European LeukemiaNet

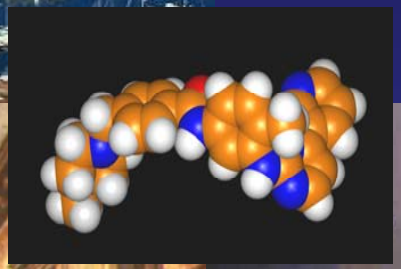
EUTOS for CML
European Treatment and Outcome Study

The management of CML: current treatment paradigms and future perspectives

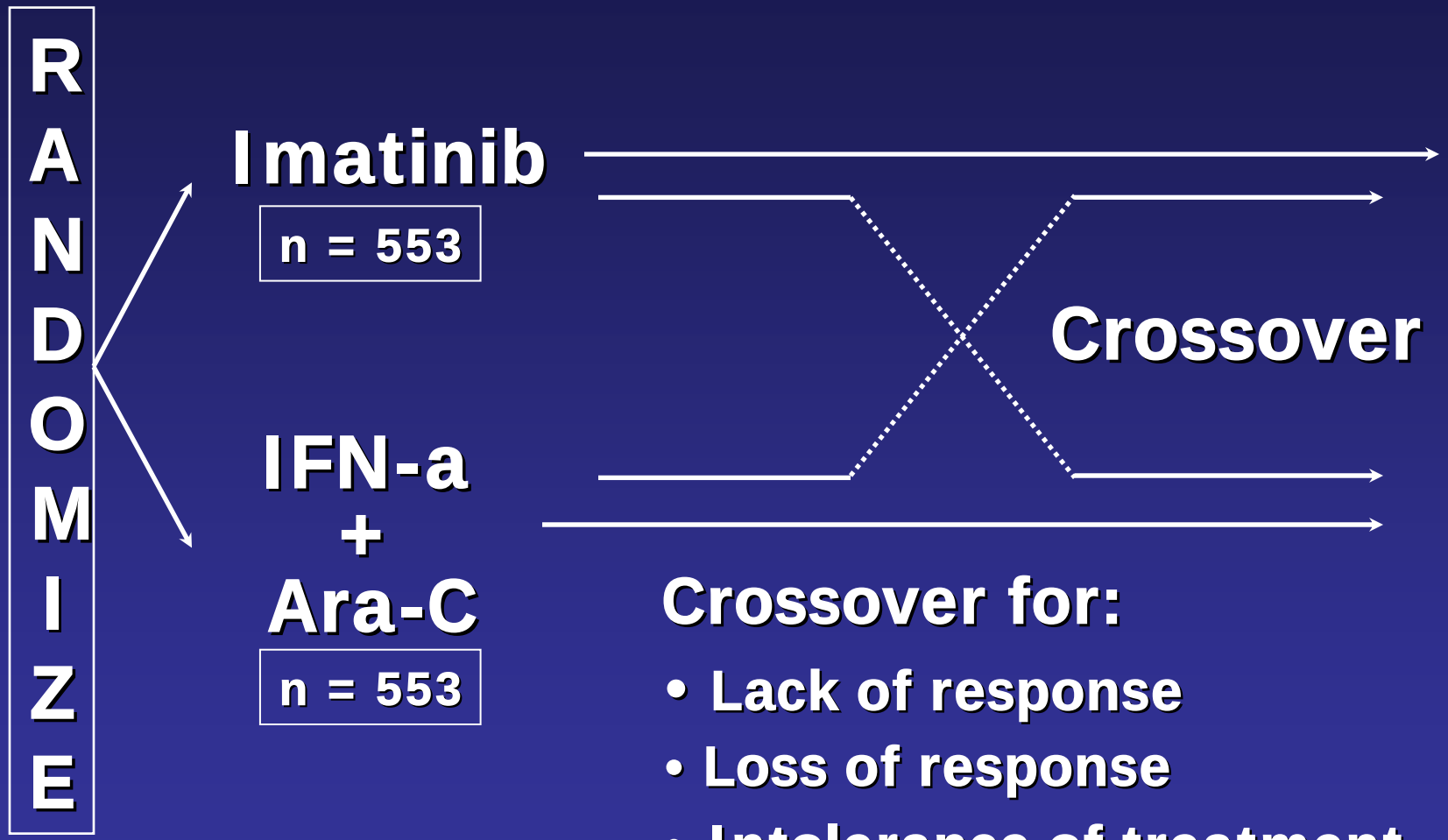
NAPLES 18 – 19 MAY 2009

First line treatment of CML with Imatinib: the IRIS trial and the GIMEMA trials

Michele Baccarani



IRIS Protocol: Study Design



Crossover for:

