

1. The IRIS Study: early chronic phase CML-
7 years follow-up

2. Integrated approach in CML

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BACKGROUND

- What is IRIS study and Imatinib to clinical hematologists?
- Introduced precise criteria for therapeutic response
- Defined strict time-frames for therapeutic response
- Provided solid scientific basis for development of new TKI , overcoming resistance
- Established the new standard of care for CML Ph + and converted a leukemia in a well-manageable chronic disease with unseen rates of OS, EFS and unreached MS. Results are significantly better than the only curative treatment SCT.
- Out-patients, excellent quality of life, complete social re-integration
- Unique features: the rates of therapeutic response increase over time, progression rates and SE decrease over time

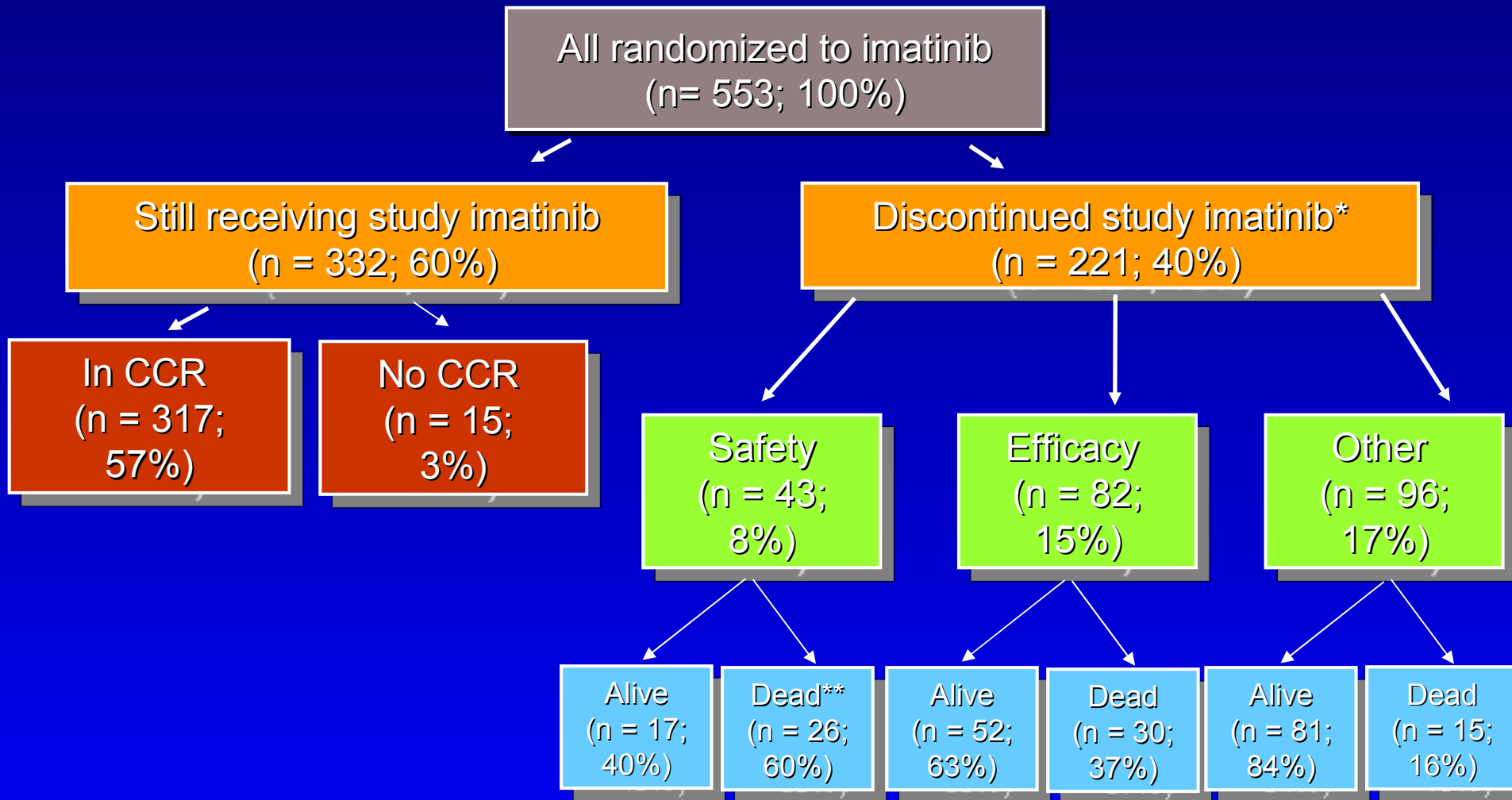
