5 Minute JournalClub

SPECIAL EDITION
Issue 1, 2011

Final Results of the SSGXVIII/AIO Study on the Treatment of Operable GIST with High Risk of Recurrence with 36 versus 12 Months of Adjuvant Imatinib

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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

- Apply recent study results to your recommended total duration of adjuvant imatinib for patients with GIST at high risk of recurrence.

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

The electric pace of oncology in 2011 means that most busy practitioners barely have time to read abstracts, let alone dive into journal articles and watch or attend meeting presentations. Addressing that challenge, this latest experiment in cancer education attempts to provide our quickest take possible on the most memorable presentations from ASCO 2011. This first issue focuses on solid tumors (hematologic cancers will be coming next week), and for each of the presentations summarized below we have created a brief, clickable slide set reviewing the most essential findings and providing the perspectives of clinical investigators (presented on the last slide of each set). Here we go:

1. Vemurafenib and ipilimumab in melanoma

Two plenary papers on Phase III trials with these agents showed important survival benefits (**ab LBA4** and **LBA5**). The findings and recent FDA approval of both of these agents heighten the importance of BRAF V600E mutation testing and create a challenging choice between these two interesting novel compounds as first-line therapy for patients with tumors harboring these mutations.

2. GI cancers: Adjuvant imatinib in GIST; neoadjuvant treatment of rectal cancer

Another compelling plenary paper (**ab LBA1**) reported a trial in patients with high-risk GIST revealing that 3 years of adjuvant imatinib resulted in much better PFS and OS than 1 year. Importantly, in both groups relapses started occurring 6 months after the discontinuation of treatment, suggesting the need for longer-duration or perhaps indefinite imatinib.

Also in GI cancer, 2 trials (**ab 3503 and 3504**) addressed a couple of old, lingering questions in terms of the choice of chemotherapy to pair with radiation therapy in rectal cancer. Bottom line: There doesn't seem to be a current role for neoadjuvant oxaliplatin, and it's pretty challenging to think of a good reason to use 5-FU instead of capecitabine.

3. Important Phase I-II studies on novel agents
In our nominee for most exciting ASCO data set (**ab 4516**), the Met/VEGFR2 TKI cabozantinib (formerly XL 184) in prostate cancer produced some of the most stunning outcomes seen in this or any other solid tumor, including dramatic improvements evident on bone scans often associated with major symptom palliation.

A close second to the cabozantinib paper (**ab 7525**) and one that kept the faculty at our recent lung cancer Think Tank buzzing demonstrated that pan-EGFR blockade with the irreversible TKI afatinib combined with cetuximab resulted in significant responses in patients with advanced NSCLC resistant to an EGFR TKI, including those with T790M mutations.

Another encouraging NSCLC paper (**ab 7505**) evaluated the monoclonal antibody MetMAb and demonstrated improved PFS in the 52% of patients with Met overexpression.

4. Iniparib in triple-negative breast cancer
We all knew it was coming, but the biggest downer of the meeting (**ab 1007**) was the pretty much negative study — presented by the diminutive genius Joyce O'Shaughnessy — of iniparib plus chemo in advanced TNBC. These disappointing findings left many scratching their heads and have forced researchers back to the drawing board in an attempt to figure out why this putative PARP inhibitor worked in the Phase II but not the Phase III setting.

5. Reinforcement of the new lung adenocarcinoma advanced-disease paradigm
The PARAMOUNT trial (**ab CRA7510**) again supported the role of some type of maintenance strategy after first-line chemo with or without bev, this time the "continuation" of pemetrexed, and while we await Phase III data from the related PointBreak trial, pem/carbo with or without bev followed by pem and/or bev maintenance are commonly employed nonprotocol approaches.

In a similar vein, the EURTAC study (**ab 7503**) again demonstrated that for patients with EGFR mutation-positive advanced lung cancer, an EGFR TKI results in better short-term outcomes than chemo.

6. Bevacizumab with chemotherapy in breast and ovarian cancer
Two neoadjuvant breast trials (**ab LBA1005 and 1006**) demonstrated more path CRs with bev, and a reanalysis of the RIBBON 2 trial evaluating this anti-angiogenic agent in the second-line setting revealed a doubling of response rates for patients with triple-negative disease (**ab 1010**).

In recurrent ovarian cancer, chemo plus bev with bev maintenance until progression resulted in longer PFS (**ab LBA5007**), and more follow-up from the ICON7 "adjuvant" trial (**ab LBA5006**) continued to show a slowing of disease progression with chemo/bev followed by bev maintenance. However, as yet no impact on survival has been observed. What this means in both cancers outside a protocol setting and from a regulatory/reimbursement perspective continues to be vociferously debated.

Next up on our condensed ASCO highlights reel: Liquid tumor snippets.

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Final Results of the SSGXVIII/AIO Study on the Treatment of Operable GIST with High Risk of Recurrence with 36 versus 12 Months of Adjuvant Imatinib

Presentation discussed in this issue

Joensuu H et al. **Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO).** *Proc ASCO* 2011;**Abstract LBA1**.