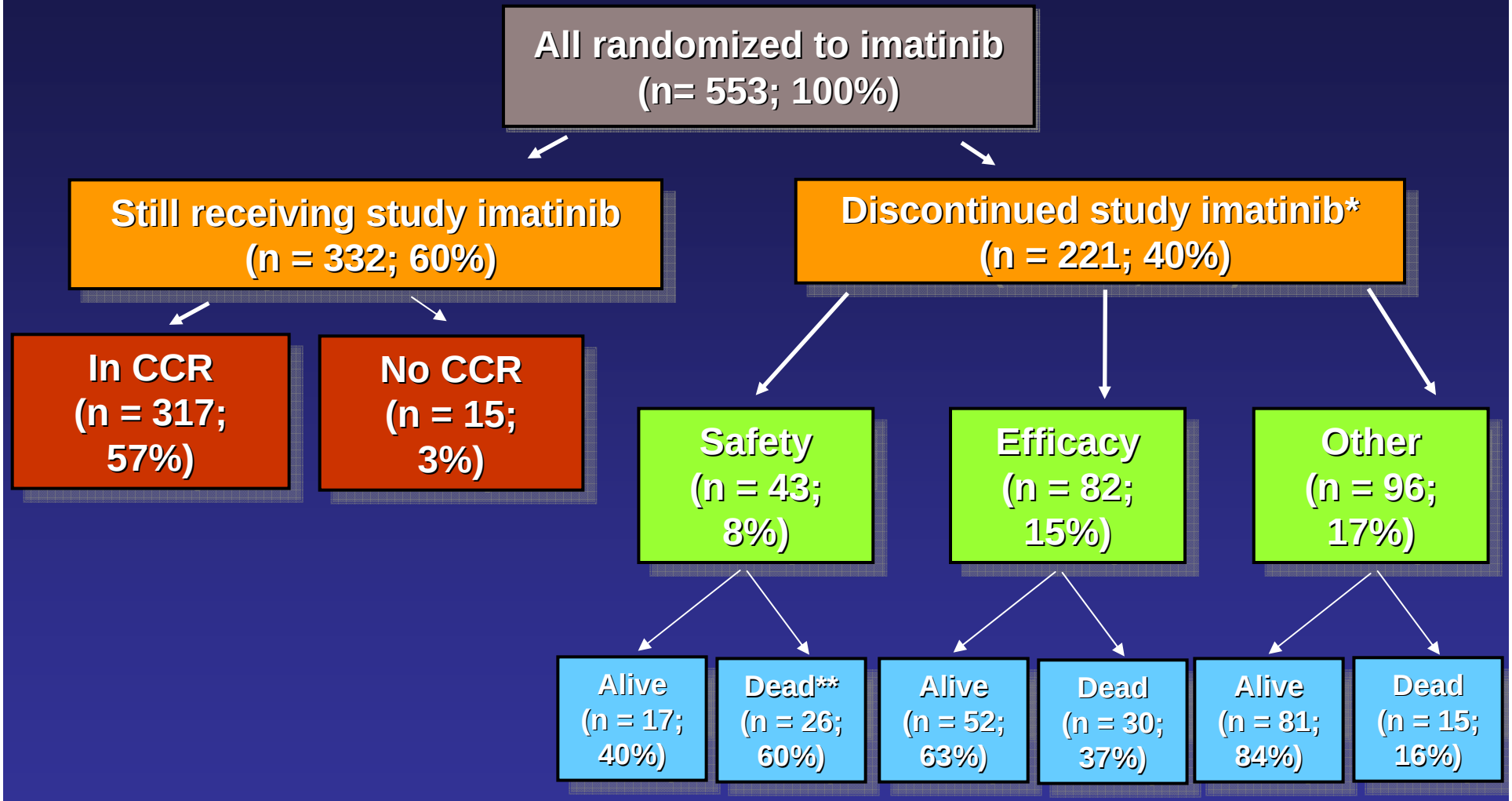
- Lack of response
- Loss of response
- Intolerance of treatment
- Reluctance to continue IFN

O'BRIEN et al, NEJM, 2003

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

What Happened To The Patients After 7 Years?



