Aims of therapy in relapsed and refractory myeloma

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UKMS Spring Day

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Synopsis

- Context
- Understanding
  - Your patient’s disease
  - Your patient’s treatment
  - Your patient
- When to treat
- What to treat with

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Improved outcomes in myeloma

- Ageing but fitter population
  - Increasing number of people suitable for treatment
- More treatments
  - Numerous NICE/SMC approvals
- More effective treatments
  - Only approved if better than previous
- Manageable toxicities
  - Can remain on treatment longer

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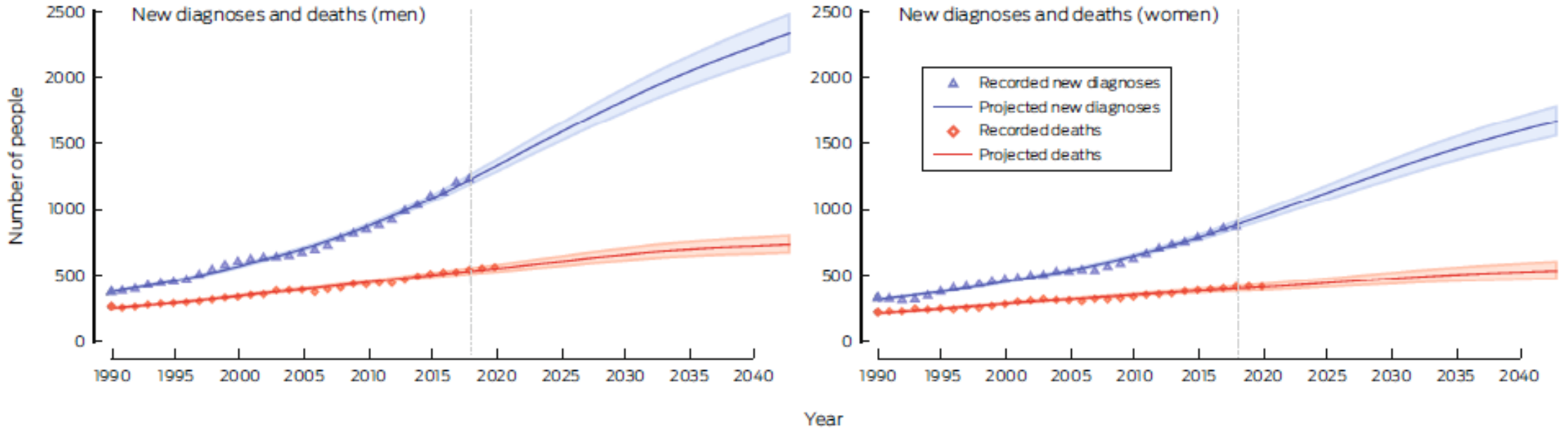
Improved outcomes with myeloma

6 Historical and projected (2019–2043) numbers of new diagnoses with and deaths from multiple myeloma, and of people living with multiple myeloma, Australia, by sex*



Luo et al, MJA July 2024

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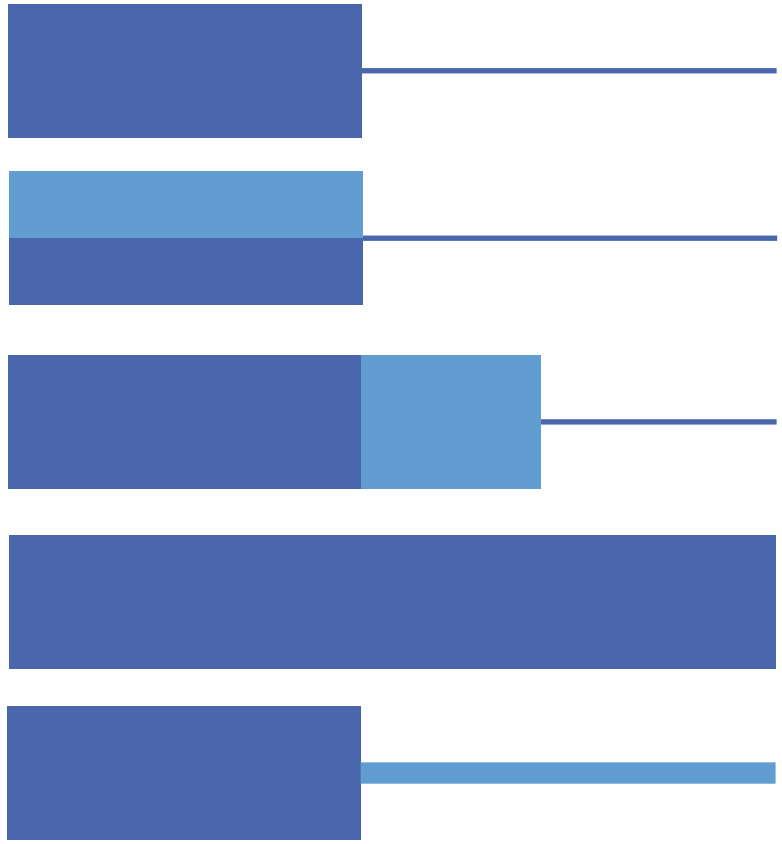
Changing patterns of treatment

