Chronic Myeloid Leukemia
Update on Available CML Treatments

Neil Shah, MD PhD
Edward S. Ageno Distinguished Professor in Hematology/Oncology
UCSF School of Medicine
San Francisco, California

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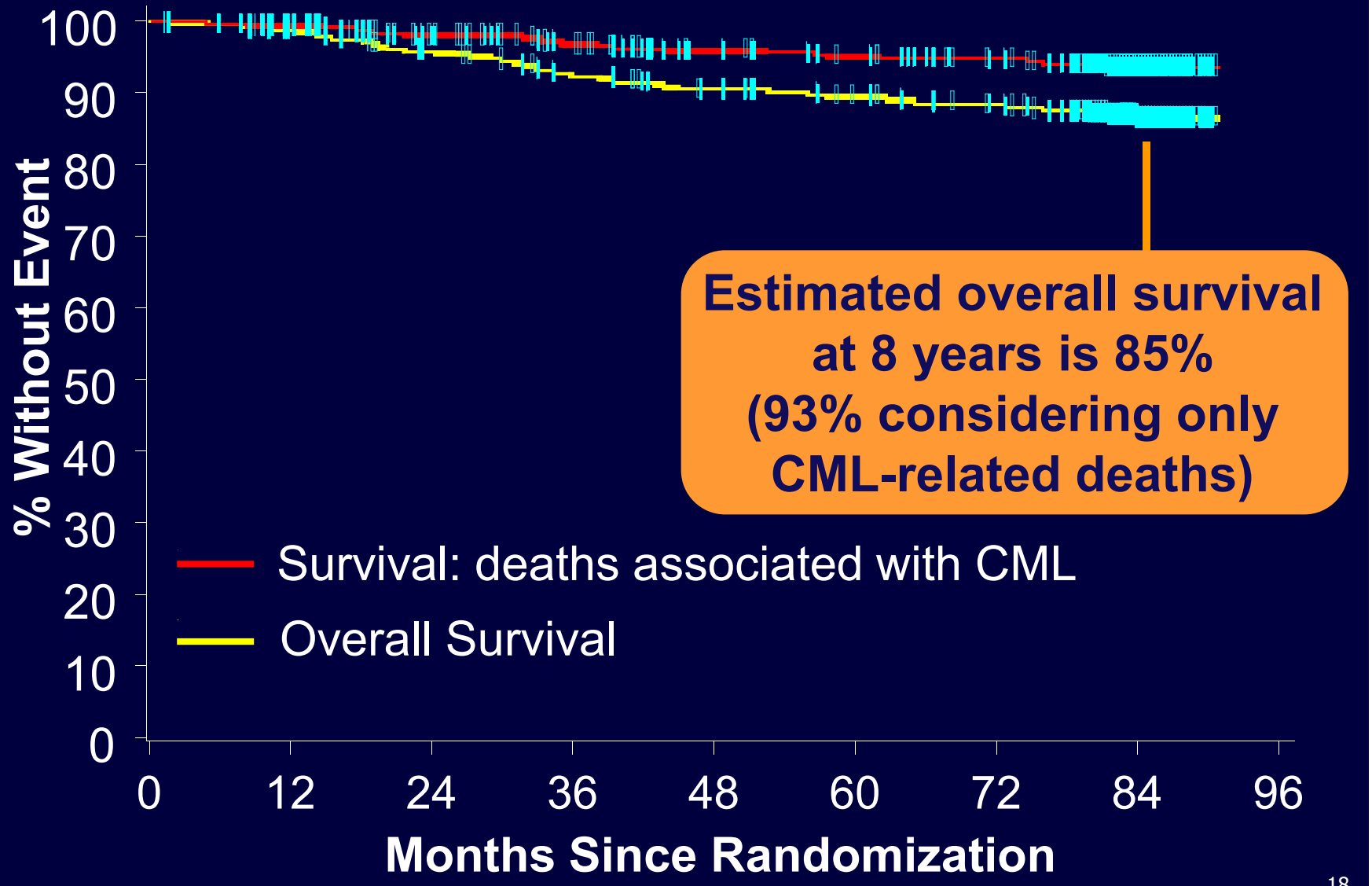
        - Signs of efficacy in CML as well as polycythemia vera

