Metro North Hospital and Health Service *Putting people first*

“Till death do us part”
Long term oral therapies that control cancer without cure

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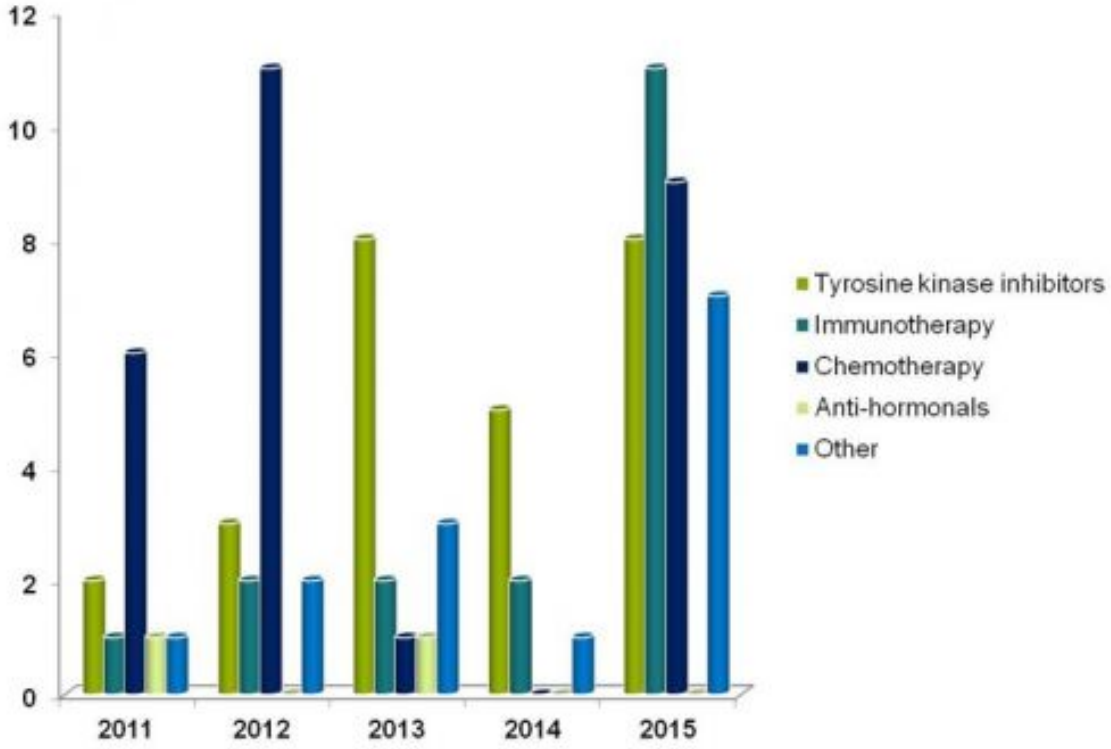
Introduction

- The pace of research in cancer is accelerating
- Better understanding of the molecular basis of haematological malignancies has led to the development of rational drug design and ‘targetted’ therapies with unique side effect profiles
- Fast-tracking of drug development and regulatory approval results in earlier dissemination into the clinic
  - First-in-class agents
  - Second and third generation agents
  - Combination therapies
- Challenging for both haematologists and patients to navigate this changing treatment landscape
- GPs are likely to see increasing number of new oral agents as haematological malignancies become chronic diseases



Source: http://www.ema.europa.eu/ema/

Outline

- CML - tyrosine kinase inhibitors
- Myeloma - immunomodulatory agents (thalidomide + derivatives)
- CLL – ibrutinib and idelalisib

Case 1

- 68 year old male painter presents with fatigue and abdominal discomfort, vague weight loss
- Massive splenomegaly on abdominal examination

