

CHRONIC MYELOID LEUKEMIA: BEYOND IMATINIB

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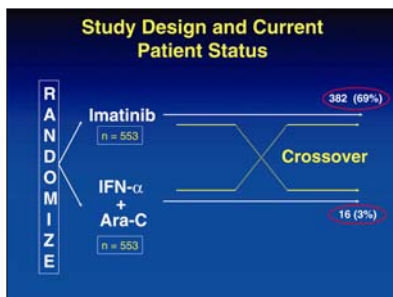
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Disclosure Information

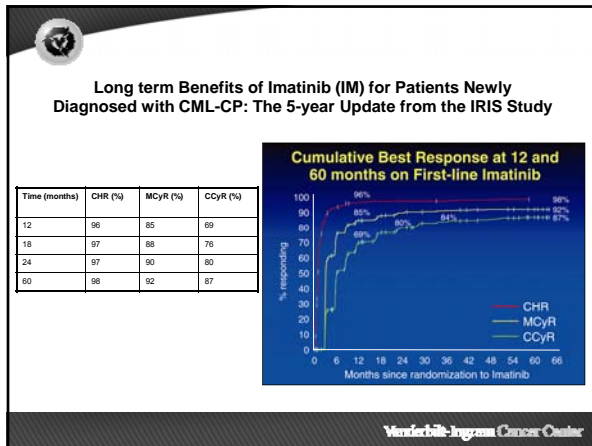
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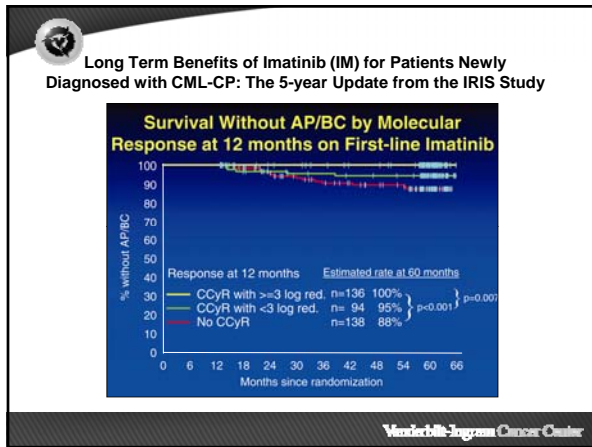
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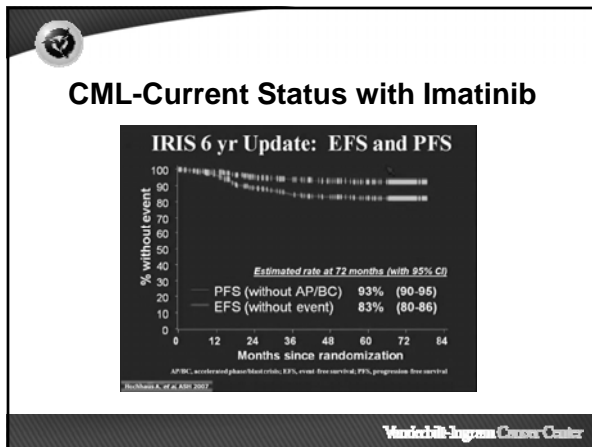
IRIS study



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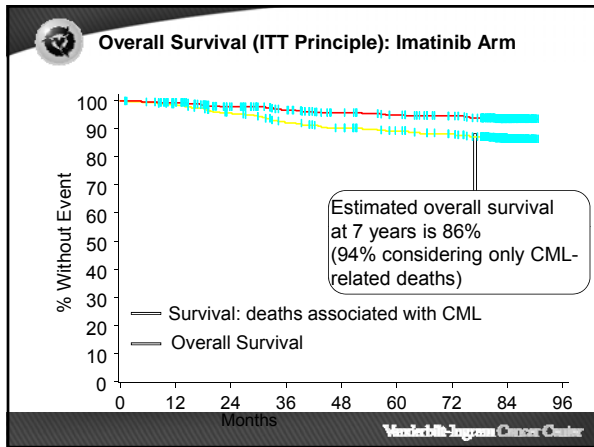