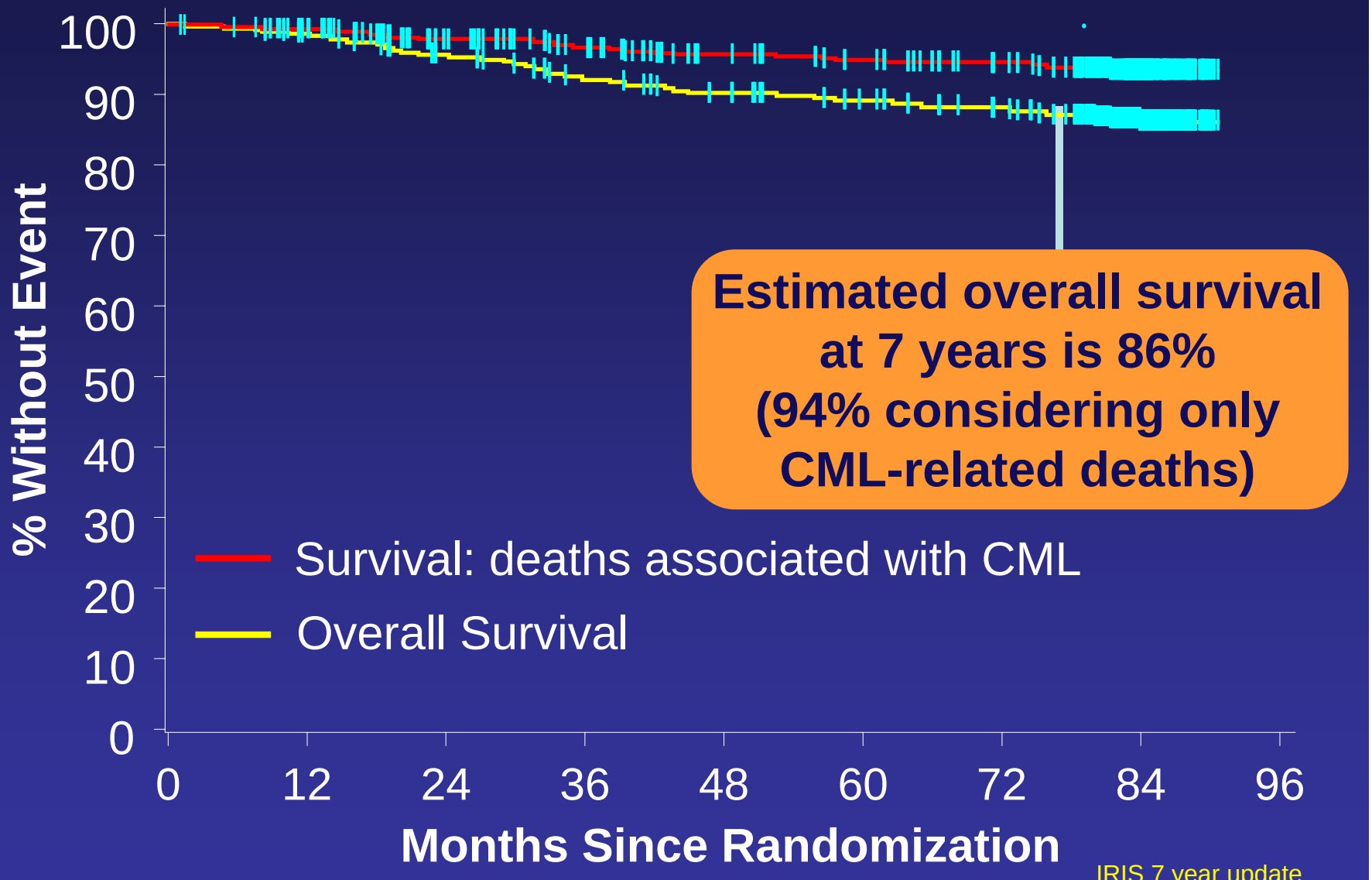
**Including primary discontinuation reason 'Death' (n=13)

*Patients may have continued imatinib off study.

