# 5 Minute JournalClub

SPECIAL EDITION
Issue 2, 2011

# Activity of Inotuzumab Ozogamicin in Refractory/Relapsed Acute Lymphocytic Leukemia

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## CME INFORMATION

## OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

## LEARNING OBJECTIVE

- Recall the activity reported in an early trial of inotuzumab ozogamicin, a CD22 monoclonal antibody, in patients with refractory/relapsed acute lymphocytic leukemia.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

An oncology specialist would be hard pressed to find a better hour of television than the first half of the oral leukemia/myelodysplasia plenary session from ASCO 2011. This riveting segment of the conference, available for your viewing pleasure as part of the virtual meeting, began with 2 complementary presentations of Phase III trials evaluating the JAK1/2 inhibitor ruxolitinib **(ab 6500**, **ab LBA6501)** in patients with myelofibrosis. These were followed by a fascinating BCR-ABL mutation analysis from the ENESTnd CML study **(ab 6502)** comparing nilotinib to imatinib and then a brilliant follow-up discussion by Dr Ross Levine outlining a new paradigm in myeloproliferative disorders focused on the search for mutations and related novel blocking agents. These 3 presentations and 14 other compelling ASCO heme-onc data sets are detailed in our slide sets and profiled below in this, the second half of our super-succinct special edition *5-Minute Journal Club*.

**1. Ruxolitinib in myelofibrosis**

As mentioned above, this trial duet occupies a unique spot on the ASCO highlights reel, and while our understanding of the exact mechanism of action of this oral TKI may be somewhat hazy and may relate to reduction in elevated cytokine levels, what is crystal clear is that this uncommon but merciless disease has instantly entered a new era. The US-based COMFORT-I study evaluating ruxolitinib versus placebo had a number of interesting and innovative features, including the use of MRI to objectively evaluate spleen size and electronic daily diaries to record patient symptoms. The dramatic waterfall plots visibly illustrate how treatment at least temporarily reversed an otherwise downhill course in most patients.

**2. CML**

Dr Giuseppe Saglio presented the other previously discussed ASCO standout — the landmark substudy from the ENESTnd trial **(ab 6502)** demonstrating that prior to treatment patients had almost no BCR-ABL mutations but after therapy a fascinating panoply of alterations was observed in some individuals. Dr Levine predicted that in the near future, mutation assays will be regularly integrated into the treatment algorithm.

Additionally, 24-month follow-up from 2 key Phase III studies (ENESTnd **[ab 6511]** and DASISION **[ab 6510]**) was also unveiled in Chicago, suggesting greater efficacy and perhaps less toxicity with up-front treatment with the second-generation TKIs nilotinib and dasatinib when compared to imatinib.

**3. Inotuzumab ozogamicin (our vote for name of the year)**
This antibody-drug conjugate in the lineage of brentuximab vedotin in lymphoma and T-DM1 in HER2-positive breast cancer links an anti-CD22 antibody to a cytotoxic agent from the calicheamicins class (runner up). The ASCO findings **(ab 6507)** in relapsed/refractory ALL demonstrated some type of CR in 61% of patients.

**4. Myeloma**
For more than a year we have witnessed the evolution of data from 2 major trials (CALGB, French IFM group) demonstrating an impressive delay in disease progression but the suggestion of an increased risk of second primary cancers (SPC) with 2 years of lenalidomide maintenance following stem cell transplant (SCT). At ASCO, 3 additional reports **(ab 8007, ab 8008, ab 8009)** have for the moment reinforced the concept that if there is an SPC signal it is relatively modest in magnitude and far outweighed by the antimyeloma benefit of maintenance len.

The other much-discussed myeloma paper was a landmark Italian study **(ab 8020)** that for the first time evaluated the role of autologous SCT in the era of novel antimyeloma agents. A progression-free survival benefit was reported with SCT, but other maturing studies are evaluating this important question.

**5. CLL**
Maybe the most exciting development in B-cell neoplasm research is the rapid evolution of small molecules that block B-cell receptor signaling, and at ASCO we saw more to be optimistic about with a report on the Bruton's tyrosine kinase inhibitor PCI-32765 in CLL. In this Phase Ib/II single-agent study **(ab 6508)**, response rates in excess of 50% were observed with minimal toxicity.

