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Multiple Myeloma – How to Make Decisions based on Pathophysiology

Chilean Society of Hematology

October 2014

Scottsdale, Arizona

Rochester, Minnesota

Jacksonville, Florida

Joseph Mikhael, MD, MEd, FRCPC, FACP
Staff Hematologist, Mayo Clinic Arizona

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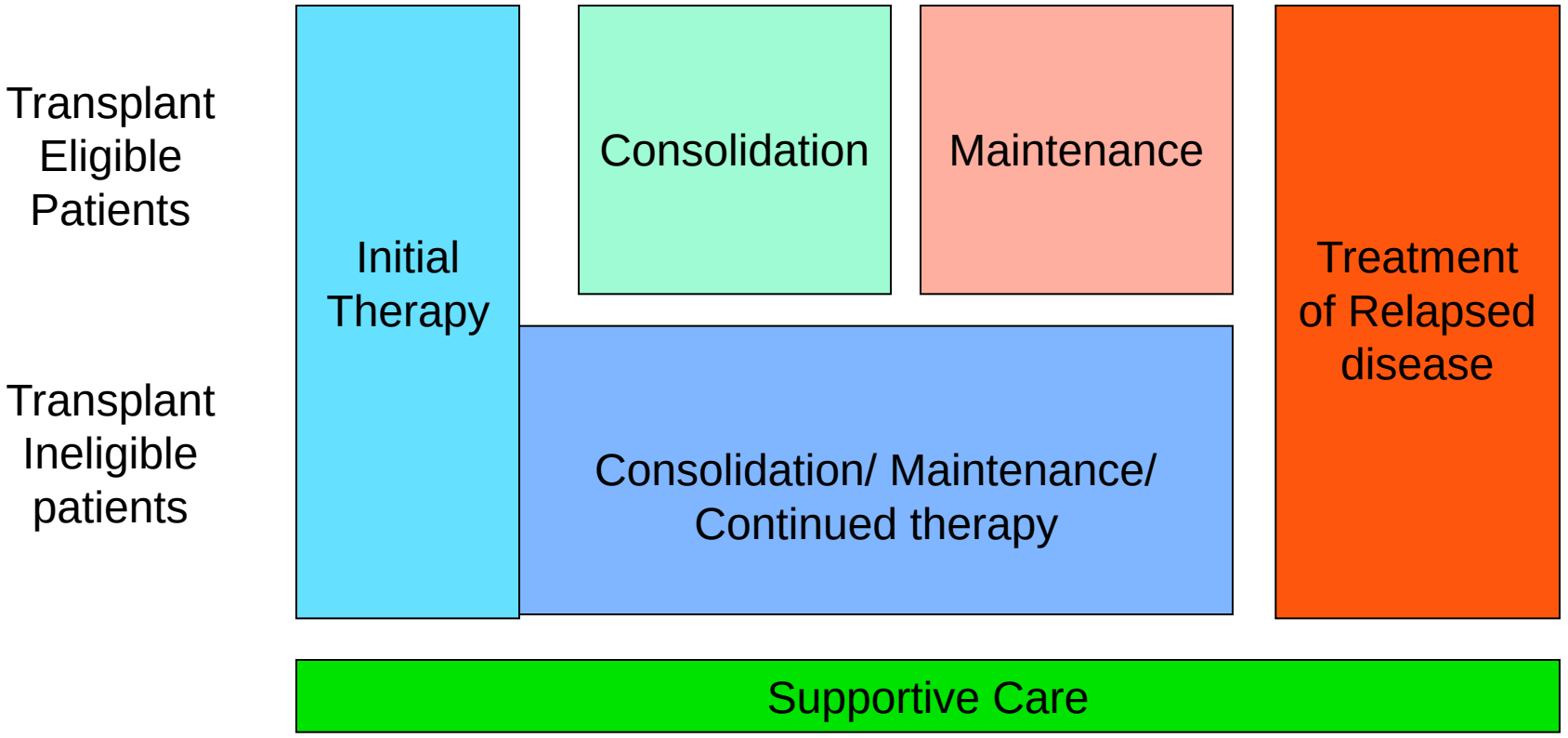
Managing myeloma: the components