IRIS 7 year update

O'BRIEN et al, ASH 2008, Blood 2008; 112(11): 76, Abstract 186

Overall Survival (ITT Principle): Imatinib Arm

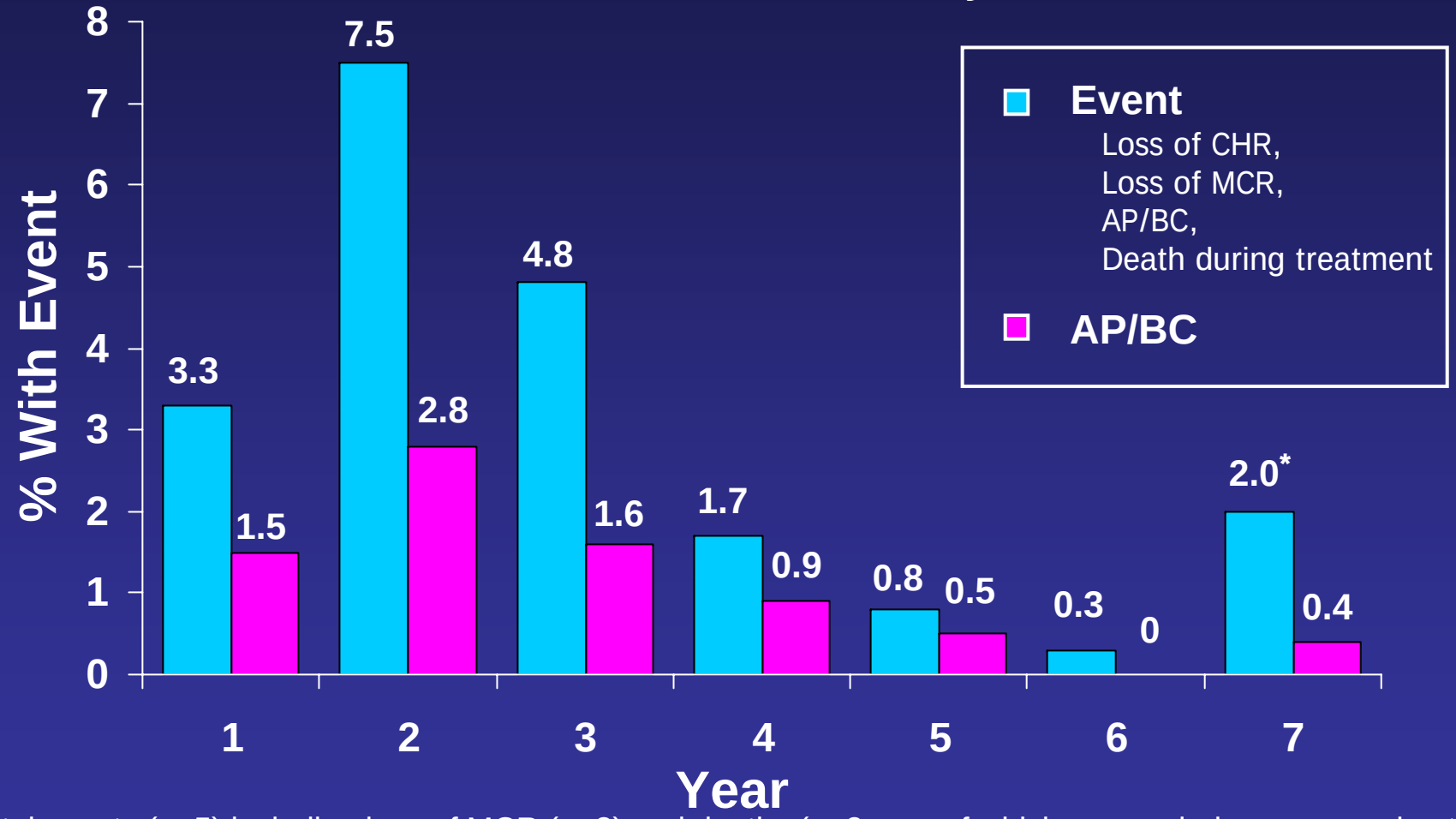


IRIS 7 year update

O'BRIEN et al, ASH 2008, Blood 2008; 112(11): 76, Abstract 186

Annual Event Rates: Imatinib Arm

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