The IRIS Study-7 year Update

Stephen O'Brien
Abstract 186

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IRIS-7 year Follow Up

- At 7 years
 - EFS 81%
 - FFP from AP/BC 93%
 - OS 86%
 - MCyR 89%
 - CCyR 82%

Abstract 186-Stephen O'Brien

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IRIS-7 Year Follow Up

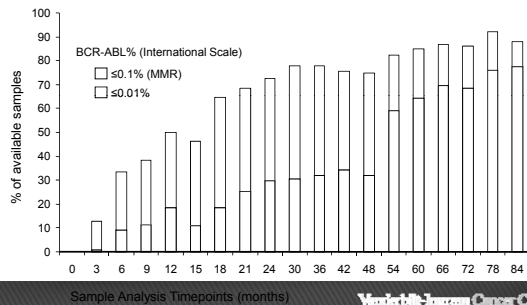
- 456 patients achieved CCyR
 - 79 lost CCyR
 - 25 remained on IM (19 regained CCyR, 6 remain in MCyR)
 - 15 patients (3%) progressed to AP/BC

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Molecular Response Rates

- Major molecular response (MMR) and the depth of molecular response increase over time



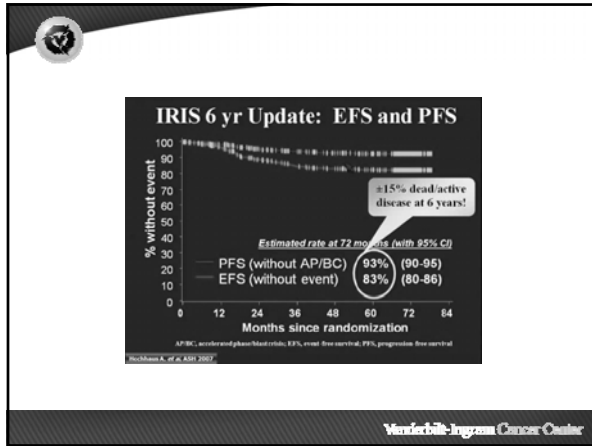
Sample Analysis Timepoints (months)

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- Responses to IM remain durable at year 7.
- MMR at year 7 is 86%.
- No new safety issues have been noted.

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Second Generation TKIs

- Nilotinib
 - Higher binding affinity and selectivity for Abl with respect to Imatinib (IM)
 - Effective in IM resistant/intolerant patients in CP/AP
- Dasatinib
 - Multi-targeted inhibitor of BCR-ABL and SRC
 - Effective in IM resistant/intolerant patients in CP/AP/BC


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High and Early Rates of Cytogenetic and Molecular Response with Nilotinib 800 mg Daily as First Line Therapy of Ph+ CML in CP: Results of a Phase 2 Trial of the GIMEMA CML Working Party

- Nilotinib is FDA Approved for CML patients resistant or intolerant to IM in CP, and AP.
- Logical to test the drug as first line.


Abstract 181-Gianantonio Rosti

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- Open label, single stage, multicenter phase II study
- Ph+ CML, early CP
- Nilotinib 400 mg po BID
- Primary Endpoint: CCyR at 1 year
- Secondary Endpoint: Kinetics of molecular response.

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- 73 patients with median age 51 yrs (18-43), median follow up 210 days (68-232)
- Completed 3 months: 100%
- Completed 6 months: 66%
- Responses at 3 months: CHR 100%, CCyR 78%
- Responses at 6 months: CHR 98%, CCyR 96%

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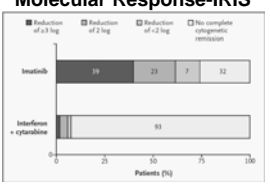


Molecular Response

MMR-Nilotinib

- 1 month: 3%
- 2 months: 22%
- 3 months: 59%
- 6 months: 74%

Molecular Response-IRIS



Response Category	Nilotinib (n)	Interferon + cytarabine (n)
Reduction of >3 log	19	1
Reduction of 2 log	23	1
Reduction of <2 log	7	1
No complete cytogenetic remission	32	91

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Compliance

- Median dose 789 mg
- Dose interruption: 47%
- Median days of dose interruption: 15
- Doses at last visit:
 - 400 mg BID: 71%
 - 400 mg QD: 27%