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Diff: Manual        Specimen: Blood      dWCH,Flg,WCVH,BH2,PB,
Hgb :  128 L     WBC    :127.7 C
PLT :  163               :127.7 H
RBC : 4.24 L     HCT    : 0.43
MCV :  101 D     MCH    : 30.2
RDW : 17.2 H     MCHC   :  299 C    Press shift-insert to view reference ranges
Neut  ( 65  %): 82.90 H     Meta  ( 12  %): 15.97 H      AbnLy (     %):
Lymph (  3  %):  3.68       Mye   (  4  %):  5.53 H      ProLy (     %):
Mono  (  7  %):  8.60 H     Prom  (  1  %):  1.23 H      Plasm (     %):
Eosin (  2  %):  3.07 H     Blast (  1  %):  1.23 H      Other (  0  %):  0.00
Baso  (  4  %):  5.53 H     AbnIm (     %):              NRC       0   /100 WBC
Band  (  0  %):  0.00       AtyLy (     %):              NRBC      0 H/100 WBC
SusFlgWBC_AS,IG%,BL?,LEFT_S
Comment:        Patient Age: 68 years    Val: lmr5                  13.0
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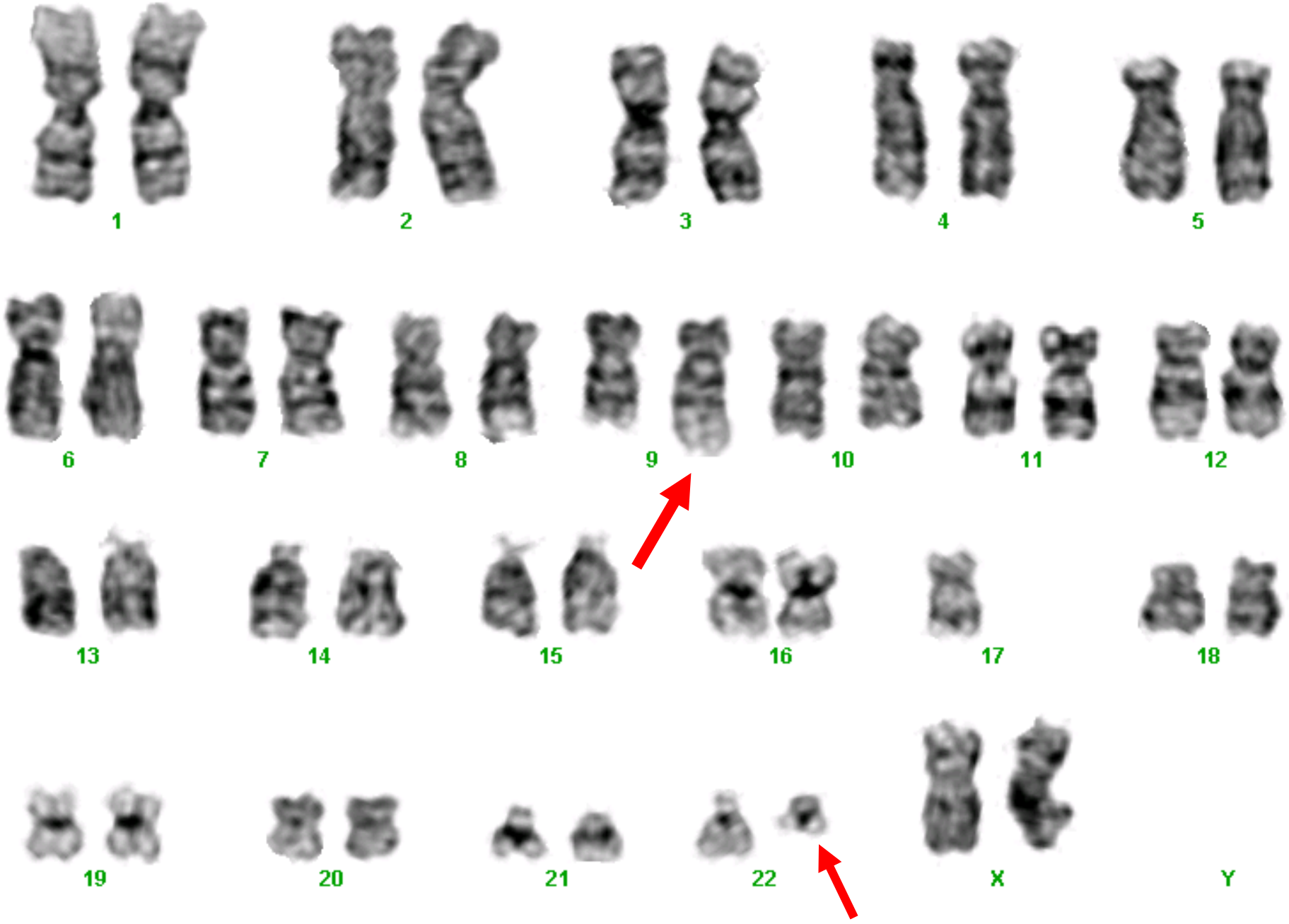
Leucocytosis: differential diagnosis