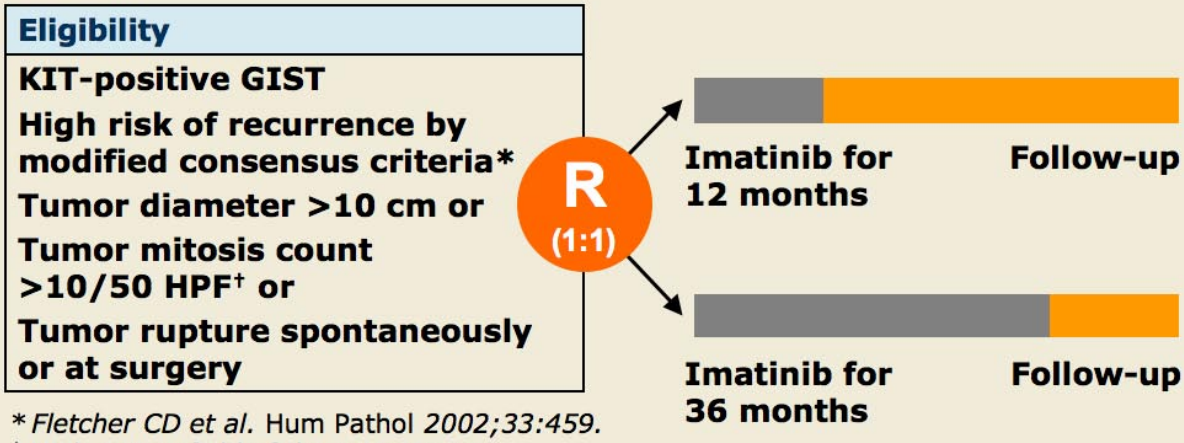
Slides from a presentation at ASCO 2011 and comments from Leonard B Saltz, MD

Background

- Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the GI tract.
- Imatinib (IM) inhibits the KIT and PDGFR alpha tyrosine kinases, which are frequently mutated in GIST, and it is effective in the treatment of advanced GIST.
- The ACOSOG Z9001 trial showed that one year of adjuvant IM improved regression-free survival (RFS) versus placebo.
- **Study hypothesis**:
  - Three years of adjuvant IM results in improved RFS compared to one year of IM in patients diagnosed with KIT-positive GIST.

Joensuu H et al. *Proc ASCO* 2011;Abstract LBA1.

SSGXVIII: Phase III Study Design



* *Fletcher CD et al.* Hum Pathol *2002;33:459.*
† *High-power field of the microscope*

Stratification:

1) R0 resection, no tumor rupture
2) R1 resection *or* tumor rupture

Both groups received IM 400 mg/day orally; KIT and PDGFRA mutation analyzed centrally.

Joensuu H et al. *Proc ASCO* 2011;Abstract LBA1.

Baseline Characteristics

	12 months (N = 199)	36 months (N = 198)
Median age, years (range)	62 (23-84)	60 (22-81)
ECOG performance status 0, %	85	86
Gastric primary tumor, %	49	53
Median tumor size, cm (range)	9 (2-35)	10 (2-40)
Median mitosis count, -/50 HPFs	10 (0-250)	8 (0-165)
Tumor rupture, %	18	22
GIST gene mutation site, %		
- KIT exon 9	6	7
- KIT exon 11	69	71
- KIT exon 13	2	1
- PDGFRA (D842V)	13 (10)	12 (8)
- Wild type	10	8

Joensuu H et al. *Proc ASCO* 2011;Abstract LBA1.

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SSGXVIII: Recurrence-Free and Overall Survival (ITT)*

	Imatinib, 12 mo (n = 199)	Imatinib, 36 mo (n = 198)	Hazard ratio	*p*-value
3-year RFS	60.1%	86.6%	0.46	<0.0001
5-year RFS	47.9%	65.6%		
3-year OS	94.0%	96.3%	0.45	0.019
5-year OS	81.7%	92.0%		

RFS = recurrence-free survival; OS = overall survival
* Median follow-up at 54 months

Joensuu H et al. *Proc ASCO* 2011;Abstract LBA1.

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Select Adverse Events

	Imatinib 12 months		Imatinib 36 months	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Anemia	72%	1%	80%	1%
Periorbital edema	59%	1%	74%	1%
Elevated LDH	43%	0%	60%	0%
Fatigue	48%	1%	48%	1%
Nausea	45%	2%	51%	1%
Diarrhea	44%	1%	54%	2%
Leukopenia	35%	2%	47%	3%
Muscle cramps	31%	1%	49%	1%

LDH = lactate dehydrogenase

Joensuu H et al. *Proc ASCO* 2011;Abstract LBA1.

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Author Conclusions

- Three years of adjuvant IM improves RFS and OS compared to one year of IM in patients who have a high estimated risk of recurrence after surgery.
  - Five-year RFS 65.6% vs 47.9%, respectively.
  - Five-year OS 92.0% vs 81.7%, respectively.
- Adjuvant IM is relatively well tolerated.
- Severe adverse events are infrequent.

Joensuu H et al. *Proc ASCO* 2011;Abstract LBA1.

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Investigator Commentary: Results of the Randomized Trial of 12 versus 36 Months of Adjuvant Imatinib Therapy for GIST at High Risk of Recurrence

This study of adjuvant therapy for high-risk GIST showed that continuing imatinib for 3 years led to a statistically and clinically significant improvement in overall and disease-free survival. These results are quite impressive.

What struck me was that somewhere in the 4-to-6 month period after imatinib was stopped in each arm, you begin to observe a worrisome drop-off. The nature of the failure pattern indicates that longer treatment is better, but it also suggests that imatinib is maintaining a population of cells in long-term stasis, rather than eradicating the disease. This begs the question of indefinite therapy.

Imatinib is a highly effective agent, and in many ways represents a gold standard of what we desire of targeted therapy. Even though it is well tolerated, in this study it was associated with some side effects which required dose modifications. This needs to be a consideration in the planning of treatment for individual patients.

Leonard B Saltz, MD