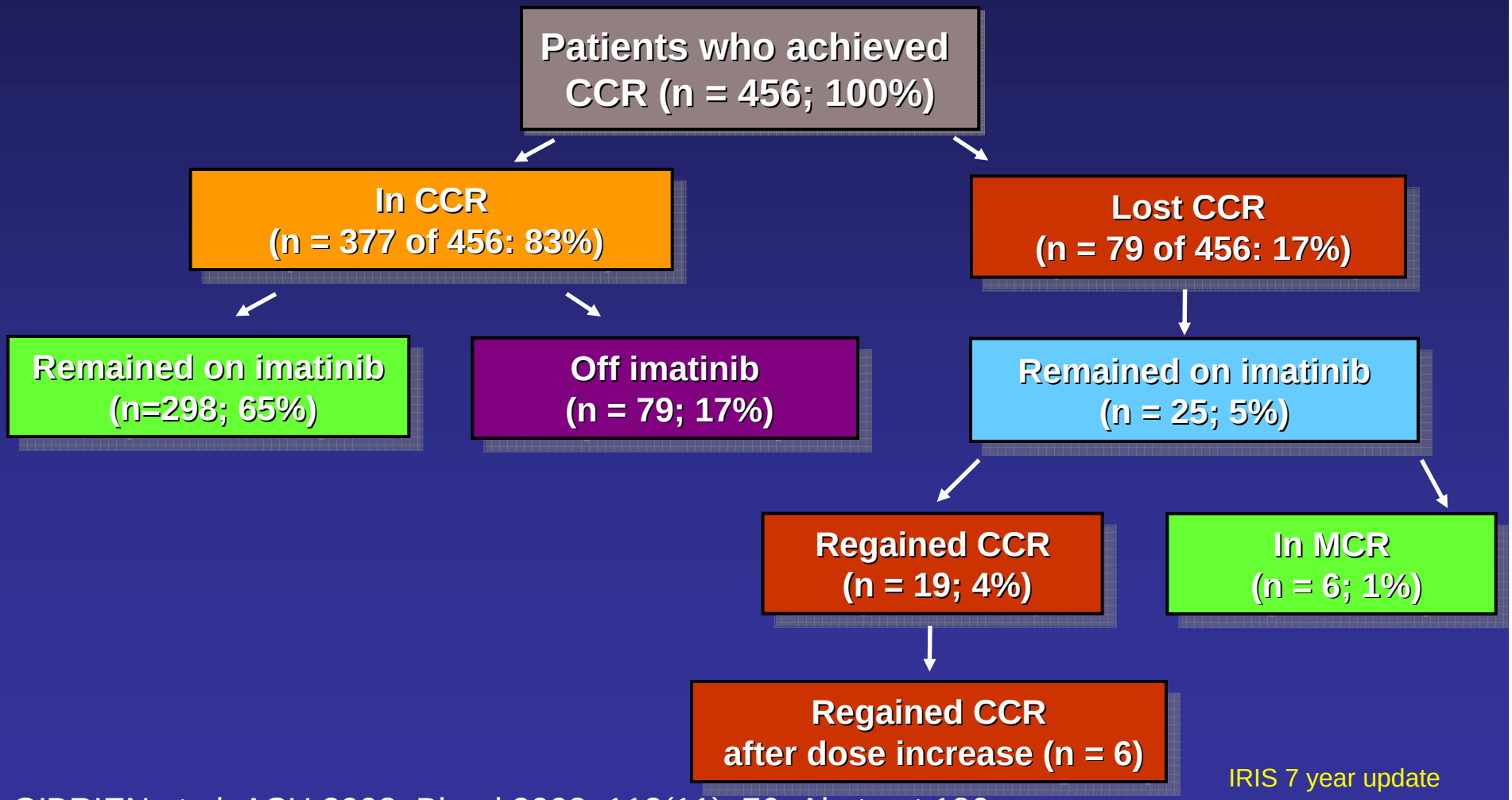
*Total events (n=5) including loss of MCR (n=3) and deaths (n=2, one of which was coded as progression to AP/BC in a patient in CMR 6 months prior to death).

O'BRIEN et al, ASH 2008, Blood 2008; 112(11): 76, Abstract 186

IRIS 7 year update

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)