1. IRIS 7 -Year Update

- IRIS established imatinib as the standard of care as initial therapy for chronic phase CML¹
- This report is the 7 year update of IRIS
 - 1106 patients originally, 553 per arm
 - 554 of 1106 (50%) patients remained on study
 - 545 of these 554 (98.4%) patients were on imatinib
 - 332 on first-line (60% of patients randomized to first-line imatinib, 400 mg daily)
 - 213 patients crossed over from IFN/Ara-C (39% of patients randomized to IFN/Ara-C)
 - 9 patients (1.6%) remained on IFN/Ara-C
- Since only 1.6% of IFN/Ara-C patients remained on therapy, this report focuses on long-term outcomes and safety of only patients randomized to imatinib

IFN, interferon; Ara-C, cytarabine.

¹Hochhaus A, et al. *Blood*. 2007; 110. Abstract 25. ASH 2007 Oral Presentation.

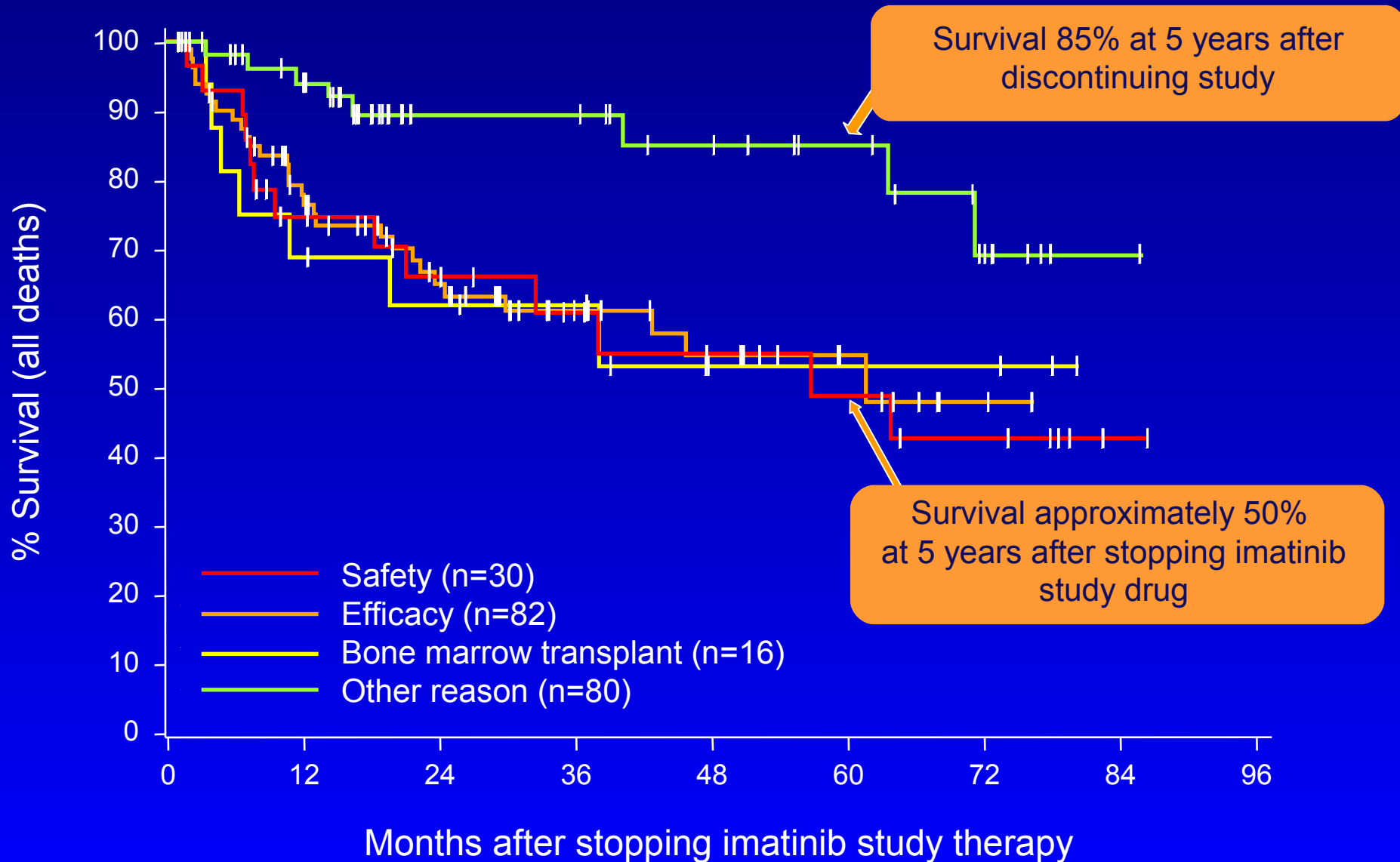
What Happened To The Patients After 7 Years?