IMATINIB AS FRONTLINE THERAPY FOR CML

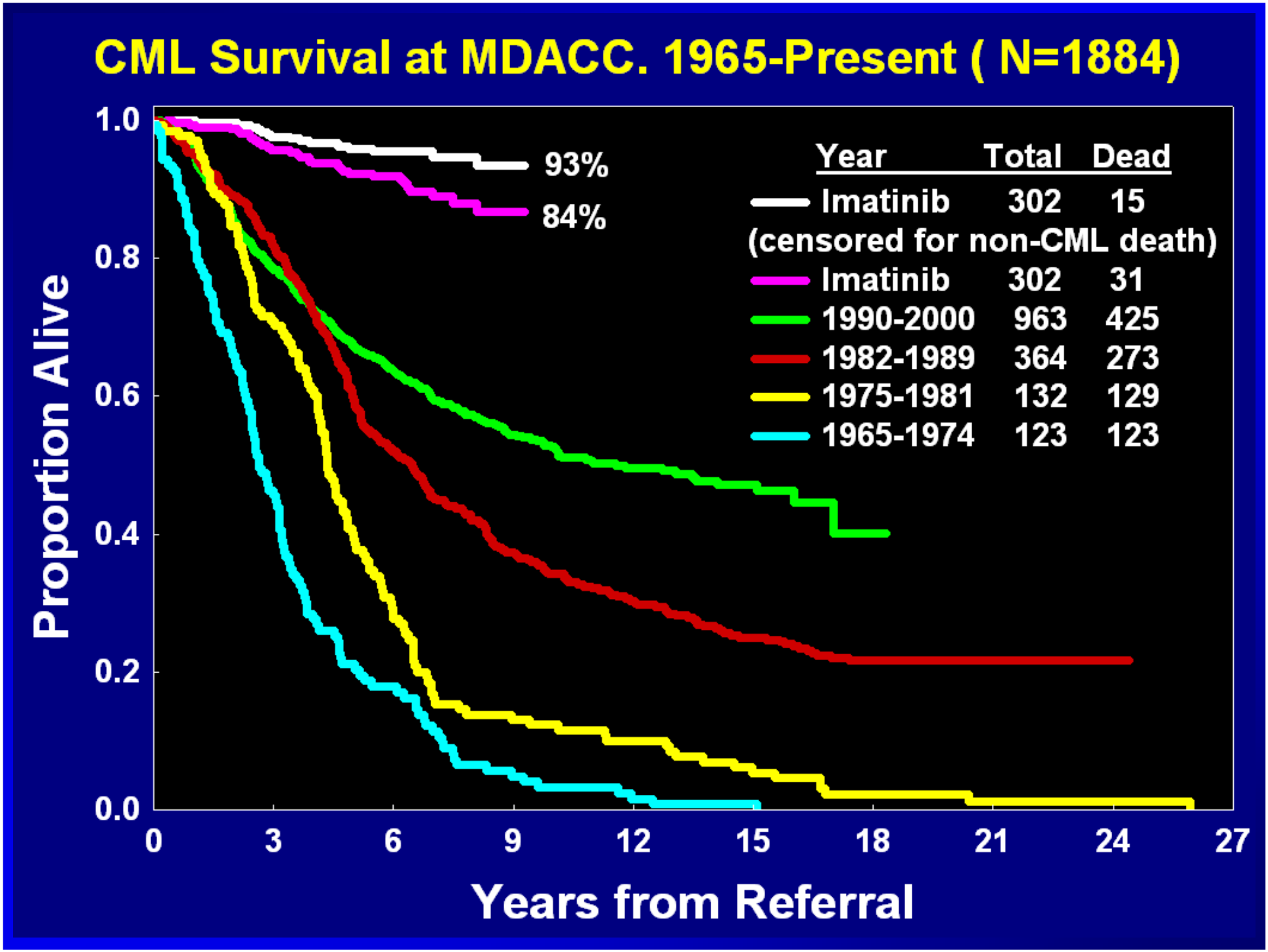
7-8 year update of newly-diagnosed Chronic Phase CML patients treated with 400 mg daily imatinib