- **Reactive leucocytosis**
  - Very common; usually mild-moderate (10-20 x 10^9/L), with variable elevation of neutrophils, lymphocytes and monocytes; *occasional* immature forms; platelets may be normal or elevated
    - infection
    - drugs (eg steroids)
    - inflammatory conditions eg inflammatory arthropathies
    - pregnancy
    - massive trauma/surgery/burns ("leukaemoid reaction")

- **Chronic myeloid leukaemia**
    - Peripheral blood ***PCR testing for BCR-ABL fusion gene*** is simple and ~99% sensitive/specific

- **Other myeloproliferative neoplasms**: polycythaemia vera, myelofibrosis
    - Generally distinguishable by associated findings of erythrocytosis, abnormal red cell morphology
    - ***JAK2 and CALR mutation testing*** can be helpful to confirm

- **Chronic myelomonocytic leukaemia:** usually older patients, dysplastic findings on film with prominent, chronic monocytosis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CML – molecular pathogenesis

t(9;22) translocation

↓

BCR-ABL fusion protein

↓

“constitutive tyrosine kinase”

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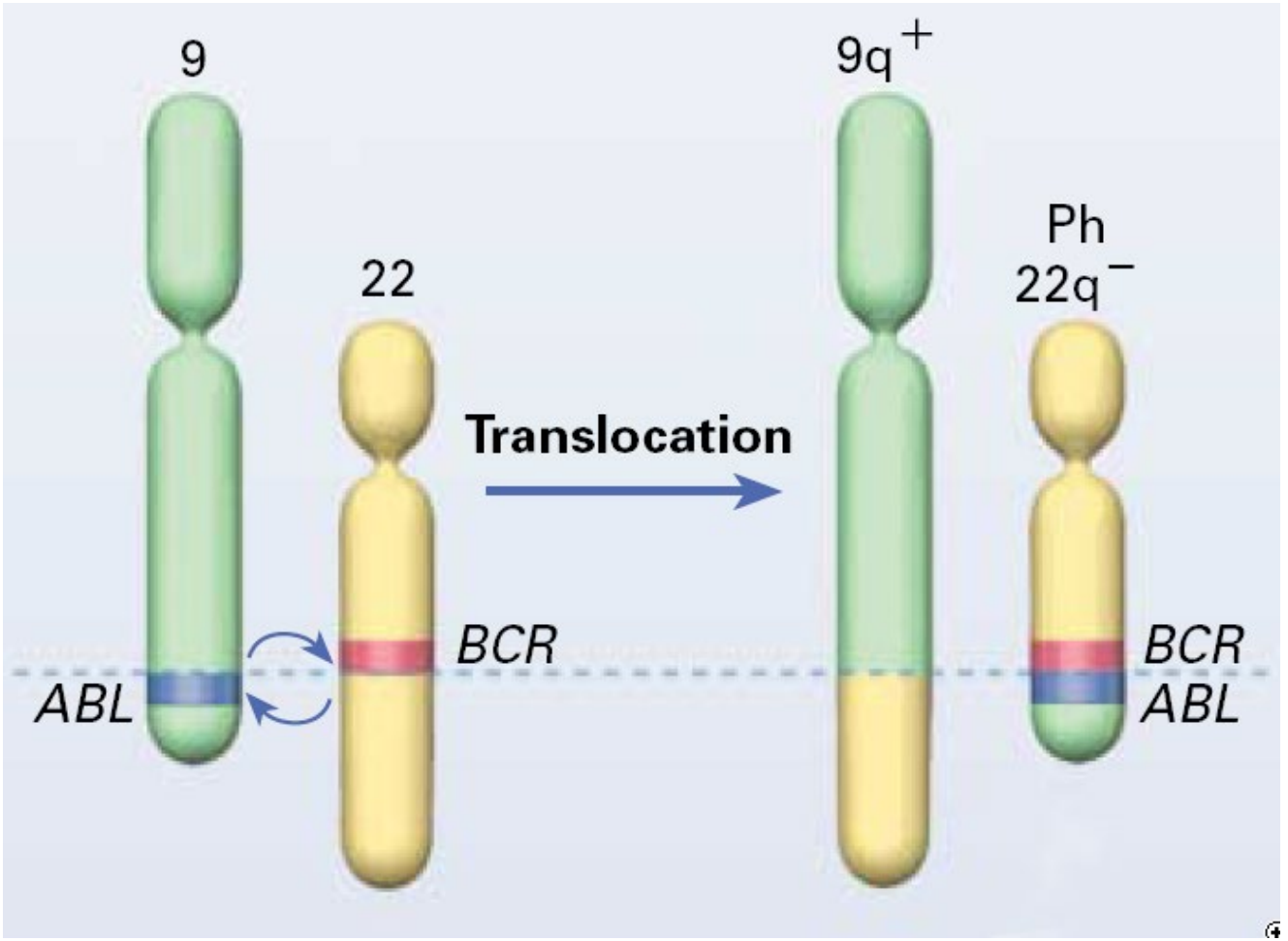
inappropriate activation of multiple downstream signal transduction pathways