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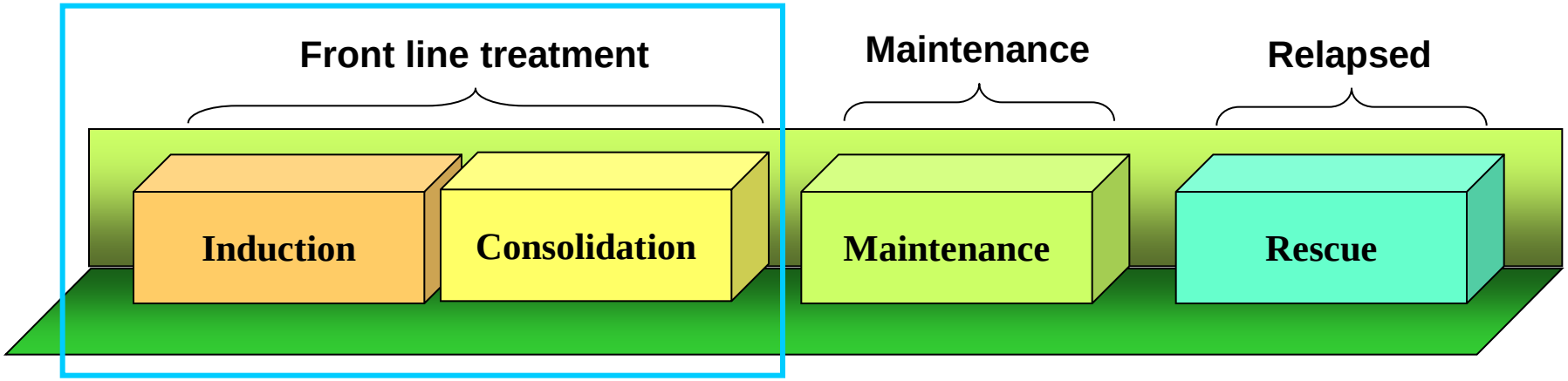
Treatment sequence



VAD DEX	SCT	Nothing Prednisone Thalidomide	Few options

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Recall the Heterogeneity of Myeloma

- **Biological and Clinical differences**
- **Myeloma, based on definition, may indeed be the most common malignancy worldwide!**
- **We surely cannot treat them all in the same way - individualize**
- **Emphasizes the importance of risk stratification**

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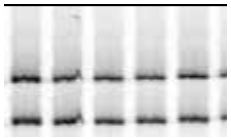
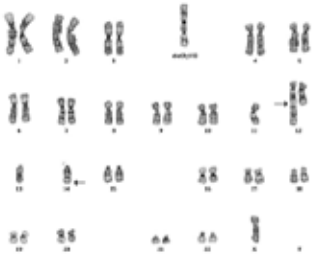
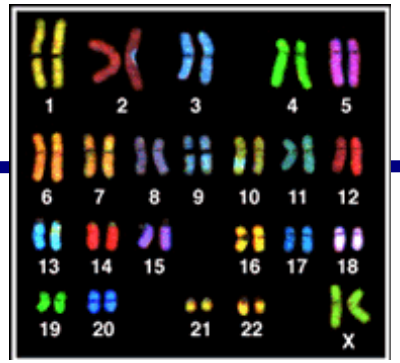
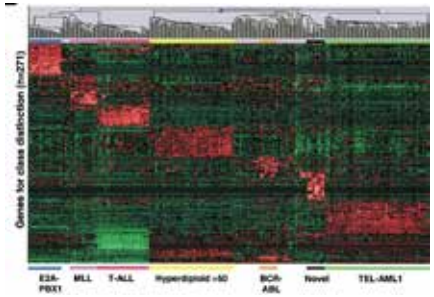
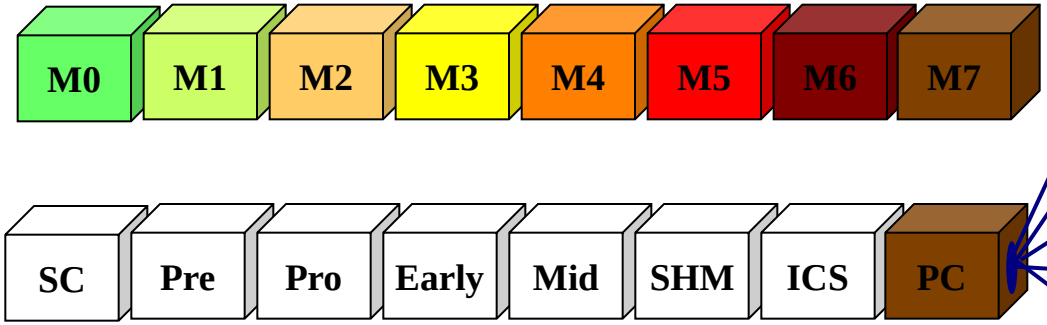
Acute Leukemia