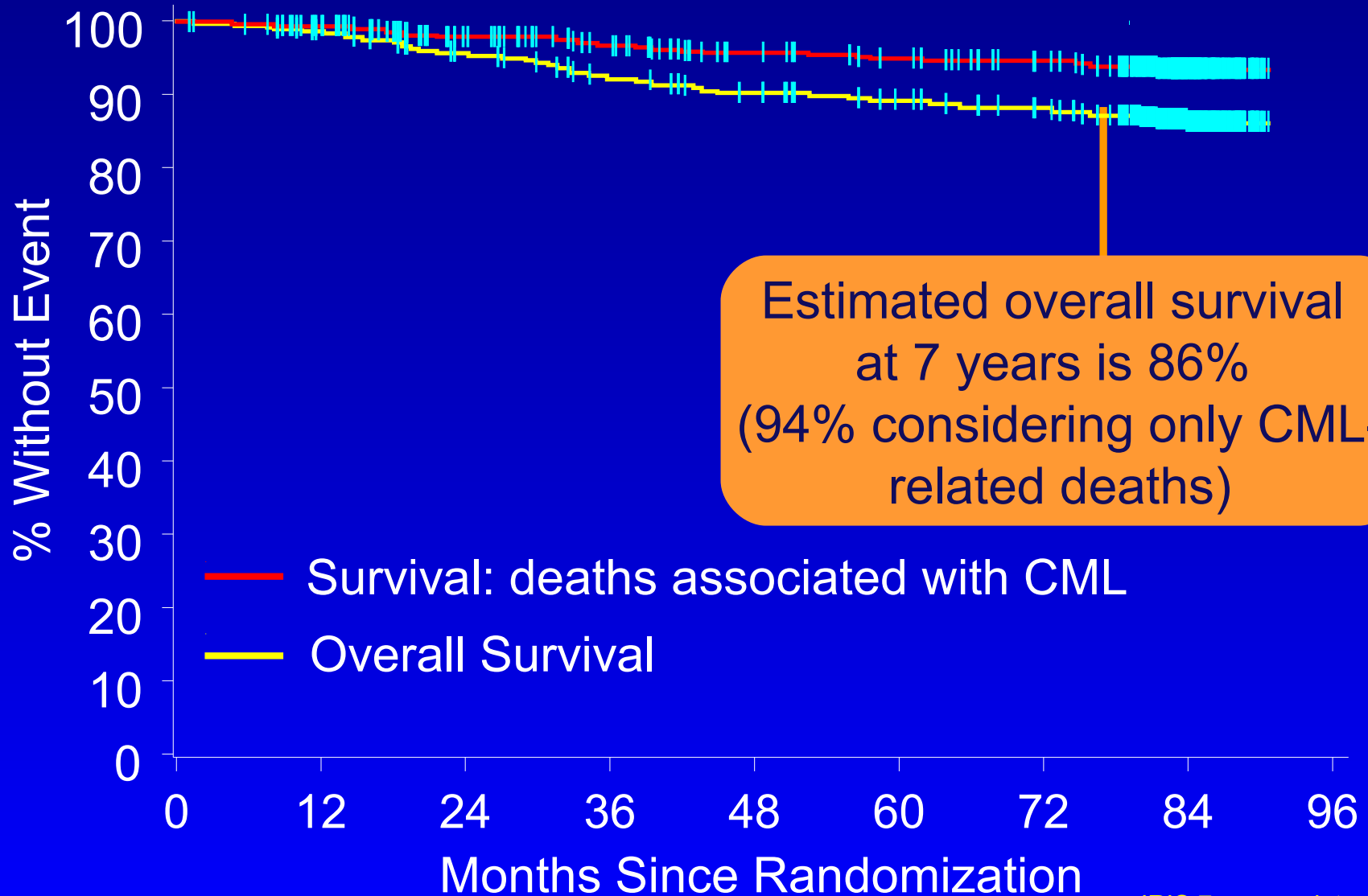
**Including primary discontinuation reason 'Death' (n=13)

*Patients may have continued imatinib off study.