**6. Diffuse large B-cell lymphoma**
The lack of progress in this common cancer since the introduction of rituximab was highlighted again this year with 1 trial failing to show an advantage with dose-dense R-CHOP **(ab 8000)** and another showing no important survival benefit to consolidation autotransplant after R-CHOP induction **(ab 8001)**.

**7. AML**
AML in the elderly — a true clinical conundrum — was the subject of 3 underwhelming ASCO reports. The first **(ab 6503)** showed a modest benefit that was counterbalanced by a relatively high early mortality rate when clofarabine was combined with Ara-C. The

second **(ab 6504)** demonstrated a modest benefit for decitabine, but discussant Dr Gail Roboz verbalized hope that better outcomes might be observed in her ongoing trial evaluating 10 days of decitabine combined with the proteasome inhibitor bortezomib. The third study **(ab 6505)** was a Phase I effort evaluating a sequential regimen of azacitidine and lenalidomide that resulted in CRs in 7 of 16 patients.

Finally, we saw another interesting AML study perhaps suggesting a new model for the real-time personalized treatment of the disease. In this Phase I/II trial **(ab 6506)**, the MEK1/2 inhibitor GSK1120212 was shown to have specific activity in patients with RAS mutations.

Coming soon, an online quintet of virtual presentations delving into new developments in non-small cell lung cancer.

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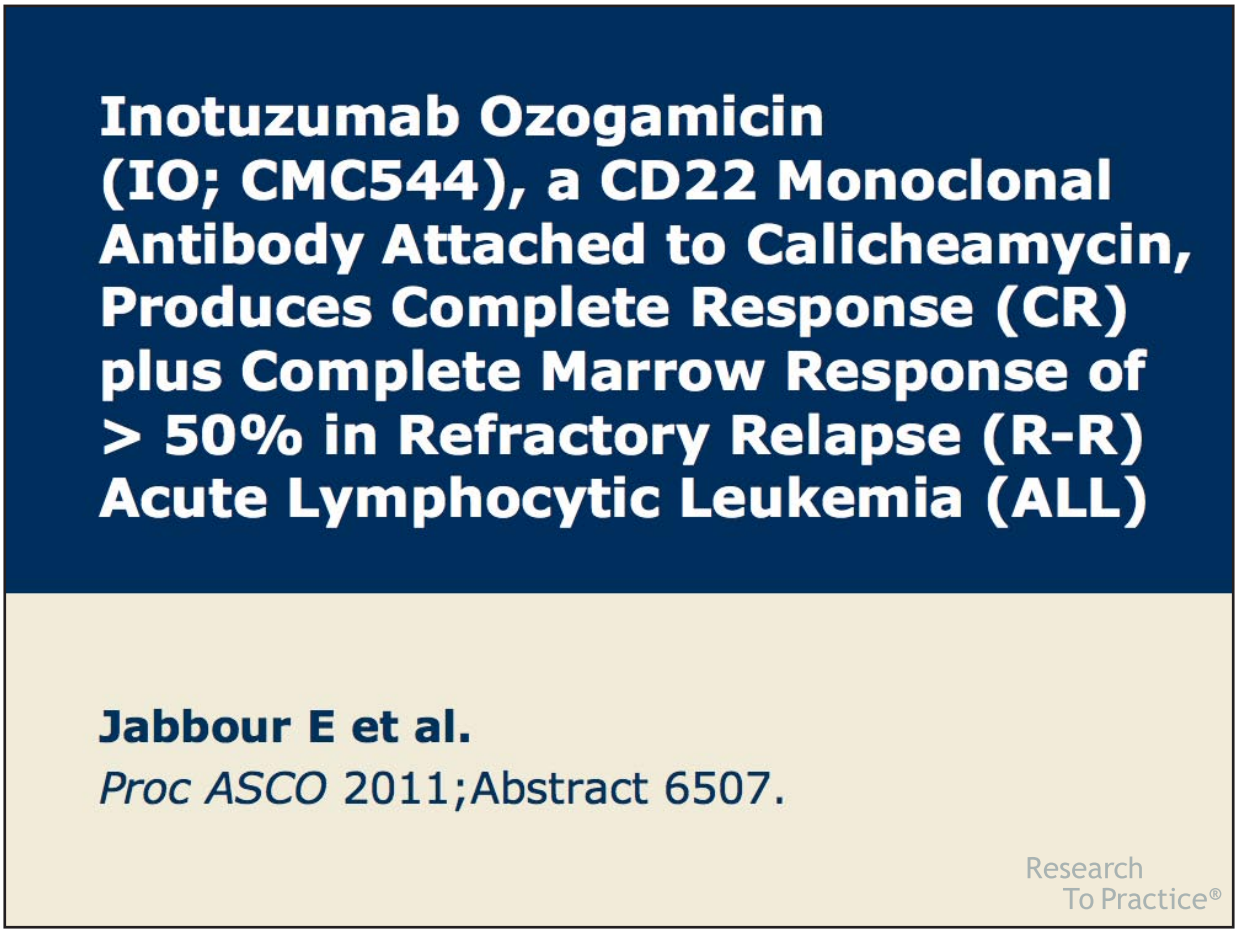
# Activity of Inotuzumab Ozogamicin in Refractory/Relapsed Acute Lymphocytic Leukemia