- Fixed duration therapy
  - Planned duration and stop at that time point, e.g.
    - VCD
- Augmentation
  - Addition of drugs to standard schedule , e.g.
    - Daratumumab to VTD during induction
- Consolidation
  - Fixed block of treatment aimed at deepening response, e.g.
    - Dara-VTD post autologous stem cell transplant
- Continuous therapy
  - Continuous therapy (same drugs) e.g.
    - Elranatamab, teclistamab
  - Maintenance (switch to different drug) to maintain tumour control, often as single agent, e.g.
    - Lenalidomide
    - DVd
  - Typically until progression or toxicity



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Impact

- Patient perspective:
  - Better longer term outcomes
  - Move to continuous therapy for almost all RRMM regimens
  - No treatment free interval
- Service perspective
  - Cost
  - Capacity
  - Need to maximise efficiency

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Definitions

- Relapsed and refractory
  - Progressed on or within 60 days of therapy
  - Virtually all myeloma patients are both relapsed AND refractory
  - Some may not be refractory to all drugs
    - E.g. second line DVD may still be bortezomib sensitive
- Relapse
  - Clinical relapse
    - New CRAB criteria
    - new SLiM criteria?
  - Progression
    - Rise in paraprotein by 25% and minimum of 5 g/L

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Newly diagnosed vs relapsed myeloma

	NDMM	RRMM
Clinical presentation	Y	Y – diagnosis and relapse
Prognostic factors	Some	Y – diagnosis and relapse
Co-morbidities	Y	Y
Efficacy of treatment	N	Y
Toxicities of treatment	N	Y
Patient priorities	Perhaps	Y
Support infrastructure	Perhaps	Y
Criteria for treatment	Y	N

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Aims of therapy in relapsed and refractory myeloma

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Aims

- Identify and prevent potential morbidity from progressive disease
- Achieve long term disease control
- Minimise toxicity from treatment

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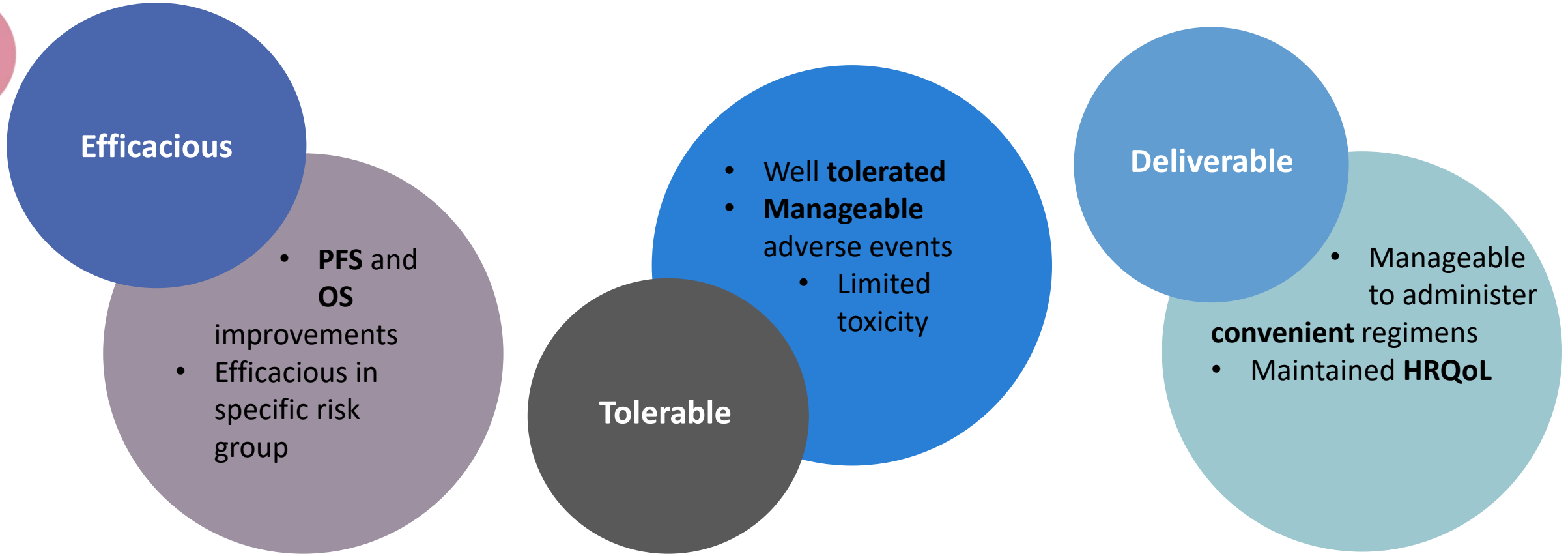
- There are three main objectives in myeloma treatment:



•HRQoL, health-related quality of life; PFS, progression-free survival; OS, overall survival.

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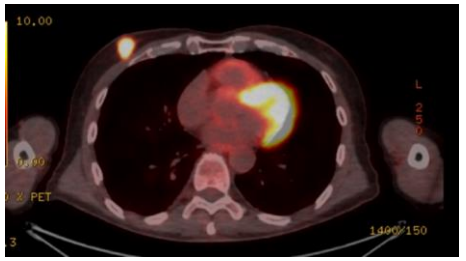
Understanding the disease

- Clinical presentation
  - At diagnosis
    - Myeloma-defining criteria e.g.
      - Bone disease/AKI/hypercalcaemia vs. anaemia or abnormal SFLC ratio
    - Nature of initial presentation
      - Florid presentation vs. MGUS/SMM gradual progression
    - Prognostic factors e.g.
      - Genetics
      - Imaging including extramedullary disease



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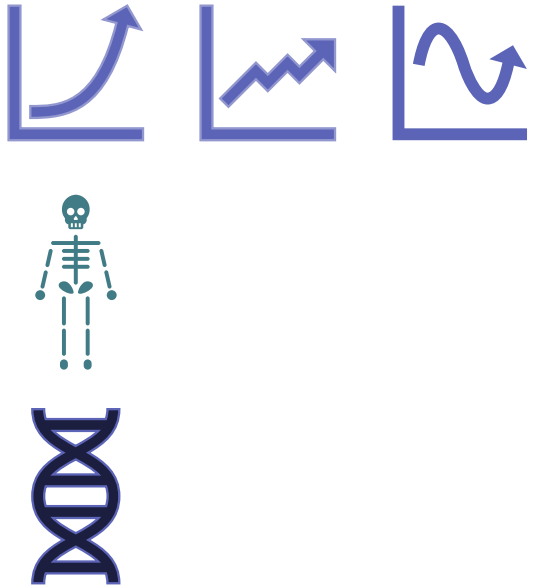
Understanding the disease

- Current status
  - Nature of progression
    - On treatment or off treatment
    - Pace of progression
    - Evolving or step-wise?
  - Functional cross-sectional imaging
    - Consider serial imaging for occult clinical relapse
  - Clinical symptoms
  - Bone marrow for clonal evolution
  - Very limited evidence base to inform decision-making and frequency of monitoring
- Evaluation of need to intervene or not
  - May not be a need to intervene immediately



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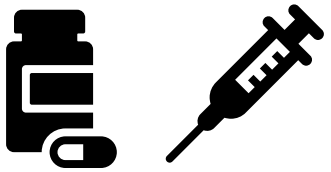
Understanding the treatment

- What treatment was received
  - Which backbone agents, alone or in combination?
    - IMiD
    - PI
    - MoAb
    - Alkylator
    - Steroid
    - T-cell engager
  - On or off treatment?
    - Duration of time since treatment
      - E.g. high dose melphalan <2 years or <3 years if maintenance?
  - Duration of treatment received
  - Duration of response
  - At what prior line was each drug/combination given in?