↓

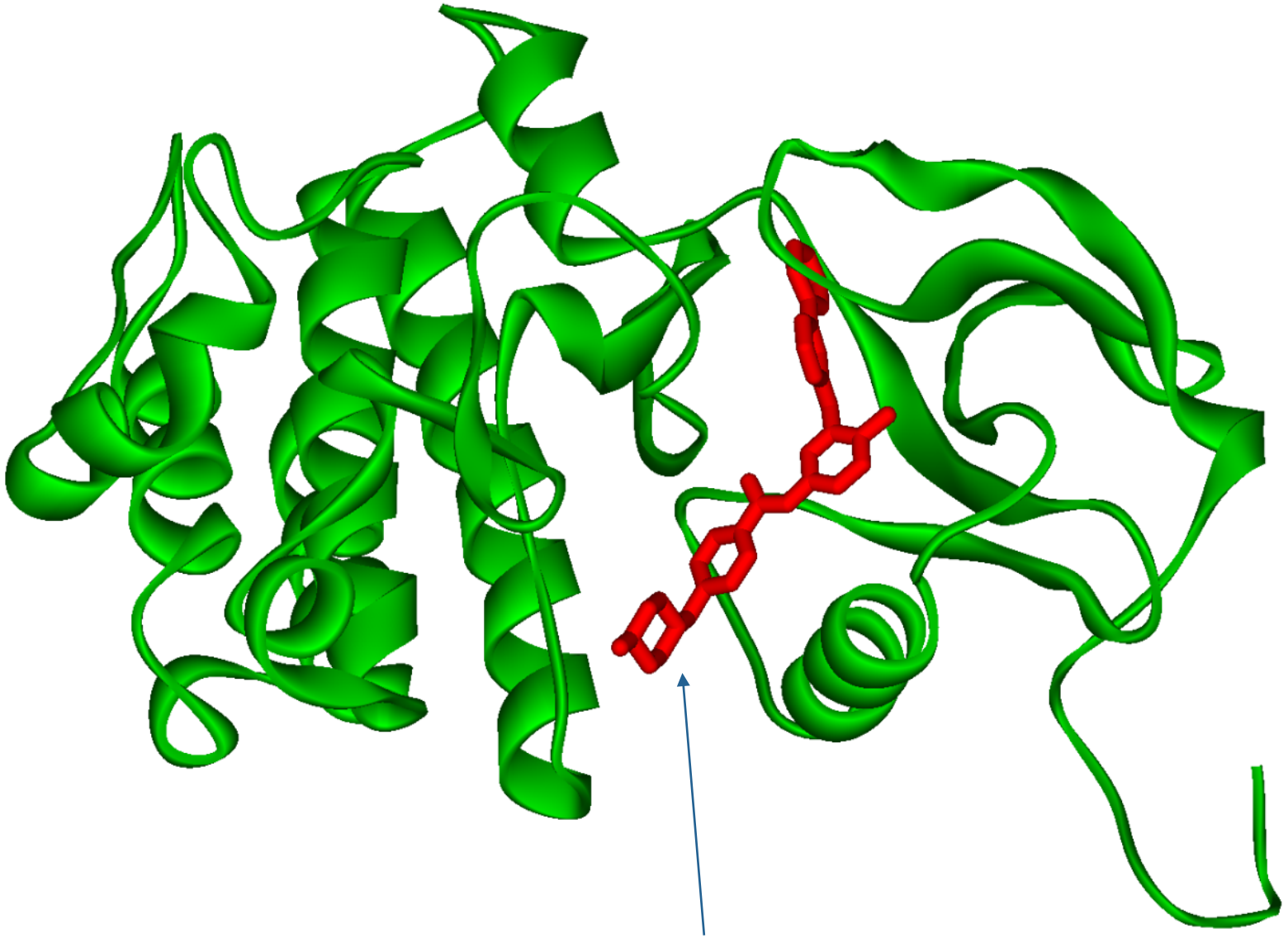
Proliferation and resistance to apoptosis

