INTERVIEW

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Tracks 1-21

Track 1 Efficacy, side effects and mechanism of action of the antibody-drug conjugate inotuzumab ozogamicin for relapsed or refractory acute lymphoblastic leukemia (ALL)

Track 2 Effect of the bispecific T-cell engaging (BiTE) antibody blinatumomab on complete remission rate in patients with relapsed or refractory B-precursor ALL

Track 3 Assessment of BCR-ABL1 transcript levels at 3 months as a predictor of favorable outcomes for patients with chronic myeloid leukemia (CML) treated with TKIs

Track 4 Monitoring responses in patients with CML receiving TKI therapy

Track 5 Selection of a second-generation TKI — nilotinib or dasatinib — for initial treatment of CML

Track 6 Mutational analysis in patients with CML

Track 7 PACE: Results from a Phase II trial of the newly FDA-approved agent ponatinib in patients with CML and Philadelphia chromosome-positive (Ph+) ALL resistant or intolerant to dasatinib or nilotinib or with the T315I mutation

Track 8 Efficacy of the newly FDA-approved oral second-generation TKI bosutinib for patients with chronic-, accelerated- or blast-phase Ph+ CML with resistance or intolerance to prior therapy

Track 9 Effectiveness of the newly FDA-approved protein translation inhibitor omacetaxine for patients with chronic- and accelerated-phase CML whose disease has progressed on 2 or more TKIs

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Track 11 Use of prognostic scoring systems — International Prognostic Scoring System (IPSS) and Dynamic IPSS (DIPSS) — to predict outcomes for patients with MF

Track 12 Long-term outcomes for patients with MF receiving the JAK1/JAK2 inhibitor ruxolitinib — survival advantage in comparison to matched historical controls

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Track 20 Therapeutic options for younger patients with ALL who experience rapid disease relapse

Track 21 Activity of FLT3 inhibitors alone and in combination with chemotherapy for relapsed or refractory acute myeloid leukemia

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you talk about the clinical activity of the novel agents inotuzumab ozogamicin and blinatumomab in acute lymphoblastic leukemia (ALL)?

DR CORTES: Inotuzumab ozogamicin is an investigational immunoconjugate that targets CD22, an antigen expressed in more than 90% of patients with ALL. The anti-CD22 antibody is attached to the toxin calicheamicin. A high durable response rate was observed in patients with ALL for whom other therapies had failed (Jabbour 2012; [3.1]). Some of these patients can be taken to transplant and thus have the potential of a cure. Liver toxicity is observed in a small proportion of patients, but it is rarely serious.

Blinatumomab is a bispecific T-cell engaging (BiTE) antibody that is designed to direct cytotoxic T cells to CD19-expressing ALL cells. A recent ASCO presentation reported responses in more than 50% of patients, with some patients experiencing complete remissions (Topp 2012; [3.2]). This agent also has been shown to have activity in patients with minimal residual disease.

3.1

Inotuzumab Ozogamicin, Administered Weekly, for Relapsed/Refractory Acute Lymphoblastic Leukemia

Response	N = 27
Overall response rate	52%
Complete response (CR)	11%
CRp (CR except platelets)	30%
Marrow CR	11%
Resistant	41%

Jabbour E et al. *Proc ASCO* 2012;**Abstract 6501**.

3.2

Effect of the Anti-CD19 BiTE Blinatumomab on Complete Remission Rate Among Adult Patients with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia

Response	All cohorts (N = 36)	Cohorts 2a + 3* (n = 23)
CR/CRh	72%	74%
Complete remission (CR)	44%	48%
CRh (CR with partial hematologic recovery)	28%	26%

* Final dose 5 μg/m^2 per day during week 1 and 15 μg/m^2 per day for the remaining treatment

Topp MS et al. *Proc ASCO* 2012;**Abstract 6500**.

Tracks 3-4

DR LOVE: Would you discuss your recent *JCO* editorial (Cortes 2012a) entitled, "Not only response but early response to tyrosine kinase inhibitors in chronic myeloid leukemia"?