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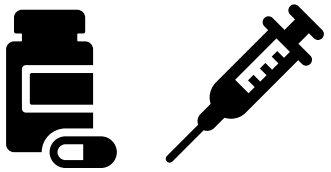
Understanding the treatment

- Toxicities of treatment:
  - Transient, reversible e.g.
    - Cytopenias
    - Infection
  - Permanent e.g.
    - neuropathy
  - Potential class effect e.g.
    - Rash
    - VTE
    - Steroids
- Likely benefit vs. risks of proposed treatment:
  - Risk-benefit ratio may change over time in either direction
    - More or less prepared to consider certain side effects



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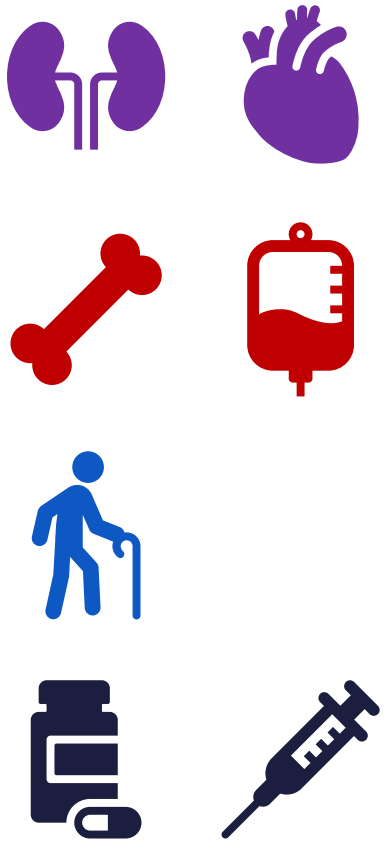
Understanding your patient

- Co-morbidities
  - Renal
  - Cardiac
  - Bone marrow reserve
    - Typically diminishes with multiple lines of therapy
    - Need to consider secondary MDS in heavily pre-treated
    - ?potential role for back up autologous stem cells
- Frailty
- Practicalities and mode of treatment delivery
  - Oral
  - IV/SC
  - Home care options
- Patient expectations



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Patient expectations - observations

- Reality of situation at relapse vs. previous successful therapy
  - Important to re-establish understanding
- Diminishing number of treatment options
  - Standard of care vs. experimental or clinical trial options
- Option of no active treatment
- Parallel planning and involvement of palliative care
- Impact of ongoing treatment
  - Time and logistics
  - Expense
  - Quality vs. quantity of life

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When to start or change treatment?

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Options at apparent progression

- True clinical progression or not?
  - Evolving pattern
  - Fluctuation
  - Apparent progression and stability
- Options
  - Continue
  - Switch therapy
  - Local radiotherapy
  - Augmentation
    - Optimisation of dosing
    - Re-introduction of steroids
    - Addition of cyclophosphamide

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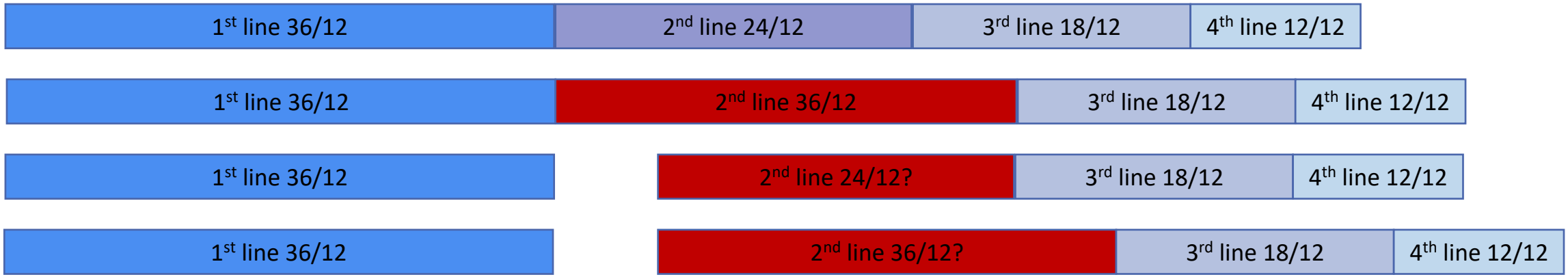
Early or later treatment switch?

- Limited data to inform decision-making
- Concepts:
  - Earlier treatment targets evolving clones?
  - Earlier treatment may induce more clonal evolution?