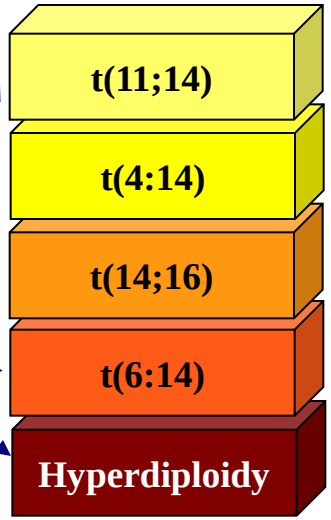




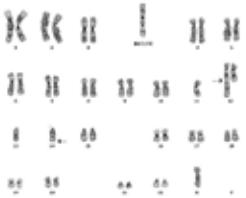


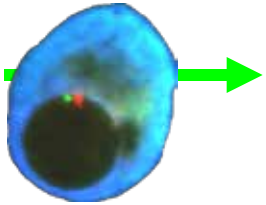


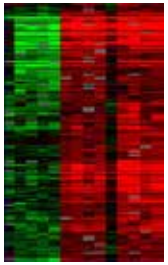




Myeloma







3 decades

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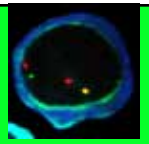
Classification of MM

	Ploidy	Prognosis	H	□	Morph	CD20	*ras*	-13	Bone DKK1	CCND
t(11;14) *(CCND3)*	NH	Good	G	k		+++	++	-/+	++	D1 D3
t(14;16) (other *MAF*)	NH	Poor	A	l		-	-	++	+/-	D2
t(4;14)	NH/h	Poor	A	l		-	-	+++	+/-	D2
Other IgH	H/NH	Poor	?	?		-	-/+	?	+	?
Hyper	H	Good	G	k		-	++	+/-	++	D1>D2

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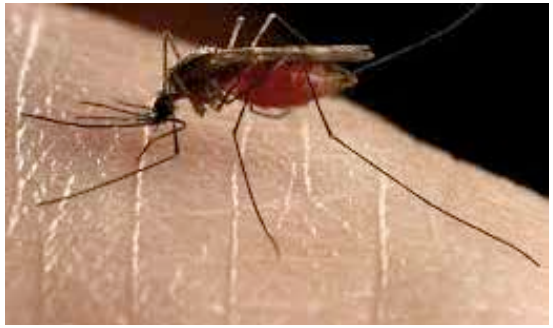
Choose the right weapon?



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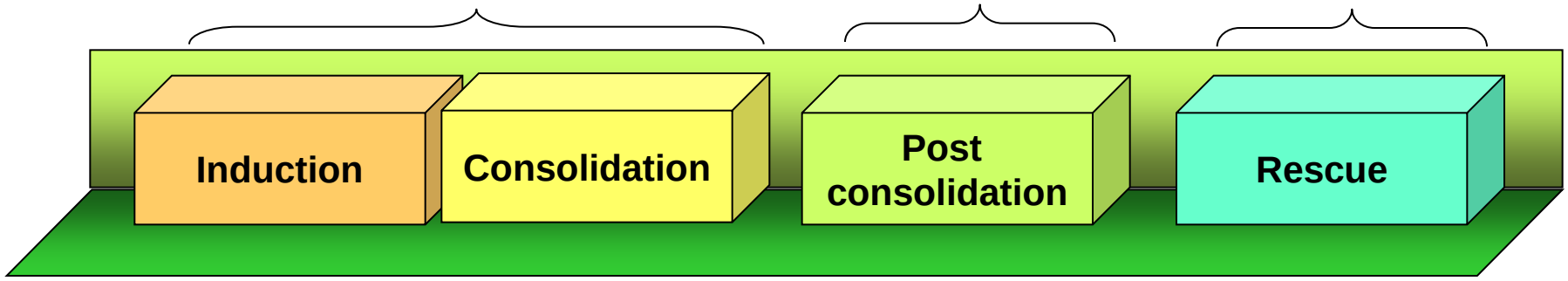
Treatment sequence