Survival of Patients Who Discontinued Imatinib Study Therapy



Overall Survival (ITT Principle): Imatinib Arm

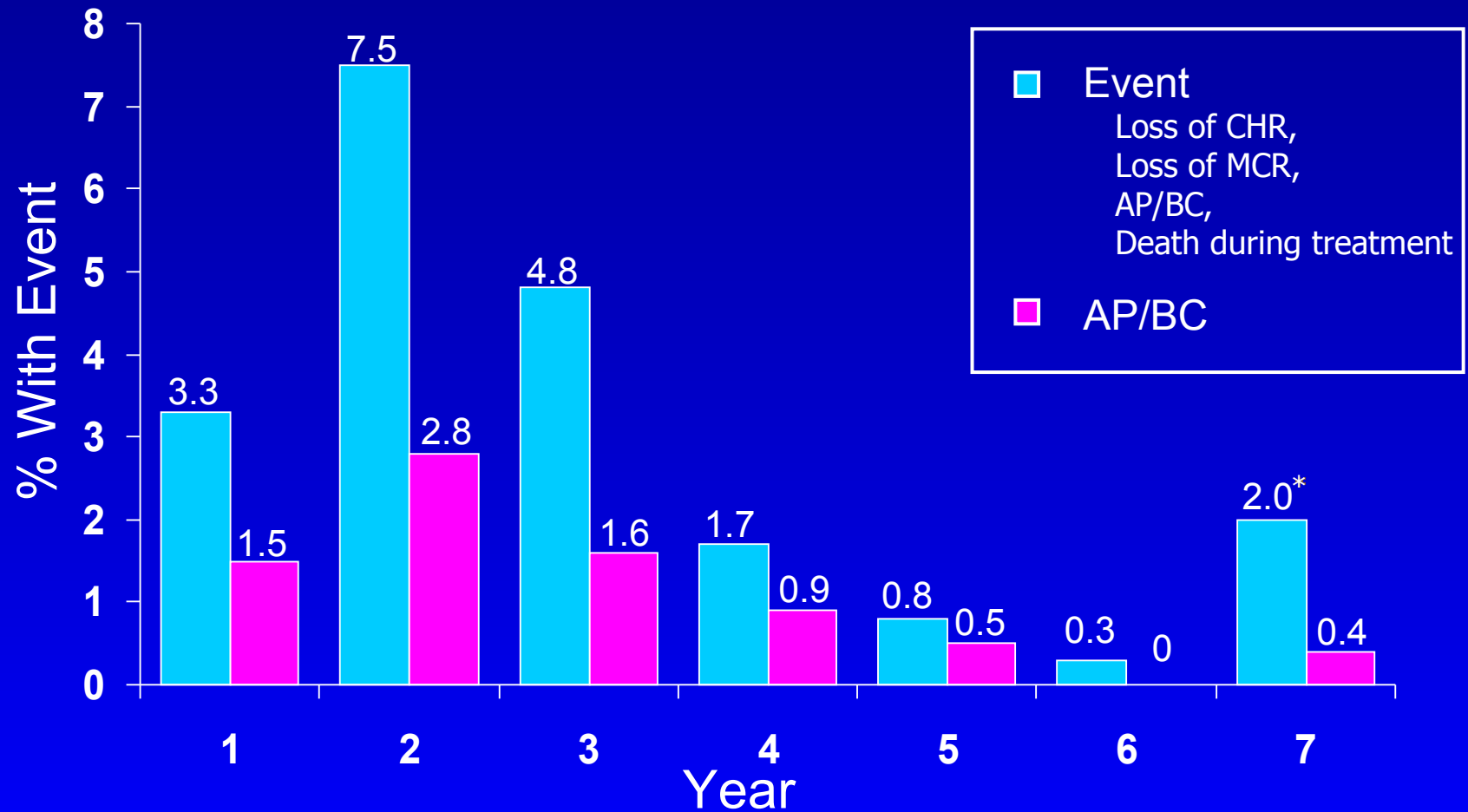


IRIS 7 Year Update: Main Points

- What happened to all the patients?
 - Discontinuation
 - Survival
- Late progression events
- Durability of complete cytogenetic response (CCR)
 - Is CCR a 'safe haven'?
- PCR data
- Adverse Events
- Conclusions