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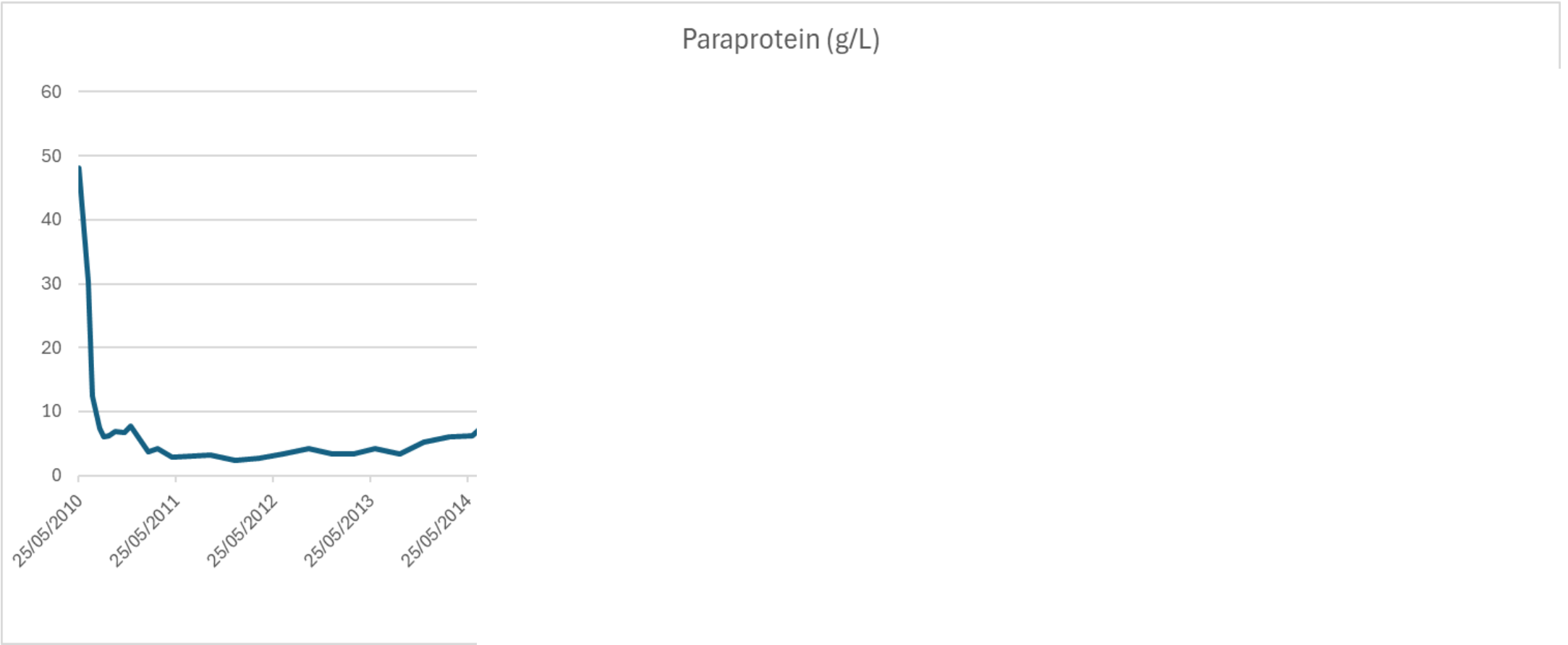
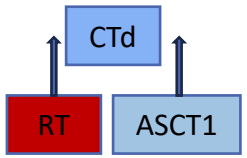
IgGL
t(11;14)
Lytic bone disease





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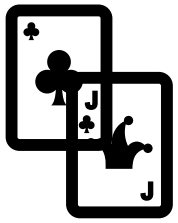
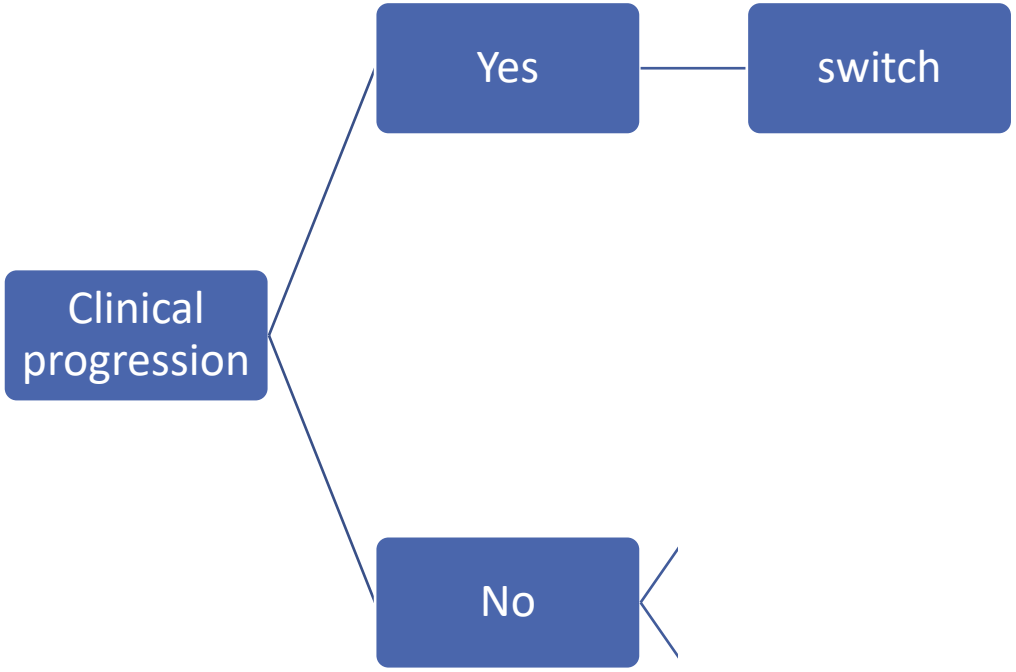
Stick or twist?