NEW

Front line treatment	Maintenance	Relapsed
Thal/Dex VD Rev/Dex CyBorD VTD VRD	SCT VD/VRD	Nothing Thalidomide? Bortezomib? Lenalidomide?	Bortezomib Lenalidomide Thalidomide Carfilzomib Pomalidomide *Monoclonal Ab (CD38)* *Elotuzumab* *HDAC* *Bendamustine*



OLD

VAD DEX	SCT	Nothing Prednisone Thalidomide	Few options

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mSMART

Mayo Stratification for Myeloma And Risk-adapted Therapy

Newly Diagnosed Myeloma

Website: www.msmart.org

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mSMART 2.0: Classification of Active MM

High-Risk 20%	Intermediate-Risk 20%	Standard-Risk 60%
§ **FISH** § **Del 17p** § **t(14;16)** § **t(14;20)** § **GEP** § **High risk signature**	§ **FISH** § **t(4;14)*** § **Cytogenetic Deletion 13 or hypodiploidy** § **PCLI ≥3%**	**All others including:** § **Hyperdiploid** § **t(11;14)** § **t(6;14)**
3 years	4-5 years	8-10 years

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Major Themes

1. **High Risk patients require more aggressive therapy – usually in combination**
2. **CR should be the goal in patients with high risk myeloma**
3. **Standard risk patients can be treated more sequentially**
4. **CR may not be as necessary in standard risk patients**

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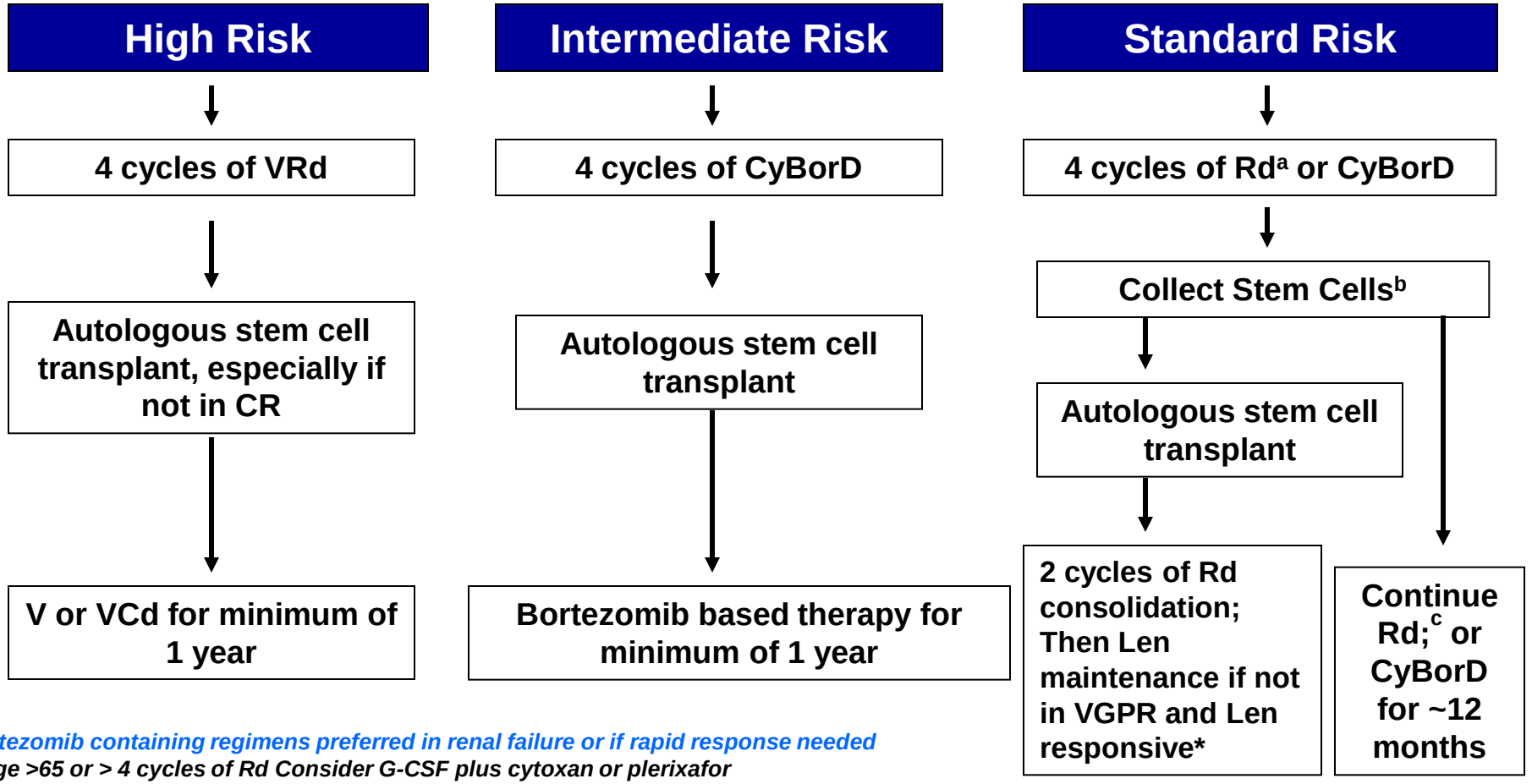
mSMART – Off-Study