↓

CML



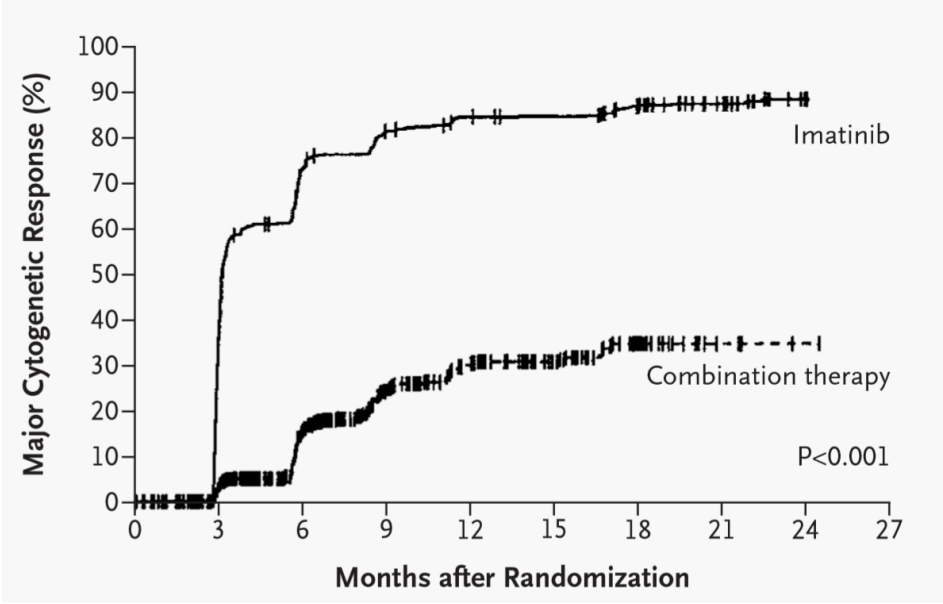
Imatinib



STI-571 / imatinib / Glivec

IRIS trial (NEJM 2003)

- Randomised comparison of “standard of care” (cytarabine + interferon) to monotherapy with imatinib
- Imatinib associated with
  - Better responses
  - Improved freedom from progression to accelerated / blast phase
  - Better tolerated
  - (subsequent studies) > 90% survival beyond 5 years



Imatinib: drawbacks

- Sounds “perfect” … but it’s not
- Treatment failure in up to 30% of patients
  - Failure to achieve molecular remission target (<0.1% transcript level)
  - Intolerance
    - Oedema
    - Asthenia, fatigue, cramps, myalgias
    - Diarrhoea
    - Rash

Second-generation TKIs

- Similar mechanism but structural differences = more “powerful” inhibitors of BCR-ABL, with differing efficacy against BCR-ABL mutations that can cause resistance to Glivec
- Clinical studies show more rapid, and potentially “deeper” responses, with very low rates of transformation to advanced stages of disease
- BUT because the overall survival of CML is so good these days (> 90% at 5 years), very difficult to demonstrate a difference in overall survival
- All are available on PBS for initial therapy of CML in chronic phase
- Choice between imatinib and second generation agents remains a matter of debate, recognising lack of absolute survival benefit and “unique” individual toxicities of the three agents