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What to treat with?

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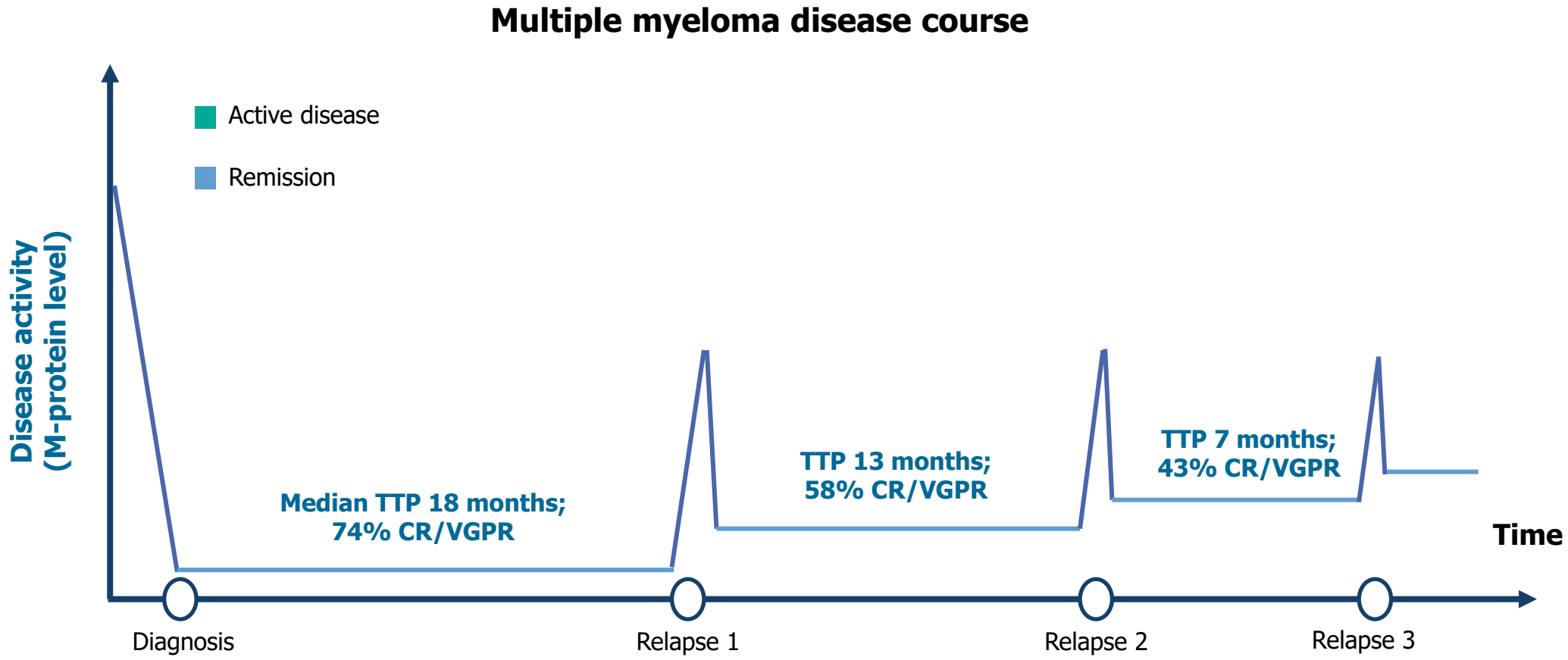
Relapse is usually associated with diminishing duration and depth of response over time[1–4]



Proportion of patients receiving treatment at each line of therapy

First line: 95%	Second line: 61%	Third line: 38%	Fourth line: 15%

•TTP, time to progression; CR/VGPR, complete response/very good partial response. Figure adapted from Durie BGM.[1] Values for duration and response data from Yong K et al.[4]

•1. Durie BGM. Concise review of the disease and treatment options. Multiple myeloma, cancer of the bone marrow. International Myeloma Foundation, 2016. Available at: www.myeloma.org/sites/default/files/images/publications/UnderstandingPDF/concisereview.pdf (accessed March 2017); 2. Kumar SK et al. Mayo Clin Proc 2004; 79: 867–874; 3. Moreau P & Touzeau C. Am Soc Clin Oncol Educ Book 2015: e504–e511; 4. Yong K et al. Br J Haematol 2016; 175: 252–264.