Transplant Eligible



[a] *Bortezomib containing regimens preferred in renal failure or if rapid response needed*

[b] *If age >65 or > 4 cycles of Rd Consider G-CSF plus cytoxan or plerixafor*

[c] *Continue Rd for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year*

** Consider risks and benefits; consider limited duration 12-24 months*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v11 //last reviewed Dec 2013

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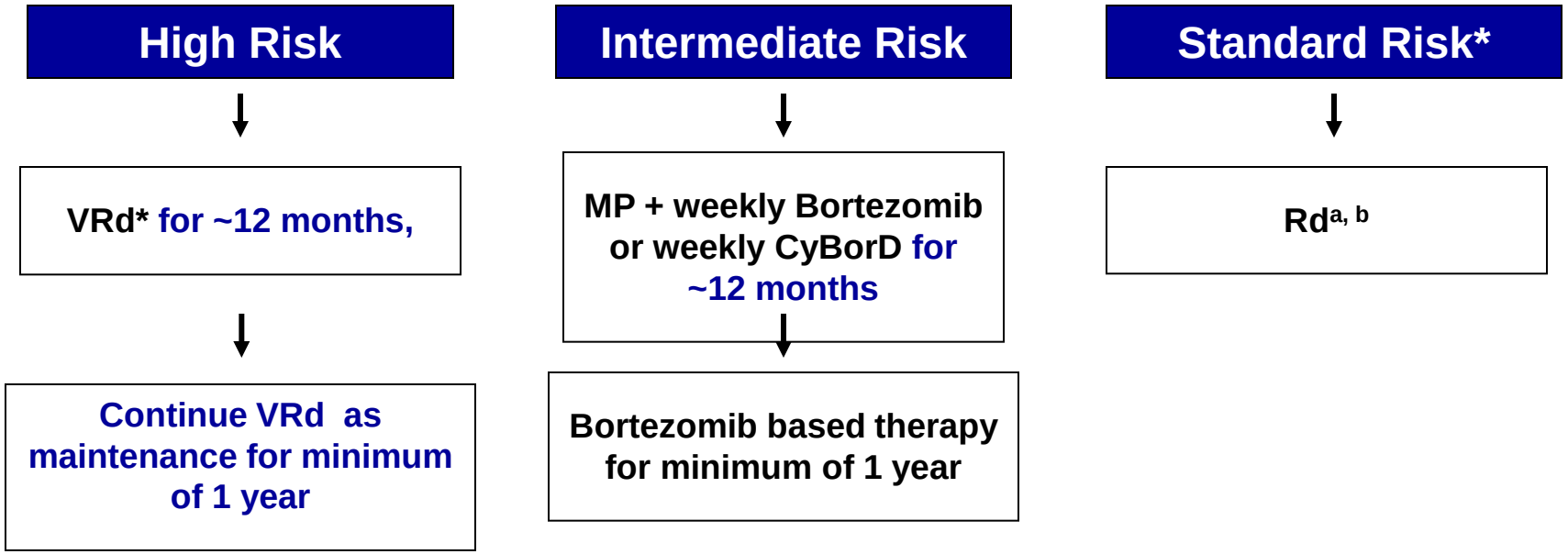

[a] Dex is usually discontinued after first year
[b] Bortezomib containing regimens preferred in renal failure or if rapid response needed
**Clinical trials strongly recommended as the first option*

Dispenzieri et al. Mayo Clin Proc 2007;82:323-341; Kumar et al. Mayo Clin Proc 2009 84:1095-1110; Mikhael et al. Mayo Clin Proc 2013;88:360-376. v11 //last reviewed Dec 2013

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What does this mean for my clinic next week?