## Presentation discussed in this issue

Jabbour E et al. **Inotuzumab ozogamicin (IO; CMC544), a CD22 monoclonal antibody attached to calicheamycin, produces complete response (CR) plus complete marrow response (mCR) of > 50% in refractory relapse (R-R) acute lymphocytic leukemia (ALL).** *Proc ASCO* 2011;**Abstract 6507**.

## Slides from a presentation at ASCO 2011



# Study Design: Inotuzumab Ozogamicin (IO) in Refractory/Relapsed (R-R) ALL

- Eligibility (n = 48, closed):
  - Refractory or relapsed CD22-positive ALL
  - ≥ 16 yrs in first 10 patients; children were allowed in the study after safety was established
- Dosing: IO at 1.8 mg/m² IV over 1 hour q3-4 wks in all patients except 6 who received 1.3 mg/m² IV over 1 hour during the first course. Patients with objective response were allowed 8 cycles of treatment.
- If stable or no response after 2 courses of treatment, rituximab was added at 375 mg/m² D1.

Jabbour E et al. *Proc ASCO* 2011;Abstract 6507.

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# Patient Characteristics (N = 48)

| Characteristic | Category | N (%) |
|---|---|---|
| Age | ≤ 18 yrs | 3 (6) |
| | ≥ 60 yrs | 12 (25) |
| Salvage status | S1 | 10 (21) |
| | S2 | 24 (50) |
| | ≥ S3 | 12 (25) |
| Prior HCVAD regimen | Yes | 28 (58) |
| Prior allo SCT | Yes | 7 (15) |
| % CD22-positive | >90 | 27 (56) |
| | 70-89 | 14 (29) |
| | 50-69 | 7 (15) |

Jabbour E et al. *Proc ASCO* 2011;Abstract 6507.

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# IO in R-R ALL: Response (N = 46*)

| Response | No (%) |
|---|---|
| Objective response | 28 (61) |
| CR (complete remission)<br>CRp<br>CRi (marrow CR)<br>Partial response | 9 (20)<br>14 (30)<br>5 (11)<br>0 |
| Resistant<br>Death < 4 wks | 18 (39)<br>2 (4) |

* 2 patients too early to evaluate

CRp = complete remission with incomplete platelet recovery
CRi = complete remission with incomplete blood count recovery

Jabbour E et al. *Proc ASCO* 2011;Abstract 6507.

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# IO in R-R ALL: Cytogenetic Response in Abnormal Karyotype

| | Cytogenetic Response, n (%) | |
|---|---|---|
| **Subgroup, patients** | **Complete** | **Partial** |
| Abnormal karyotype and morphologic response, n = 18 | 16 (88%) | — |
| Complete response (CR), n = 6 | 5 (83%) | 1 (17%) |
| CRp, n = 8 | 8 (100%) | — |
| CRi, n = 4 | 3 (75%) | — |
| All patients with abnormal karyotype, n = 34 | 16 (47%) | — |

CRp = complete remission with incomplete platelet recovery
CRi = complete remission with incomplete platelet or neutrophil recovery

Jabbour E et al. *Proc ASCO* 2011;Abstract 6507.