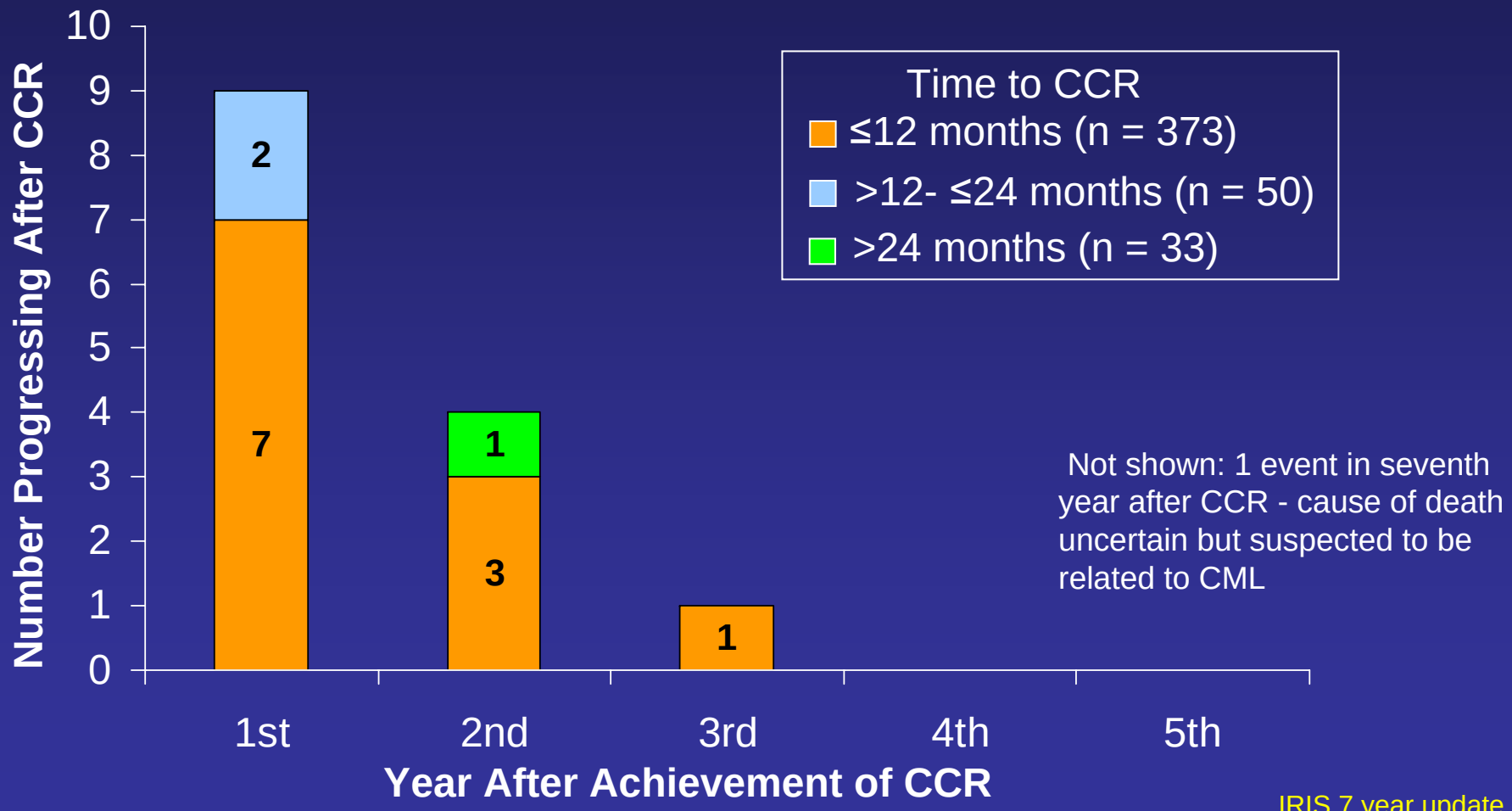


IRIS 7 year update

O'BRIEN et al, ASH 2008, Blood 2008; 112(11): 76, Abstract 186

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

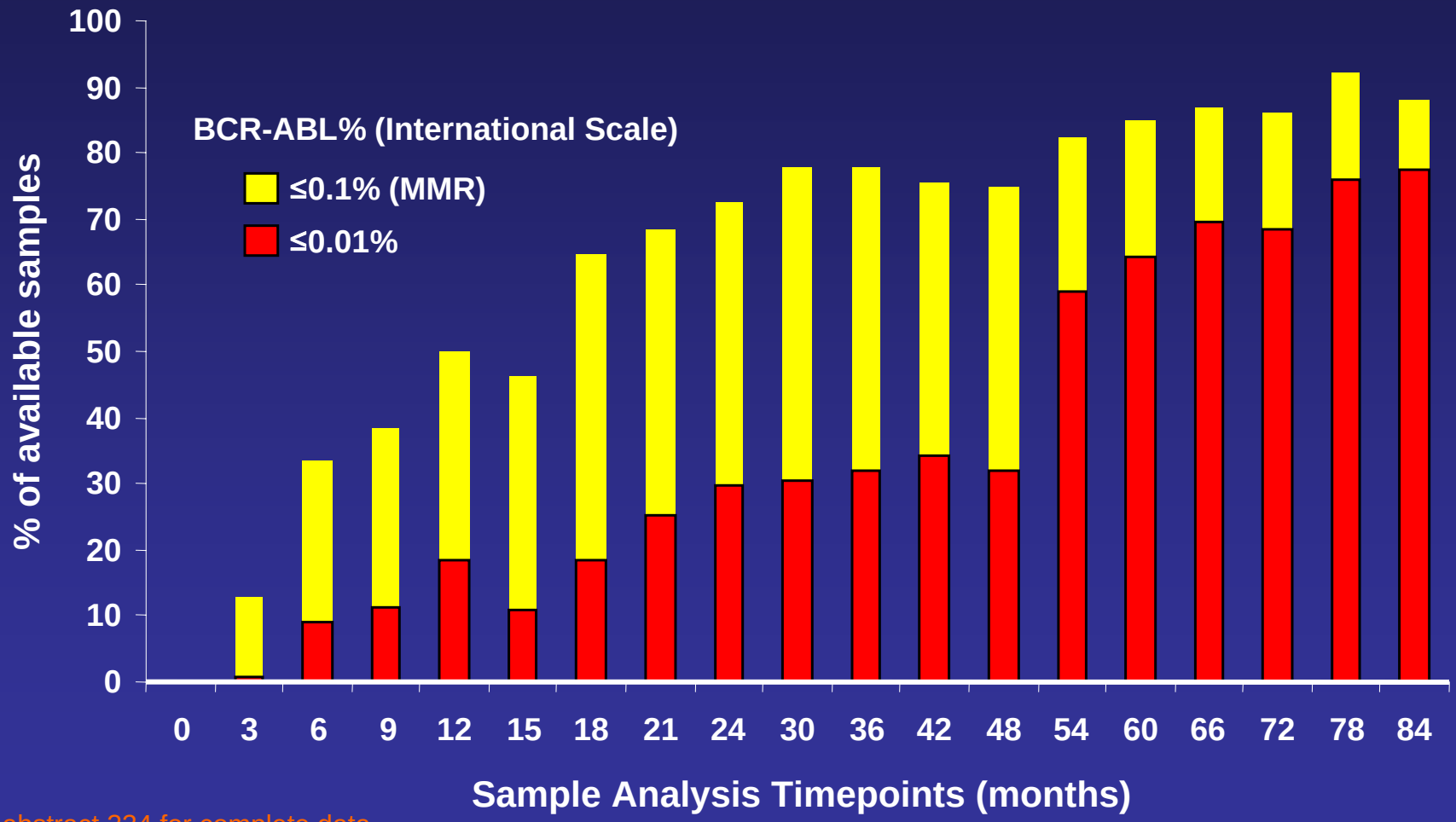


IRIS 7 year update

O'BRIEN et al, ASH 2008, Blood 2008; 112(11): 76, Abstract 186

Molecular Response Rates

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



See abstract 334 for complete data

IRIS 7 year update

O'BRIEN et al, ASH 2008, Blood 2008; 112(11): 76, Abstract 186

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

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

O'BRIEN et al, ASH 2008, Blood 2008; 112(11): 76, Abstract 186

LONG-TERM OUTCOME OF 559 PH+ CML PATIENTS TREATED WITH IMATINIB IN EARLY CHRONIC PHASE

GIMEMA CML WP

ANALYSIS

559 Early Chronic Phase patients accrued between Jan 2004 and Apr 2007 in 3 multicentric studies:

- **CML/021, phase II** **82 pts**
  imatinib 800 mg in intermediate Sokal risk
- **CML/022, phase III, randomized** **112 pts**
  imatinib 400 vs 800 mg in high Sokal risk
- **CML/023, observational** **365 pts**
  imatinib 400 mg, all risks

PATIENTS

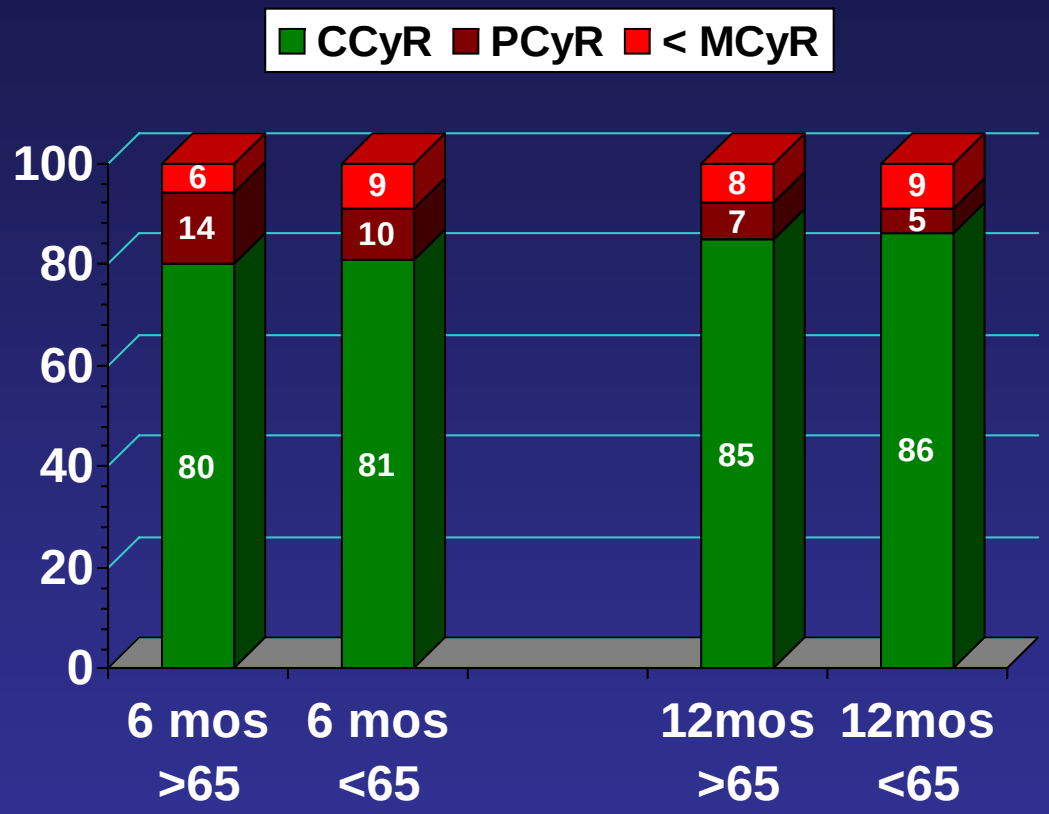
	N = 559	
Age, years; median (range)	52 (18-84)	
65 years or older; n (%)	115 (21)	
Splenomegaly, cm; median (range)	1 (0-24)	
Platelet count, 10^9/L; median (range)	352 (74-4553)	
Peripheral blasts, %; median (range)	1.0 (0-10.0)	
Eosinophils, %; median (range)	3.0 (0-15.0)	
Basophils, %; median (range)	2.0 (0-19.0)	
Relative Risk; n (%)	Sokal	Hasford
• Low	219 (39)	243 (43)
• Intermediate	216 (39)	277 (50)
• High	124 (22)	39 (7)
Variant Translocations; n (%)	30 (5)	
CCA Ph+; n (%)	21 (4)	
Der(9) deletions; n (%)	60 (11)	
400 mg; n (%)	423 (76)	
800 mg; n (%)	136 (24)	
Follow-up, months; median (range)	42 (1-64)	