- **CR is a noble goal and is generally sought after, especially in high risk disease…**
- **However, it is NOT the goal in all, especially in 3 groups:**

1. Genotypically indolent (hyperdiploid, low risk GEP)

2. Phenotypically indolent (prolonged MGUS/SMM)

3. Elderly patients

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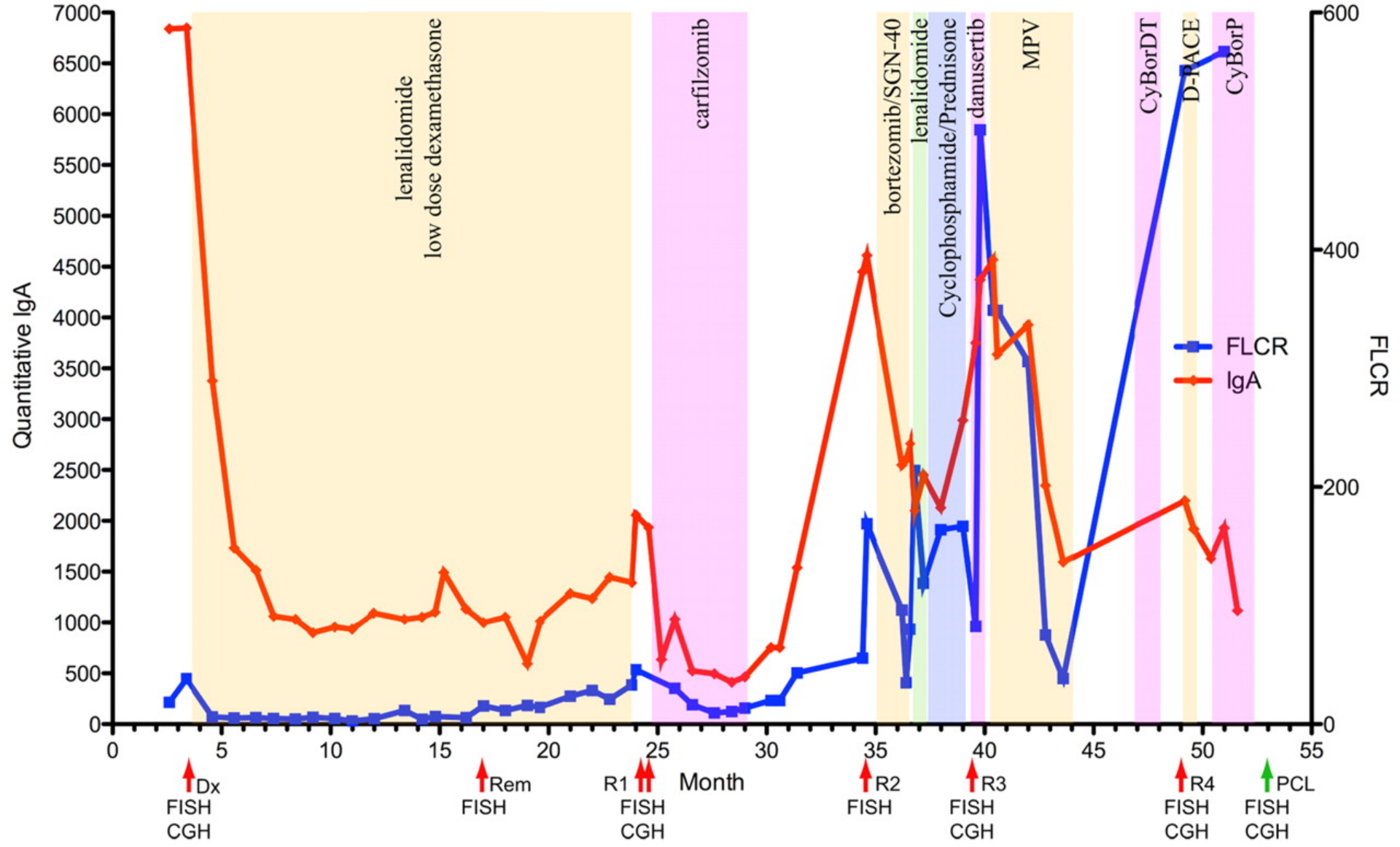
Clonal Evolution