O'Brien et al. ASH 2008, Abstract 186

Overall Survival: Imatinib Arm (IRIS Study)



Deininger et al. ASH 2009. Abstract 1126


CML Survival at MDACC. 1965-Present (N=1884)
Proportion Alive
1.0
0.8
0.6
0.4
0.2
0.0
0
3
6
9
12
15
18
21
24
27
Years from Referral
93%
84%
Year Total Dead
Imatinib 302 15
(censored for non-CML death)
Imatinib 302 31
1990-2000 963 425
1982-1989 364 273
1975-1981 132 129
1965-1974 123 123

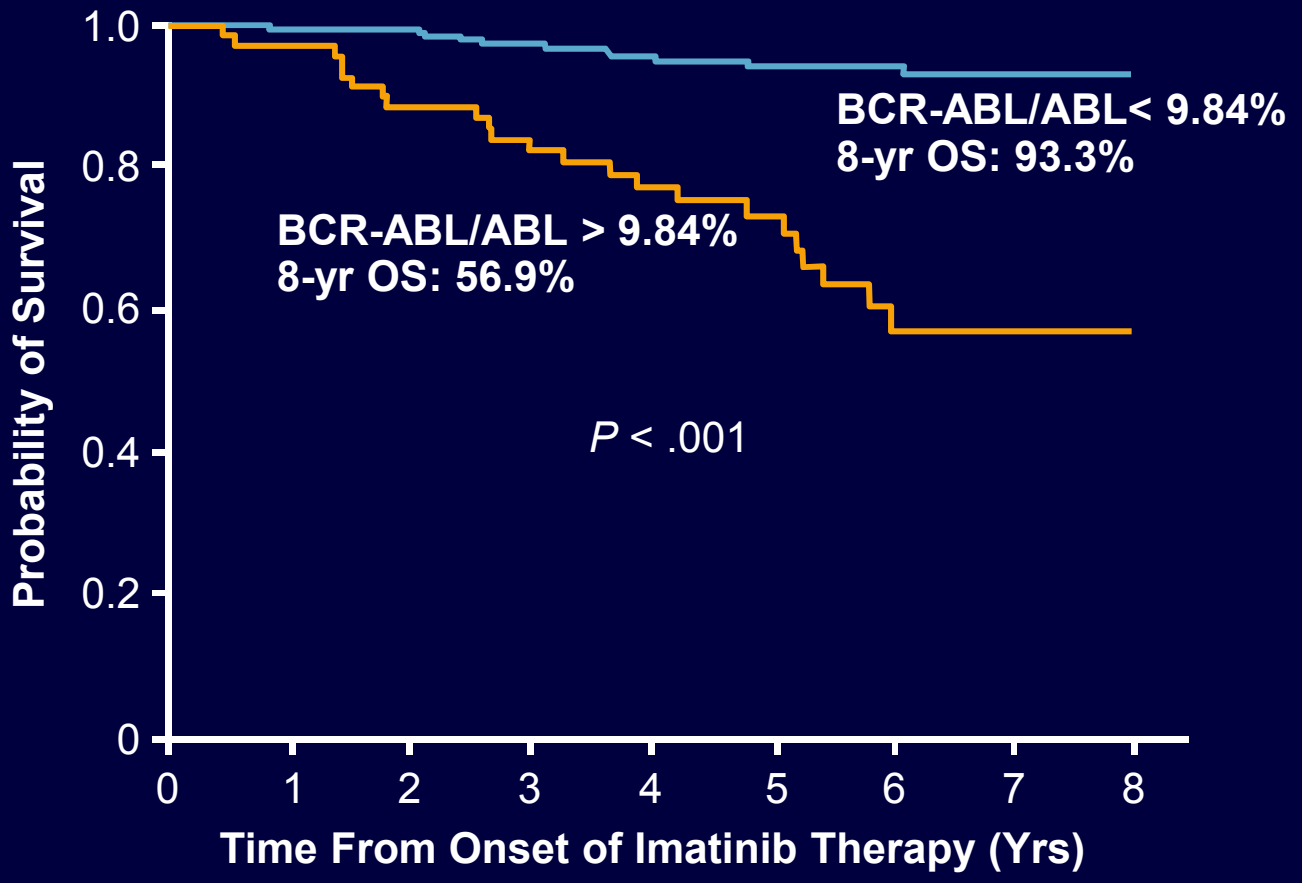
Most Frequently Reported Adverse Events: First-Line Imatinib