Nilotinib (“Tasigna”)

- More rapid, and overall “deeper” response compared to imatinib
- BUT:
  - Must be taken on an empty stomach, twice a day: compliance difficulties
  - Exacerbation of **diabetes**
  - LFT derangement, pancreatitis
  - ? Increased **risk of cardiovascular disease**

    Requires ongoing (ie lifelong) monitoring and management of cardiovascular risk factors

Dasatinib (“Sprycel”)

- More rapid, and overall “deeper” response compared to imatinib
  - (but no direct comparison to Tasigna ever likely to occur)
- Once daily dosing, no dietary requirement (← ? better compliance)
- BUT as with nilotinib, significant toxicities
  - Pleural effusions – unpredictable, often late in course
  - Peripheral oedema
  - Pulmonary hypertension
  - Cytopenias

Case 2

- 69 year old retired farmer, presents with fatigue

Diff: Reviewed		Specimen: Blood		
Hgb :	76 C	WBC :	3.6 L	
PLT :	132 L	:	3.6 L	
RBC :	2.58 L	HCT :	0.23 L	
MCV :	89	MCH :	29.5	
RDW :	17.8 H	MCHC :	332	Pres
Neut	(61* %):	2.17		
Lymph	(29* %):	1.04		
Mono	(8* %):	0.28		
Eosin	(2 %):	0.06		
Baso	(0 %):	0.01		
NRBC	/100 WBC			
SusFlgATY_LY				
Comment:	Patient Age: 69 years			

Specimen type	Blood		Urate	0.44	mmol/L (0.15 - 0.50)
Sample Appearance	Clear		Protein	110 H	g/L (60 - 80)
Sodium	142	mmol/L (135 - 145)	Albumin	23 L	g/L (35 - 50)
Potassium	4.1	mmol/L (3.5 - 5.2)	Globulin	87 H	g/L (25 - 45)
Chloride	110	mmol/L (95 - 110)	Bilirubin	10	umol/L (< 20)
Bicarb.	27	mmol/L (22 - 32)	Bili(Conj)	< 4	umol/L (< 4)
Anion Gap	5	mmol/L (4 - 13)	ALP	49	U/L (30 - 110)
Glucose	4.7	mmol/L (3.0 - 7.8)	Gamma GT	37	U/L (< 55)
Fasting RR	-->	(3.0 - 6.0)	ALT	25	U/L (< 45)
Urea	5.1	mmol/L (2.9 - 8.2)	AST	27	U/L (< 35)
Creatinine	81	umol/L (64 - 108)	LD	200	U/L (120 - 250)
Urea/Creat.	63	(40 - 100)	Calcium	2.32	mmol/L (2.10 - 2.60)
eGFR	85	mL/min/(> 60)	Corr Ca	2.66 H	mmol/L (2.10 - 2.60)
lab use	85	1.73m^2			
Comment:	Age:69 years I 1	H 1	L 0	KC 4.0	

SERUM PROTEIN ELECTROPHORESIS

Total Protein	110 H	g/L	(60 - 80)
Albumin	23 L	g/L	(35 - 50)
Total Globulin	87 H	g/L	(25 - 45)
Monoclonal Protein	DETECTED		
Alpha 1	3	g/L	(3 - 6)
Alpha 2	7	g/L	(4 - 10)
Beta	4 L	g/L	(5 - 11)
Total Gamma	72 H	g/L	(7 - 18)
Lambda IgG	65 H	g/L	(0 - 0)
Gamma (Residual polyclonal)	7	g/L	(7 - 18)

COMMENT:
Decreased residual gamma globulins.