Clinical Course of t(4;14) High Risk Patient



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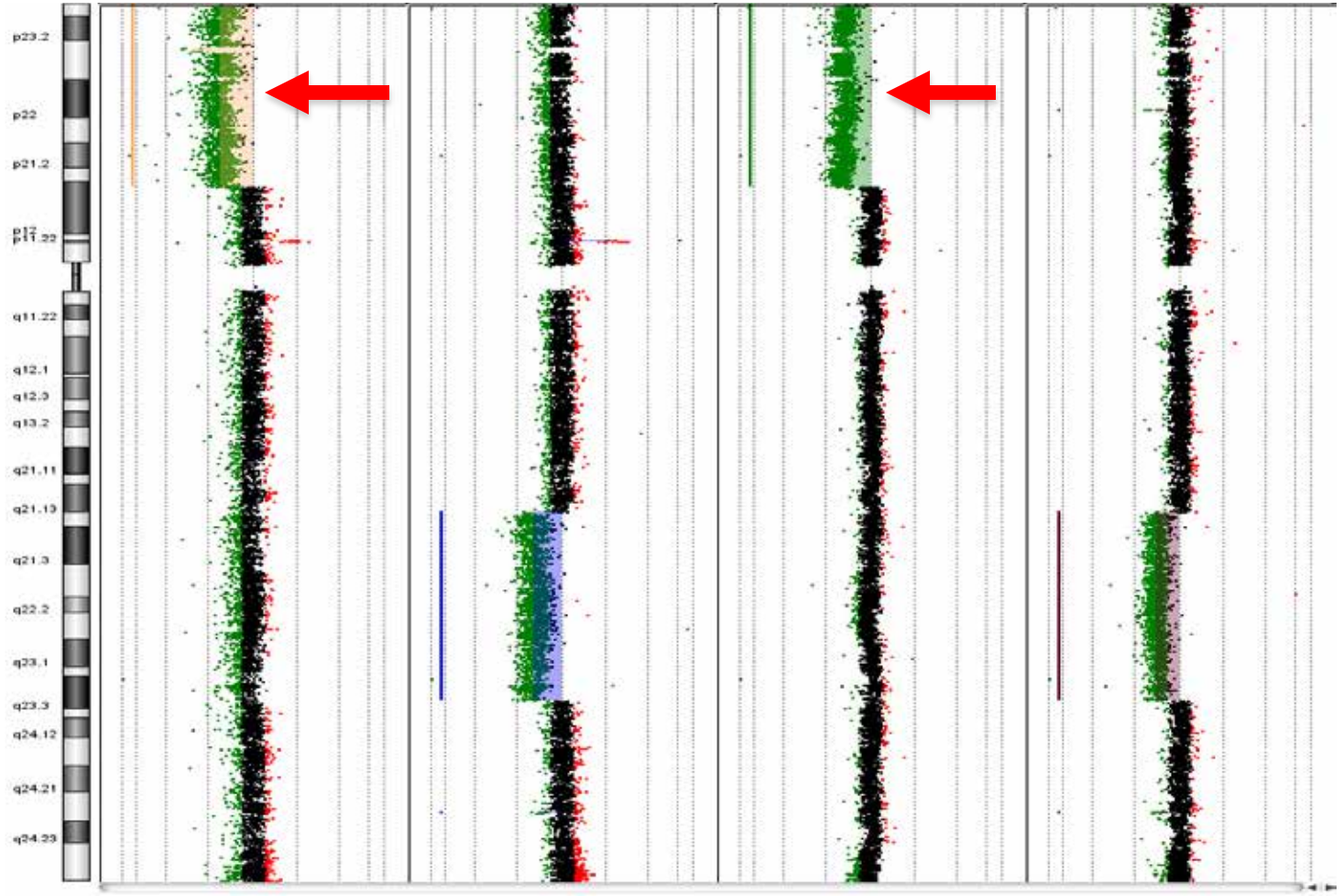
Clonal Tides