Annual Event Rates: Imatinib Arm

- KM estimated EFS at 7 years = 81%
- KM estimated rate without AP/BC at 7 years = 93%



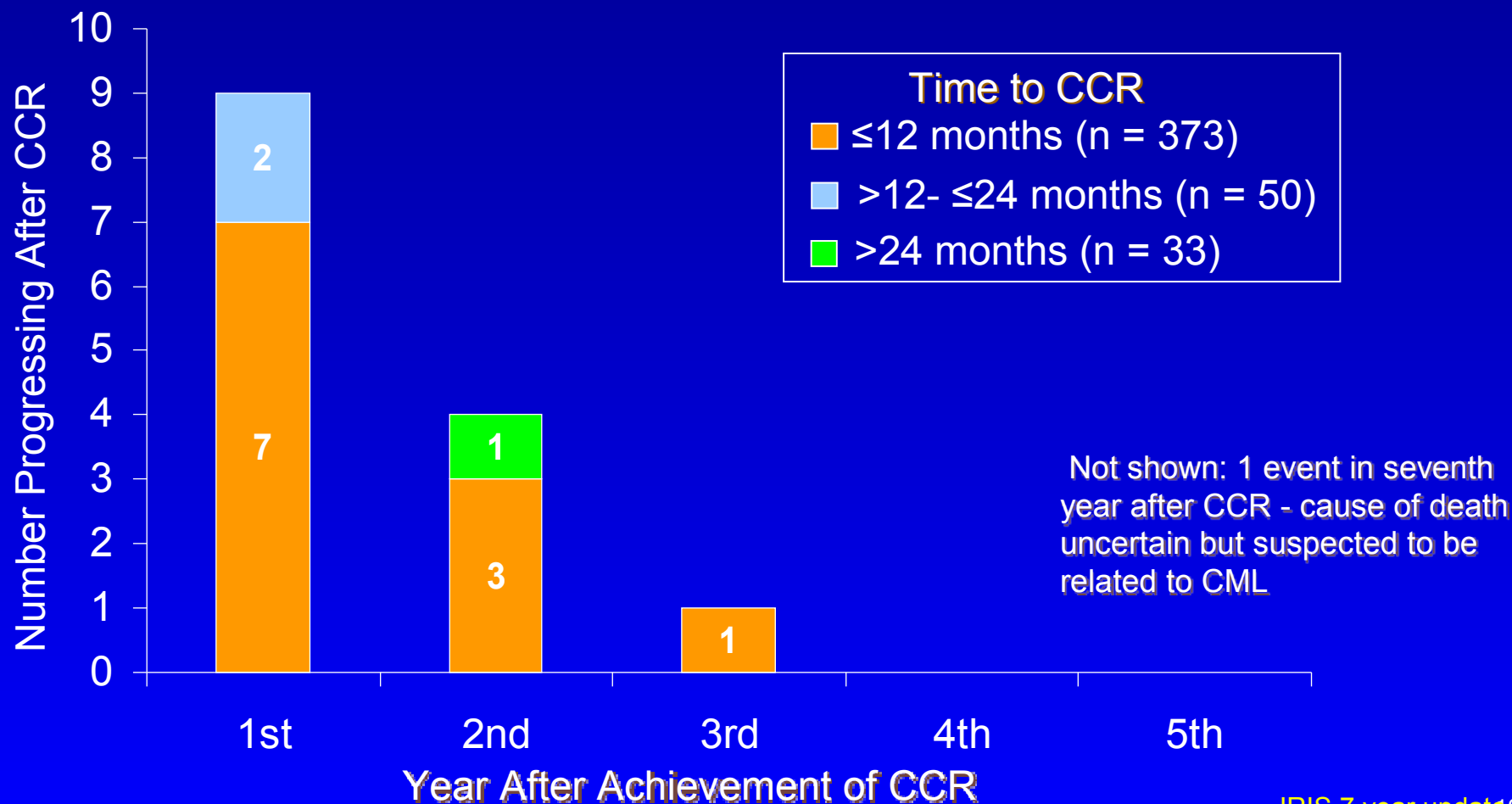
*Total events (n=5) including loss of MCR (n=3) and deaths (n=2, one of which was coded as progression to AP/BC in a patient in CMR 6 months prior to death). IRIS 7 year update

