsed on Blina or on the hyper-CVAD ponatinib – most of them did receive a blinatumomab/ponatinib combination and achieve a CMR and were able to get transplantation. So, yes, they were salvageable.

However, we are trying to identify patients with early relapse, mainly patients who are lower in their molecular relapse, and go for transplant from there, instead of waiting for the full relapse when the salvage is not as effective.

**Discussion points: safety profile of ponatinib**

**Marks:** Finally, perhaps could you talk about the toxicity of ponatinib in your study?

**Jabbour:** One of the major concerns, David, of ponatinib is the vascular events, it was up to 24% in the CMR trials and at the beginning we used the 45mg approved dose. With 45mg/day we saw two patients who had fatal problems, essentially death from vascular events, and that pushed us to hold the study to revise it, and then we used lower dose schedules. Today, we have 45mg for the first 14 days and then from cycle 2 and beyond we use 30mg/day, and once we have a CMR we reduce it to 15mg/day. Since we amended the study and we have treated 35 patients, we have not had any significant vascular events encountered and we know from CML as well that the lower dose is safer than 45mg/day, so I think we are on the right track and if somebody needs to use ponatinib we should pay for a lower dose of ponatinib.
Marks: Okay, I think we will finish there, and I would just like to sum-up some of the key messages from the EHA 2017 conference.

So, after a long period of relative lack of progress in adult ALL we now have new agents to investigate, particularly in the relapsed/refractory setting, and we have discussed those three targeted therapies, blinatumomab, inotuzumab ozogamicin and CAR T-cells. Also, and still very exciting, is some early data of ponatinib in Philadelphia-positive ALL and the data that Elias Jabbour has just discussed of getting 77% of patients into a complete molecular response may mean that these patients can be spared an allograft and the risks of that procedure.

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Finally, I would like to thank Dr Kantarjian and Dr Jabbour for their excellent discussion.

So, this was a CME activity supported by an independent educational grant from Amgen and provided by the Elsevier Office of Continuing Medical Education.

Thank you all very much for participating and I hope this was useful for you and your practice.

Kantarjian: Thank you very much, Dr Marks.

[Ends]