DR CORTES: Because therapy for chronic myeloid leukemia (CML) has improved, we now want responses that are durable and patient survival that extends well beyond 5 years. Patients who have the best responses to tyrosine kinase inhibitor (TKI) therapy at 3 months, by cytogenetics or by molecular testing, are the ones who are more likely to have good outcomes in the long term (Marin 2012). So the major point I wanted to emphasize in the editorial is that an early response to TKI therapy is a good predictor of a durable response and longer survival.

DR LOVE: What algorithm do you follow for monitoring response in CML, and how does it affect your decision regarding which TKIs you use?

DR CORTES: At baseline, a bone marrow aspiration should be performed to make sure that the patient's disease is appropriately staged. It is important to do a cytogenetic analysis at least by FISH and PCR at 3, 6 and 12 months from the start of treatment to determine response. Once a complete cytogenetic response and a major molecular response are achieved, monitoring can be continued every 6 months.

I administer second-generation TKIs for all my patients as initial therapy because they offer a better outcome than imatinib. However, imatinib is recommended in many settings, and the fact that a generic version will be available soon is beneficial. Early monitoring becomes critical because by identifying patients who are faring well at 3 months, you don't have to worry about the second-generation TKIs.

If a patient does not have a good molecular or cytogenetic response at 3 months, the patient is unlikely to fare well in the long term. The other question that arises is, what agent could be used to improve outcomes in this setting? If the patient is receiving imatinib, then dasatinib or nilotinib could be used as salvage therapy. If dasatinib or nilotinib are used for treatment, no other agent is significantly more effective. The newly FDA-approved drug ponatinib is active in the salvage setting when other therapies have failed and is now an option for these patients.

Tracks 7-9

DR LOVE: Would you discuss what is known about the efficacy and side effects of ponatinib and the other newly FDA-approved agents bosutinib and omacetaxine in CML?

DR CORTES: Ponatinib, bosutinib and omacetaxine are interesting agents because they offer us additional tools to manage CML.

Ponatinib is a third-generation TKI that is effective in patients with the T315I mutation. We reported the results of a Phase II study at ASCO 2012, which indicated that about 60% of patients whose disease is resistant to other TKIs respond to ponatinib (Cortes 2012b). A major cytogenetic response to ponatinib was observed in approximately 70% of patients with the T315I mutation. So it has potential in this setting. The dose-limiting toxicity for ponatinib is pancreatitis. At the 45-mg dose used in the Phase II study, less than 10% of patients develop pancreatitis. Ponatinib is a well-tolerated drug overall, with a toxicity profile similar to other drugs in this setting.

Bosutinib is a second-generation TKI. It does not inhibit the T315I mutation, but about 30% of patients whose disease failed to respond to prior TKI therapy respond to bosutinib (Khoury 2012; [3.3]). The toxicity profile is favorable. It causes transient diarrhea, which is manageable. Liver toxicity may occur, so liver enzymes need to be monitored.

3.3

Activity of Bosutinib in Chronic-Phase Chronic Myeloid Leukemia After Disease Progression on Imatinib and Dasatinib and/or Nilotinib Therapy

Endpoint	
Hematologic response (n = 116)*	
Complete response	73%
Cytogenetic response (n = 108)*	
Major response	32%
Complete response	24%
Molecular response (n = 105)*	
Major response	15%

* Total number of evaluable patients out of 118 patients enrolled in study
Responses were seen across BCR-ABL mutations, including those associated with dasatinib and nilotinib resistance, except T315I.

Khoury HJ et al. *Blood* 2012;119(15):3403–12.

Omacetaxine acts by inhibiting the synthesis of proteins and is effective in patients with the T315I mutation. It can be effective in about 25% of patients, even when other agents have failed (Cortes 2012c; [3.4]). So it'll be a useful drug for a subset of patients with CML who will need an agent other than a TKI to achieve a response. Omacetaxine is a little more myelosuppressive than the other drugs, but it does not have any significant side effects.