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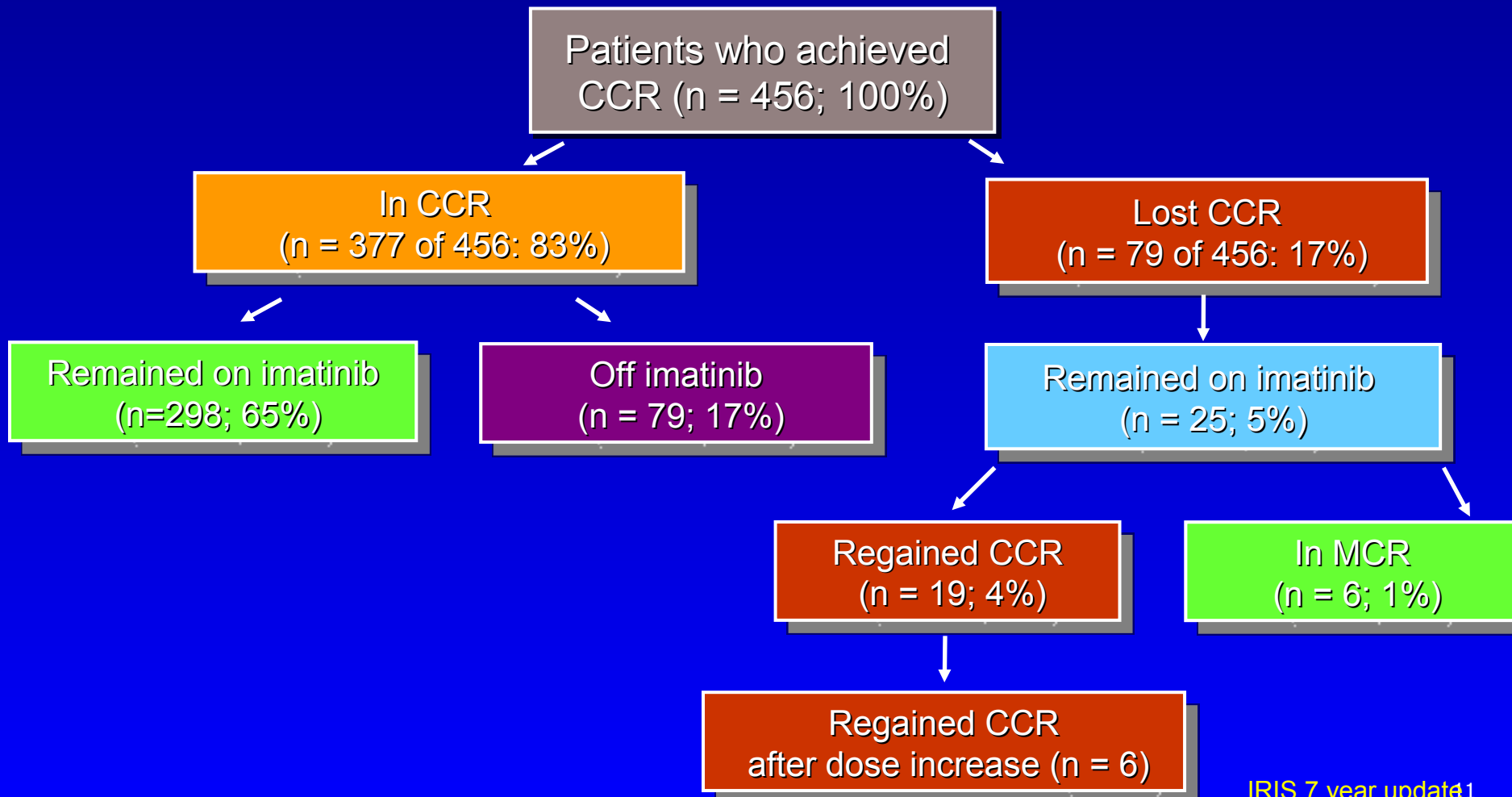
Rates of Progression in Patients After CCR