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# Efficacy of IO in R-R ALL Compared to Standard Chemotherapy*

| Parameter | % Overall Response Rate | | *p*-value |
|---|---|---|---|
| | Inotuzumab (n = 48) | Chemotherapy (n = 459) | |
| **Overall** | **61** | **32** | **<0.001** |
| Salvage 1 | 71 | 38 | 0.004 |
| Salvage 2 | 48 | 23 | 0.032 |
| ≥ Salvage 3 | 67 | 13 | <0.001 |

* Historical data from MD Anderson Cancer Center

Jabbour E et al. *Proc ASCO* 2011;Abstract 6507.

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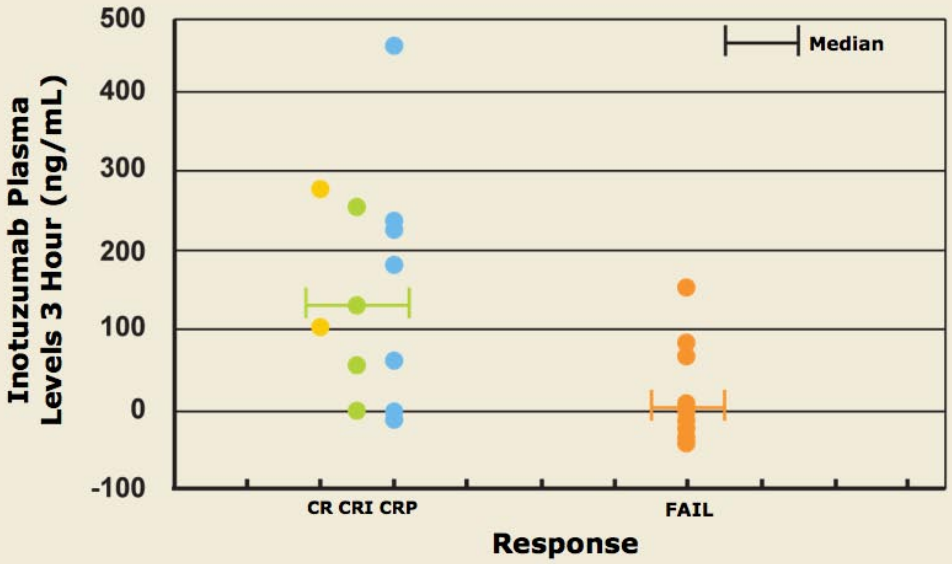
# IO in R-R ALL: Response by IO Level in Plasma 3 Hr After End of Infusion (EOI)




Response = 89% for plasma level >100 ng/ml versus 33% for plasma level <100 ng/ml at 3 hr post EOI, *p*-value = 0.008

With permission from Jabbour E et al. *Proc ASCO* 2011;Abstract 6507.

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# IO in R-R ALL: Adverse Events

| Adverse events (n) | Grade 1-2 | Grade 3-4 |
|---|---|---|
| Drug fever | 19 | 9 |
| Hypotension | 12 (4 with fever) | 1 |
| LFT abnormalities | | |
| Bilirubin | 12 | 2 |
| SGPT/SGOT | 27 | 1 |
| Lipase/amylase | 0 | 1 |
| Veno-occlusive disease | — | 4 (post ASCT) |
| Periportal fibrosis | 2 (C1D38, C4D45) | |

Jabbour E et al. *Proc ASCO* 2011;Abstract 6507.

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# Author Conclusions

- IO demonstrated very high response rate (ORR = 61%) for single-agent therapy in R-R ALL.
- There is correlation of response with drug plasma levels.
- Toxicities include thrombocytopenia (data not shown) and abnormalities of LFTs.
- Plans include the assessment of IO administered at alternative schedules (weekly) and studies on combinations of IO with chemotherapy.

Jabbour E et al. *Proc ASCO* 2011;Abstract 6507.

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