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Adverse Effects

- 1 grade 4 neutropenia
- Any hematologic toxicity: 5 patients
- Grade 3 biochemical abnormality
 - Bilirubin: 15%
 - GOT/GPT: 11%
 - Lipase: 4%
 - QTc prolongation: 3% (all transient, >450 but <499 msec)

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- Nilotinib is safe and effective as a front line drug
- Kinetics of both, cytogenetic and molecular responses are substantially faster compared to imatinib

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Efficacy of Dasatinib in Patients with Previously Untreated CML in ECP

- Open label, single center, phase II study
- Primary endpoint: MMR at 12 months
- Secondary endpoint: safety and compared to IM historical control
- Dose: Randomized between 50 mg BID or 100 mg QD

Abstract 182-Jorge Cortes

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50 patients (25 on each arm)

Median age 45 years (18-76)

Median follow up of 24 months

44/45 evaluable patients (98%) achieved a CCyR

Months of Therapy	Percent with CCyR (no. evaluable)			P value
	Dasatinib 400 mg	Imatinib 400 mg	Imatinib 800 mg	
3	78 (45)	37 (49)	62 (202)	0.0003
6	93 (41)	54 (48)	82 (199)	<0.0001
12	97 (35)	65 (48)	86 (197)	0.0001
18	88 (33)	68 (38)	89 (179)	0.004
24	80 (25)	70 (40)	88 (173)	0.006

MMR

12 months 12/35 (34%)

24 months 12/25 (48%)

EFS-24 months 81%


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Adverse Effects


- Grade 3-4 non-hematologic toxicity
 - Pruritis-13%; fatigue 6%; neuropathy 4%
 - Pleural effusion 21% (2% grade 3-4)
- Grade 3-4 hematologic toxicity
 - Thrombocytopenia 11%; neutropenia 21%; anemia 9%
- 54% required dose interruption

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- Dasatinib is safe, and effective as front line treatment for ECP CML
- Grade 3-4 hematologic and non-hematologic toxicity is significant and 22% patients develop pleural effusions.

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Is it Possible to Stop Imatinib?


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Is It Possible to Stop IM in Patients with CML? An Update from a French Pilot Study and First Results from the Multicenter Stop Imatinib (STIM) Study


Francois-Xavier Mahon
Abstract 187

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- Patients on IM for at least 5 years
- CMR (undetectable RQ-PCR corresponding to a 5 log reduction) for at least 2 years
- Molecular relapse defined as two positive PCRs

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- 50 patients
- Median age 62 years (range, 32-81)
- IM-25 patients, IFN-IM-25 patients
- Median follow up >6 months
- Relapse-19 patients
 - M2: 3 patients -M4: 4 patients
 - M3: 8 patients -M5: 3 patients

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- IFN-IM 10 patients with > 6 month follow-up not relapsed
- IM 5 patients with > 6 month follow-up not relapsed


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The Majority of CML Patients Who Cease IM after Achieving a Sustained CMR Remain in CMR, and Any Relapses Occur Early

David Ross
Abstract 1102


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- Non-randomized, prospective study of imatinib withdrawal in adult patients
- Patients in CMR \geq 2 years
- Multiple centers in Australia
- RQ-PCR for BCR-ABL monthly for first year and the every 2 months in second year

Abstract 1102-David Ross

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- Molecular Relapse
 - Any PCR above level of MMR
 - Any two positive PCR
- Treatment of molecular relapse
 - Treated with IM
 - Monthly monitoring of PCR for 12 months

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- N=18 (IM only=5; IFN-IM=13)
- Median age 58 years
- Median duration of IFN 39 months
- Median duration of IM 60 months



- Sustained CMR at 12 months off treatment- 67% (95% CI 40-85)
- IFN-IM group
 - CMR off treatment 10/13 (77%)
 - 7/10 in CMR >12 months
- IM group
 - 3/5 in CMR
 - Median follow up 5 months



- Molecular relapse
 - All relapses within 5 months of stopping therapy
 - All patients regained CMR within 5 months of restarting IM
 - No hematologic relapses, no mutations



- Withdrawal of IM in a subset of patients may be possible
- NOT recommended outside of a clinical trial
- Clinical and molecular predictors need to be identified

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