3.4

Phase II Study of Omacetaxine After Tyrosine Kinase Inhibitor Failure in Patients with Chronic-Phase Chronic Myeloid Leukemia with the T315I Mutation

Endpoint	N = 62
Hematologic response	
Complete response	77%
Cytogenetic response	
Major response	23%
Complete response	16%

Cortes J et al. *Blood* 2012c;120(13):2573–80.

Track 12

DR LOVE: Let's chat about myelofibrosis (MF). Would you talk about your recent publication in *Blood* (Verstovsek 2012b), which evaluated the long-term outcomes of patients who received ruxolitinib?

DR CORTES: This study evaluated patients with MF who received treatment with ruxolitinib on clinical trials before it was approved. The improvement in the spleen size and in MF symptoms with ruxolitinib has been well established. The question we wanted to address was whether ruxolitinib had an effect on survival compared to matched historical controls. Our study demonstrated a clear improvement in survival for patients who received ruxolitinib (Verstovsek 2012b; [3.5]).

More than 50% of patients were still receiving treatment with ruxolitinib more than 3 years after starting therapy. Most of the patients who respond can maintain their responses. The discontinuation rate due to adverse events was low. That was confirmed by the COMFORT-I study, in which ruxolitinib was compared to placebo (Verstovsek 2012a). In the last analysis of the COMFORT-I study, a small but significant survival benefit with ruxolitinib was noted, which is remarkable given the short follow-up. ■

3.5

Long-Term Outcomes for 107 Patients with Myelofibrosis Receiving Ruxolitinib in Comparison to Matched Historical Controls

Overall survival rate in the high-risk group	Ruxolitinib (n = 63)	Control (n = 165)	HR, *p*-value
One year	95%	81%	HR = 0.5 *p* = 0.006
Two years	83%	58%	
Three years	63%	35%	

- After a median follow-up of 32 months, 54% of patients were still receiving ruxolitinib, with an overall survival of 69%.
- Overall survival among 107 patients who received ruxolitinib was significantly better than that of the 310 matched historical controls ($p = 0.005$).

Verstovsek S et al. *Blood* 2012b;120(6):1202-9.

SELECT PUBLICATIONS

Cortes JE. **Not only response but early response to tyrosine kinase inhibitors in chronic myeloid leukemia.** *J Clin Oncol* 2012a;30(3):223-4.

Cortes J et al. **PACE: A pivotal phase II trial of ponatinib in patients with CML and Ph+ ALL resistant or intolerant to dasatinib or nilotinib, or with the T315I mutation.** *Proc ASCO* 2012b;**Abstract 6503**.

Cortes J et al, on behalf of the Omacetaxine 202 Study Group. **Phase 2 study of subcutaneous omacetaxine mepesuccinate after TKI failure in patients with chronic-phase CML with T315I mutation.** *Blood* 2012c;120(13):2573-80.

Jabbour E et al. **Inotuzumab ozogamycin (I0), a CD22 monoclonal antibody conjugated to calecheamicin, given weekly, for refractory-relapse acute lymphocytic leukemia (R-R ALL).** *Proc ASCO* 2012;**Abstract 6501**.

Jain P et al. **Early molecular and cytogenetic responses predicts for significantly longer event free survival and overall survival in patients with newly diagnosed chronic myeloid leukemia in chronic phase — An analysis of 4 tyrosine kinase inhibitor modalities (standard dose imatinib, high dose imatinib, dasatinib and nilotinib).** *Proc ASH* 2012;**Abstract 70**.

Khoury HJ et al. **Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure.** *Blood* 2012;119(15):3403-12.

Marin D et al. **Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors.** *J Clin Oncol* 2012;30(3):232-8.

Topp M et al. **Effect of anti-CD19 BiTE blinatumomab on complete remission rate and overall survival in adult patients with relapsed/refractory B-precursor ALL.** *Proc ASCO* 2012;**Abstract 6500**.

Verstovsek S et al. **A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis.** *N Engl J Med* 2012a;366(9):799-807.

Verstovsek S et al. **Long-term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: Survival advantage in comparison to matched historical controls.** *Blood* 2012b;120(6):1202-9.