Diagnosis Relapse 1 Relapse 2 Relapse 3

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Clonal Tides

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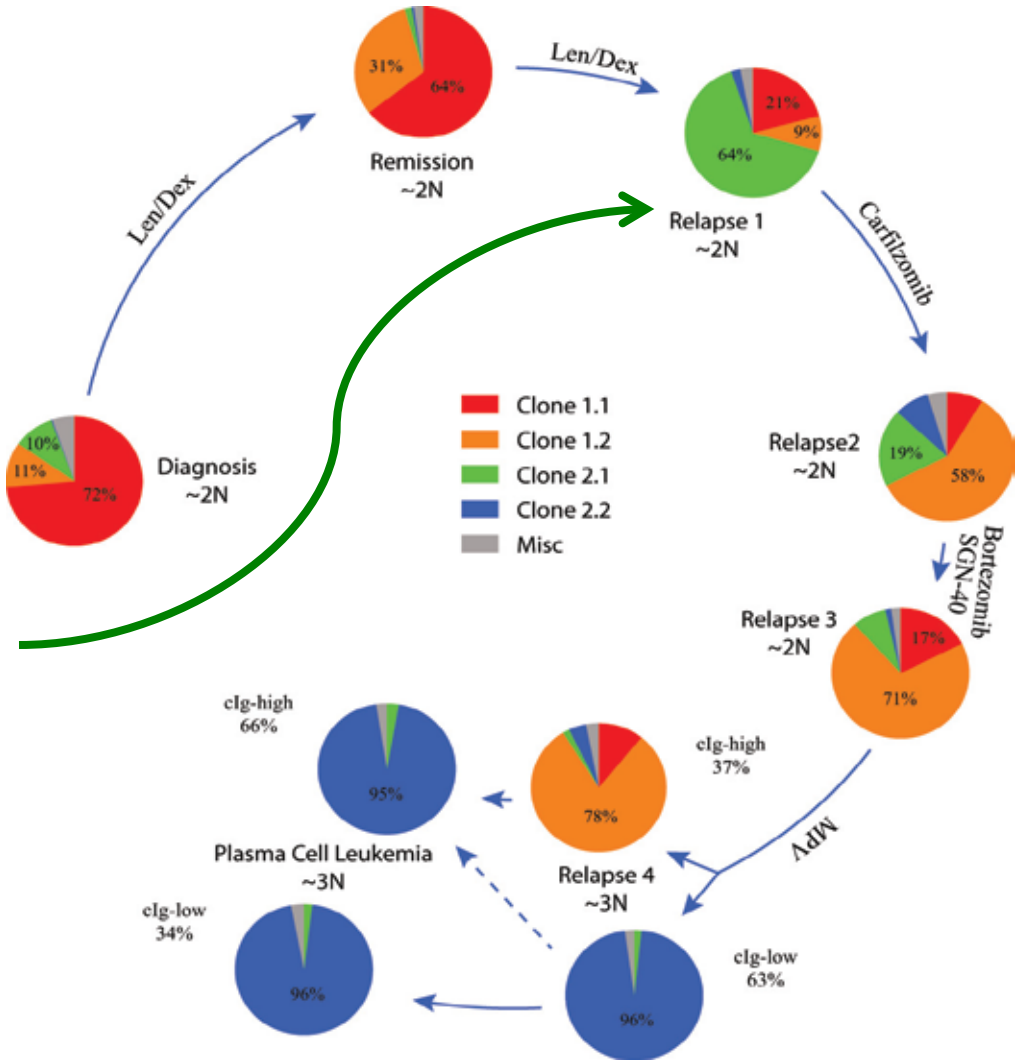
Clonal Tides

- 5 unique clones at diagnosis
- Variable chemotherapy response
- Minor drug resistant clone lethal



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Implications

- Multiple clones with variable drug sensitivity
  - *Combination chemotherapy a necessity*
- Re-emergence of drug sensitive clones
  - *Once resistant not always resistant*
  - *Continuous suppressive therapy logical*
- Minor drug resistant clones lethal
  - *Need to understand mechanism of resistance as a means to eradicate*
- In high risk disease genome is unstable
  - *Avoid DNA damaging agents ?*


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