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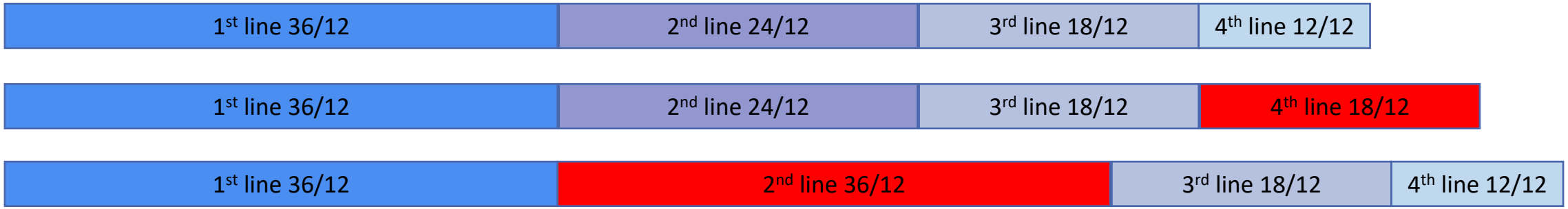
What to treat with

- Aim for best available therapy next
  - Best may not always be longest PFS if toxicity or practicalities are paramount
  - Always consider clinical trial options
  - Better therapies generally more efficacious if used in earlier line
    - E.g. 50% improvement compared with current line of therapy:



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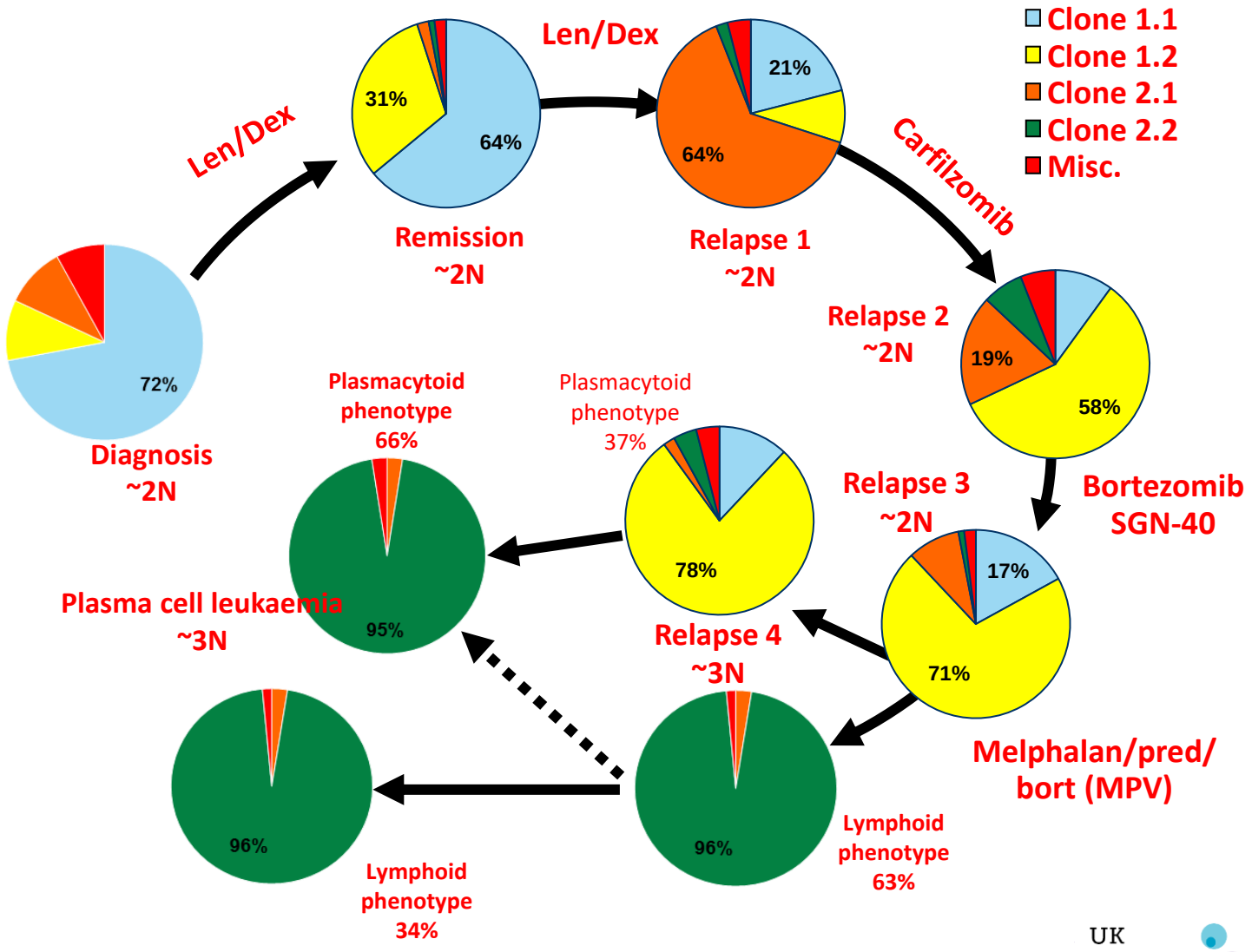
Clonal tides