Most Common Adverse Events (by 5 Years)	All Grade Adverse Events: Patients, %	Grade 3/4 Adverse Events: 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 were collected after 2005
- Grade 3/4 adverse events decreased in incidence after years 1-2

O'Brien et al. ASH 2008, Abstract 186

BCR-ABL/ABL after 3 Months of Imatinib Predicts Overall Survival Outcomes



Marin D, et al. J Clin Oncol. 2012;30:232-238.

Imatinib - Conclusions

- 85% overall survival with imatinib exceeds that of all other CML therapies, with 7% patients dying from CML after eight years
- 82% of patients treated with imatinib achieved a complete cytogenetic remission
  - 55% of all imatinib randomized patients are still on study treatment, and nearly all of these are in complete cytogenetic remission
- Responses are typically durable, and the annual risk of progression generally decreases with time
- Imatinib is generally well-tolerated, without any serious, irreversible toxicities
  - Mild-moderate side effects are common and can be problematic in some patients

NILOTINIB AND DASATINIB AS FRONTLINE THERAPY FOR CML

IMATINIB, NILOTINIB AND DASATINIB AS FIRST-LINE THERAPY FOR CML

	NILOTINIB (ENESTnd)	DASATINIB (DASISION)
COMPLETE CYTOGENETIC RESPONSE RATE BY 12 MONTHS (%; VS IMATINIB)	80 vs 65	83 vs 72
BCR-ABL/ABL ≤10% RATE BY 3 MONTHS (%; VS IMATINIB)	91 vs 67	84 vs 64
MAJOR MOLECULAR RESPONSE RATE BY 48 MONTHS (%; VS IMATINIB)	76 vs 56	74 vs 60
MOLECULAR RESPONSE (4.5) RATE BY 48 MONTHS (%; VS IMATINIB)	40 vs 23	34 vs 21
DISEASE TRANSFORMATION RATE (VS IMATINIB AT LAST FOLLOW-UP)	3.5 vs 7.1	4.6 vs 6.9