- Progression to AP/BC occurred in 15 (3%) of the 456 patients who had achieved a CCR
- Of 456 patients who achieved CCR, 10 (2%) died from CML



Durability of Cytogenetic Response

- 456 of 553 (82%) of first-line imatinib patients achieved CCR
- 317 (57%) patients randomized to imatinib remained on protocol and were in complete cytogenetic response (CCR)



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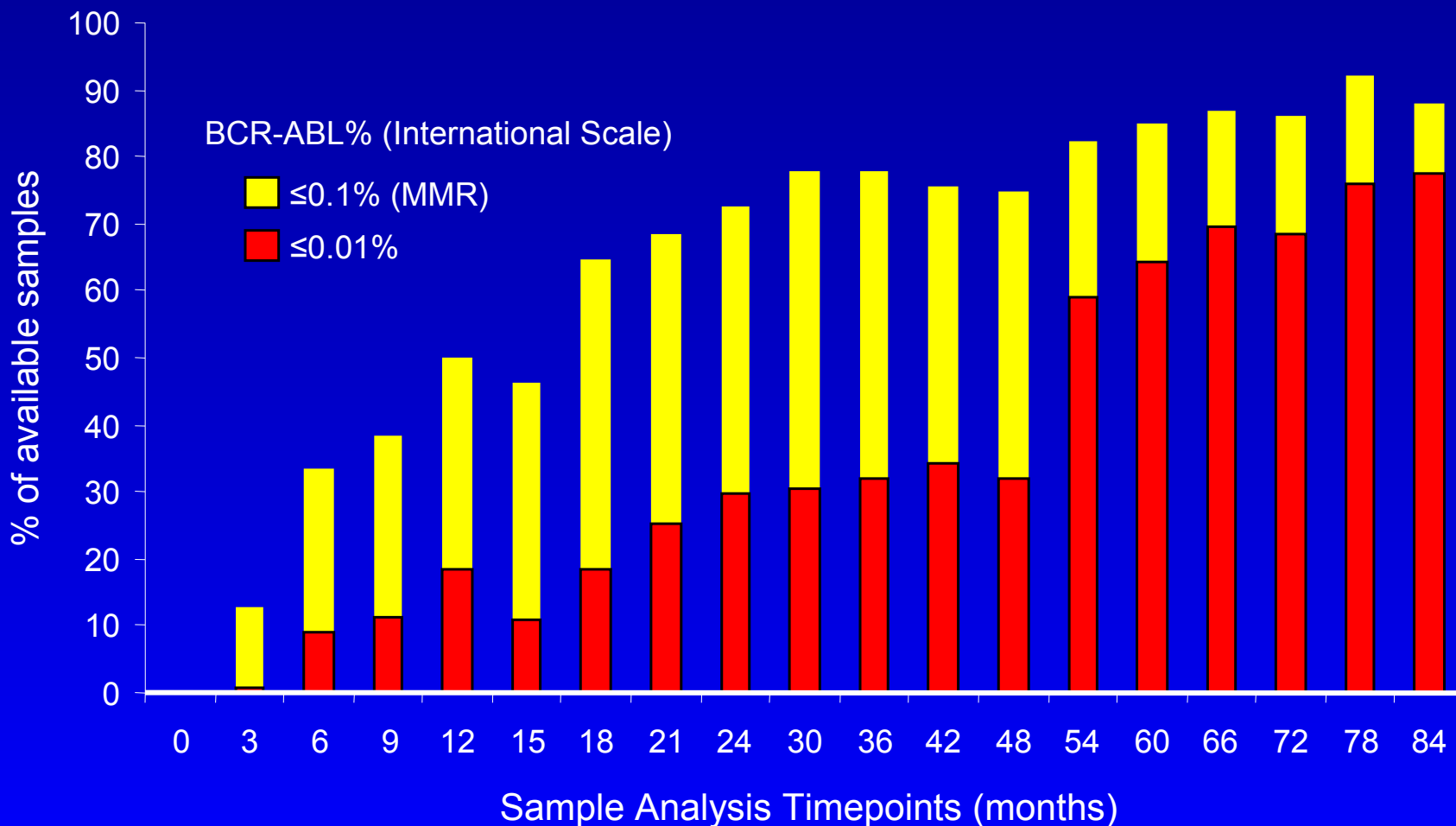
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IRIS PCR studies