RESPONSE TO TREATMENT (ITT)

	6 months	12 months	18 months
Cytogenetic Response			
Complete, n (%)	381 (68)	441 (79)	439 (79)
Partial, n (%)	67 (12)	35 (6)	15 (3)
Minor, n (%)	14 (3)	6 (1)	3 (1)
Minimal, n (%)	15 (3)	6 (1)	1 (0)
Absent, n (%)	16 (3)	28 (5)	42 (8)
Not evaluable, n (%)	66 (12)	43 (8)	59 (11)
Failures (cumulative), n (%)	21 (3.8)	41 (7.3)	63 (11.3)

GIMEMA CML WP
EARLY CHRONIC PHASE - RESPONSE TO IMATINIB AND AGE

CYTOGENETIC RESPONSE



105 PATIENTS MORE THAN 65 YEARS OLD
(MEDIAN 71, INTERVAL 65-84) vs
382 PATIENTS LESS THAN 65 YEARS OLD
(MEDIAN 56, INTERVAL 18-64)

ROSTI G et al, Haematologica 2007; 92: 101-105

Overall responses and long-term outcome

CCgR at 12 months; %	79
MMolR at 12 months; %	54
MMolR % of CCg responders	68
Overall Survival; %	93
Progression-Free Survival; %	92
Failure Free-Survival; %	82
Event-Free Survival; %	74

Failures (ELN criteria): no CHR at 6 mos, no CgR at 6 mos, no PCgR at 12 mos, no CCgR at 18 mos, loss CHR or CCgR, progression to accelerated/blastic phase and death.
Events: failures, off-treatment for toxicity, refusal and lost to follow-up.

CCgR durability

491 patients (88%): CCgR as best CgR

26 patients (5%): CCgR not confirmed

465 patients (83%): confirmed CCgR (2 or more times)

24 patients (4%): lost CCgR

CCgR duration (months)
median (range): 13 (3 - 42)

441 patients (79%): stable CCgR

CCgR duration (months)
median (range): 35 (4 - 55)

384 patients $\geq$ 24 months
211 patients $\geq$ 36 months

Patients on Study / Discontinuations

TOTAL	**N = 559**
Follow-up, months; median (range)	**42 (1 - 64)**
On imatinib study treatment, n (%)	**415 (74.2)**
Discontinuation, n (%)	**144 (25.8)**
- Side effects/SAEs	25 (4.5)
- Deaths (unrelated to CML)	9 (1.6)
- Lack of efficacy / progression	83 (14.8)
- Other reason (refusal, lost to follow-up)	27 (4.8)

SUMMARY OF THE RESULTS OF IMATINIB TREATMENT (STANDARD DOSE 400 MG, FRONT-LINE) IN Ph POS CHRONIC MYELOID LEUKEMIA

COMPLETE HEMATOLOGIC RESPONSE	≥ 95%
COMPLETE CYTOGENETIC RESPONSE	75-90%
MAJOR MOLECULAR RESPONSE	50-70%
"COMPLETE" MOLECULAR RESPONSE	10-40%
6-YEARS EVENT-FREE SURVIVAL AND ON IMATINIB	60-70%
6-YEARS PROGRESSION-FREE SURVIVAL	85-90%
6-YEARS OVERALL SURVIVAL	90-95%

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