- The summarised results of 8 different FISH assays are shown to indicate the relative abundance of each clone defined by aCGH at the 5 time points studied
- Minor drug resistance clone lethal
- Role for multi-drug therapy
- Rationale for understanding disease at a subclonal level
- Immediate prior exposure is probably more important than lines of therapy or historical exposure



Keats JJ, et al. Blood 2012;120:1067–76.

Len/Dex, Lenalidamide & Dexamethasone.

- *aCGH, array comparative genomic hybridisation*.

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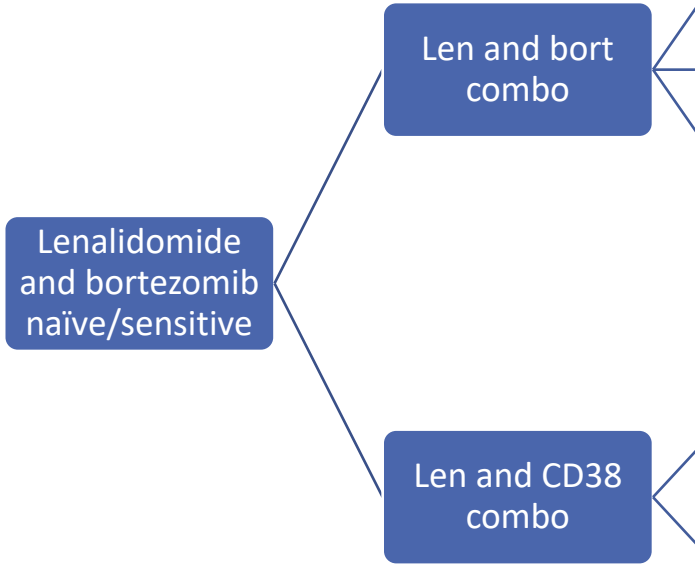
Treatment choice based on prior exposure



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Treatment choice based on prior exposure

	Lenalidomide naïve/sensitive Bortezomib naïve/sensitive	Lenalidomide refractory Bortezomib naïve/sensitive	Bortezomib refractory Lenalidomide naïve or sensitive	Len and bort refractory	Triple class exposed
Preferred	Dara-RD KRD Ixa-RD Dara-VD Elo-RD	Dara-VD PVD Dara-PD Dara-KD Isatux-KD Isatux-PD KD Elo-PD Bela-PD Bela-VD	Dara-RD KRD Elo-RD Ixa-RD Isatux-PD Bela-PD	Isatux-PD Isatux-KD Bela-PD	Ide-cel Cilta-cel Teclistamab Elranatamab Bela-PD Talquetamab
Alternatives	CRD CVD KCD RD KD VD	CVD VD Selinexor-Vd	CRD RD	KD CPD Dara-PD Dara Elo-PD Pano-VD Pano-VTD Alkylators+/- thal	Belantamab Pano-VD Alkylators +/- thal Dara-KD Elo-PD Selinexor

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Conclusions

- Decision-making in relapsed and refractory myeloma complex
- Key principles
  - Understand your patient's disease, treatment response and preferences
  - Consider whether clinical progression or not and risk of developing end organ damage
    - Switch, augment or stick
- Low threshold for functional cross-sectional imaging
- Consider bone marrow primarily for clonal evolution
- Balance that against what is actually available!

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