- The IRIS protocol mandated measurement of molecular responses once patients achieved CCR
- Additional samples were submitted by some sites at intervals independent of cytogenetic response status
- Preplanned substudies at sites in Australia and Germany conducted PCR measurements at intervals independent of cytogenetic response status (n=100)
 - By 7 years > 85% of patients had at least one PCR measurement submitted with a large number of samples available at baseline and every follow-up point
- First presentation of expanded data set today
 - Hughes *et al.* [abstract 334] 11:45 AM; Room 2009-2011 West

Molecular Response Rates

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



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Most Frequently Reported AEs: First-Line Imatinib

Most Common Adverse Events (by 5 Years)	All Grade AEs Patients, %	Grade 3/4 AE's Patients %
Superficial Edema	60	2
Nausea	50	1
Muscle cramps	49	2
Musculoskeletal pain	47	5
Diarrhea	45	3
Rash/skin problems	40	3
Fatigue	39	2
Headache	37	<1
Abdominal pain	37	4
Joint pain	31	3

- Only Serious Adverse Events (SAEs) were collected after 2005
- Grade 3/4 adverse events decreased in incidence after years 1-2

IRIS SAEs in Years 6 and 7

- No unique, previously unreported AEs attributed to imatinib observed over the past 24 months
- In years 6 and 7, 13 SAEs with suspected relationship to imatinib were reported:
 - Congestive Heart Failure (n=3): all of the patients had pre-existing cardiac disease prior to study entry
 - Second malignancy (n=3)*
 - Myositis (n=1); elevated CK (n=1); multiple sclerosis (n=1)
 - Pancreatitis (n=1); vomiting (n=1)
 - Renal failure (n=1)
 - Dermatitis (n=1)

*With >400,000 patient years of estimated imatinib exposure, the analysis of clinical safety data from clinical trials and spontaneous reports did not provide evidence for an increased incidence of malignancies for patients treated with imatinib compared to that of the general population

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IRIS 7-Year Update: Conclusions

- Overall Survival 86%
- Event Free Survival 81%; 7% progressed to AP/BC on imatinib
- 40% patients discontinued *study* imatinib
- CCR achieved by 456 of 553 (82%) of patients
 - 17% of those achieving CCR subsequently lost CCR
 - 3% of those achieving CCR progressed to AP/BC
 - Of 456 patients who achieved CCR, 10 (2%) died from CML
 - Time taken to achieve CCR did not correlate with rates of progression to AP/BC
- MMR rates and the depth of molecular responses in patients increase over time
- No new safety issues observed
- Imatinib 400 mg daily confirmed as the standard of care for the initial therapy of chronic-phase CML

Integrated approach in the treatment of CML

Integrated approach in treating CML (1/3)

- Involvement of all stakeholders is key for the successful treatment of all newly diagnosed patients with CML
- The aim is to prolong and delay the transformation to advanced phases of the disease in all patients with CML, providing excellent quality of life and as close as possible to normal life expectancy

Integrated approach in treating CML (2/3)

The integrated approach must include support from as many stakeholders as possible

- **Treating physicians:** Early diagnosis, unified monitoring (ELN guidelines), submission of request for treatment (imatinib, etc), dialogue with patient in order to ensure compliance and understanding, follow-up
- **MOH:** Fast dissemination of the requested therapy, adequate track of the patients included and long-term planning according to country and physicians needs of therapy
- **Nurses and Pharmacists:** Dialogue with patients to ensure high level of understanding the disease, importance of monitoring and most of all reinforcing compliance and following physicians orders.

Integrated approach in treating CML (3/3)

- **Pharma Industry:** Respond to physicians needs to deliver latest scientific data for the therapy, educational materials for patients, providing state of the art support and programs for CML treatment (Blood level monitoring of imatinib)
- **Patient groups:** Produce and disseminate latest information for the disease, produce education and compliance materials, patient-centric projects to support the community in reaching treatment goals (patient hotline), ensure civil-control of the treatment process, patient inclusion and adequate long-term planning of the state.

The integrated approach is as strong as its weakest link, thus we have to involve as many as possible stakeholders and empower their activity