OPTIONS AFTER IMATINIB FAILURE

ACTIVITY OF TKIs FOLLOWING PREVIOUS TKI FAILURE

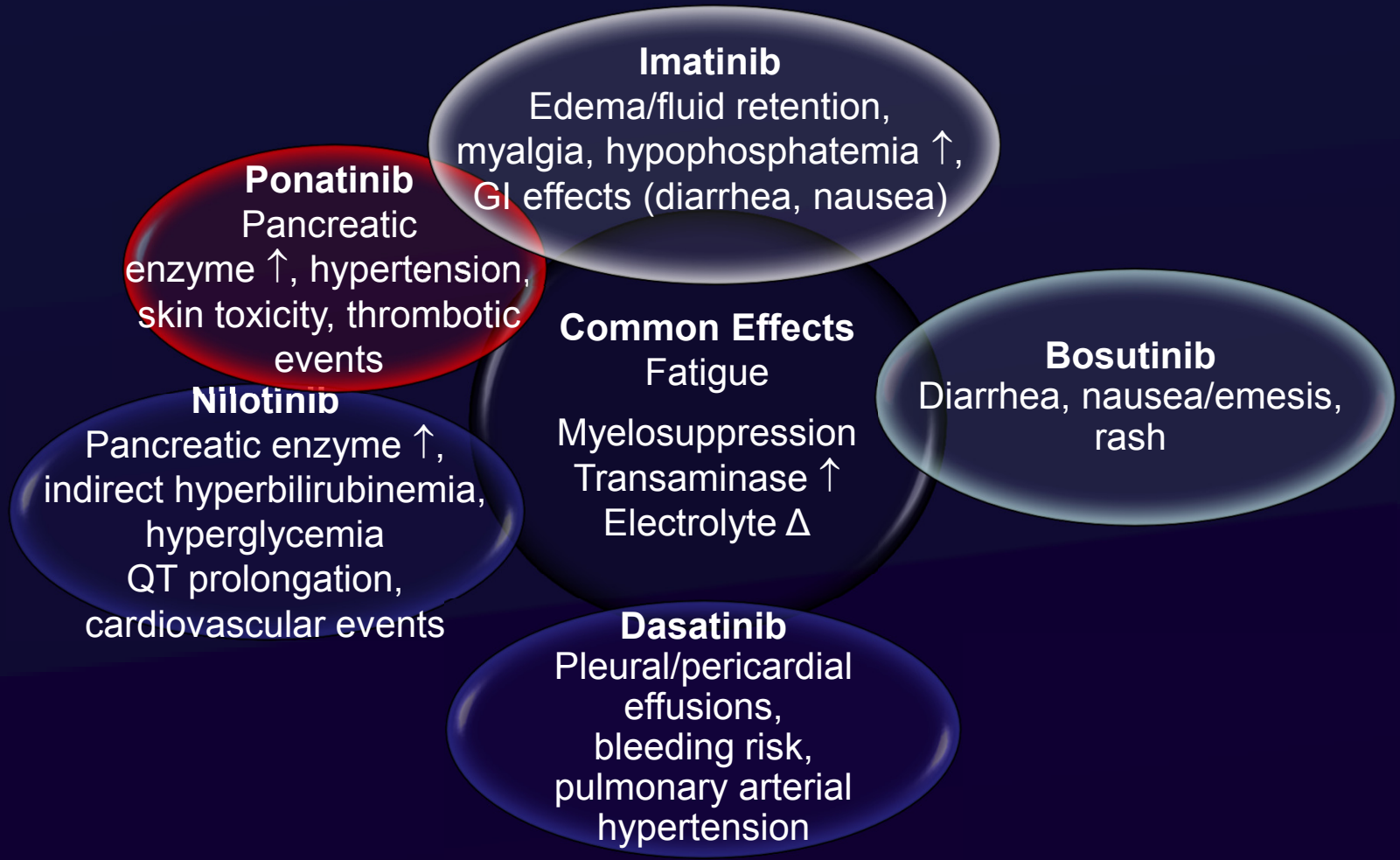
	DASATINIB	NILOTINIB	BOSUTINIB*	PONATINIB**
COMPLETE CYTOGENETIC RESPONSE RATE	50	45	48	54

*Bosutinib is most commonly used in patients with resistance or intolerance to imatinib, dasatinib and nilotinib due to its side effect profile

**Ponatinib is most commonly used in patients with the BCR-ABL/T315I mutation and patients with resistance/intolerance to imatinib, dasatinib, nilotinib and bosutinib due to its side effect profile

SIDE EFFECTS OF TKIs

Treatment Options Based on Adverse Event Spectrum of TKIs in CML



NON-TKIs

ACTIVITY OF OMACETAXINE FOLLOWING PREVIOUS TKI FAILURE

	OMACETAXINE
COMPLETE CYTOGENETIC RESPONSE RATE (%)	10
MEDIAN DURATION OF RESPONSE (MONTHS)	12.2

Omacetaxine is most commonly used in patients with resistance or intolerance to imatinib, dasatinib, nilotinib, bosutinib and ponatinib due to its rather modest efficacy

ACTIVITY OF INTERFERON IN TKI-NAIVE PATIENTS

	INTERFERON + CYTARABINE
COMPLETE CYTOGENETIC RESPONSE RATE (%)	15

Interferon (with or without cytarabine) is most commonly used in patients with resistance or intolerance to imatinib, dasatinib, nilotinib, bosutinib and ponatinib, and patients who are pregnant or breast-feeding due to its relatively modest efficacy and side effect profile

Conclusions

- TKIs are effective and generally well-tolerated
- Nilotinib and dasatinib achieve higher rates of cytogenetic and molecular response than imatinib
  - Associated with fewer transformation events
- Bosutinib and ponatinib are effective treatment options for patients with resistance/intolerance to prior TKI therapy
- Some TKIs are associated with serious and potentially irreversible toxicities
- Interferon can be durably effective for a small proportion of CML patients but it has not been extensively investigated in patients with resistance/intolerance to prior TKI therapy
  - Believed to be safe during pregnancy
- CML patients who educate themselves through contact with advocacy groups can maximize their chance of a favorable therapeutic outcome