Specimen Type: Blood

K/L Ratio (NL) Rpt:		K Dil (NL):	L Di
IgG	*	g/L	(7.0 - 16.0)
IgA	0.1 L	g/L	(1.0 - 4.0)
IgM	0.1 L	g/L	(0.4 - 2.3)
Kappa FLC (N Latex)	3 L	mg/L	(7 - 22)
Lambda FLC (N Latex)	32 H	mg/L	(8 - 27)
K/L Ratio (N Latex)	0.10 L		(0.31 - 1.56)

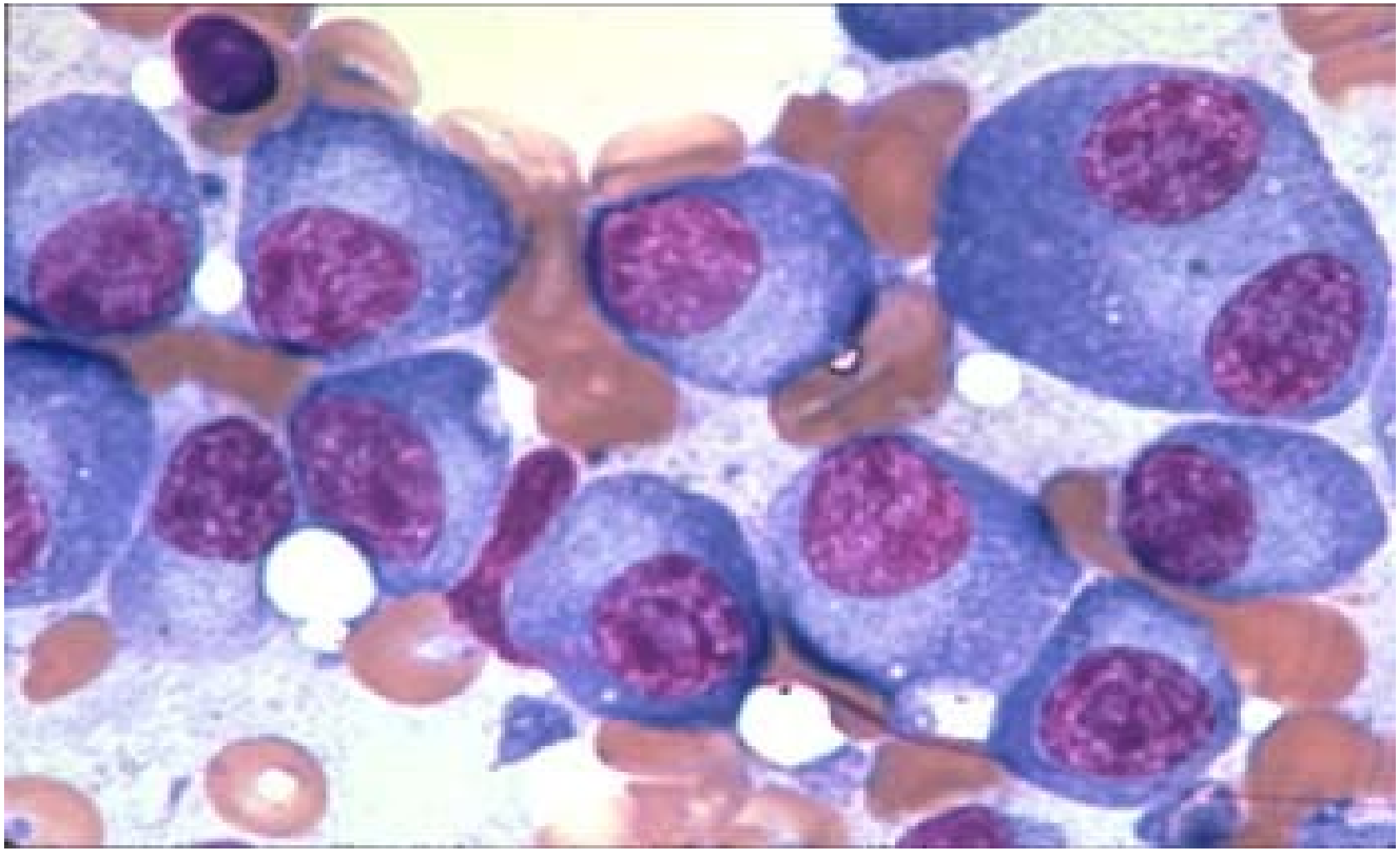
The current reference ranges for Free Light Chains are
those recommended by the manufacturer.

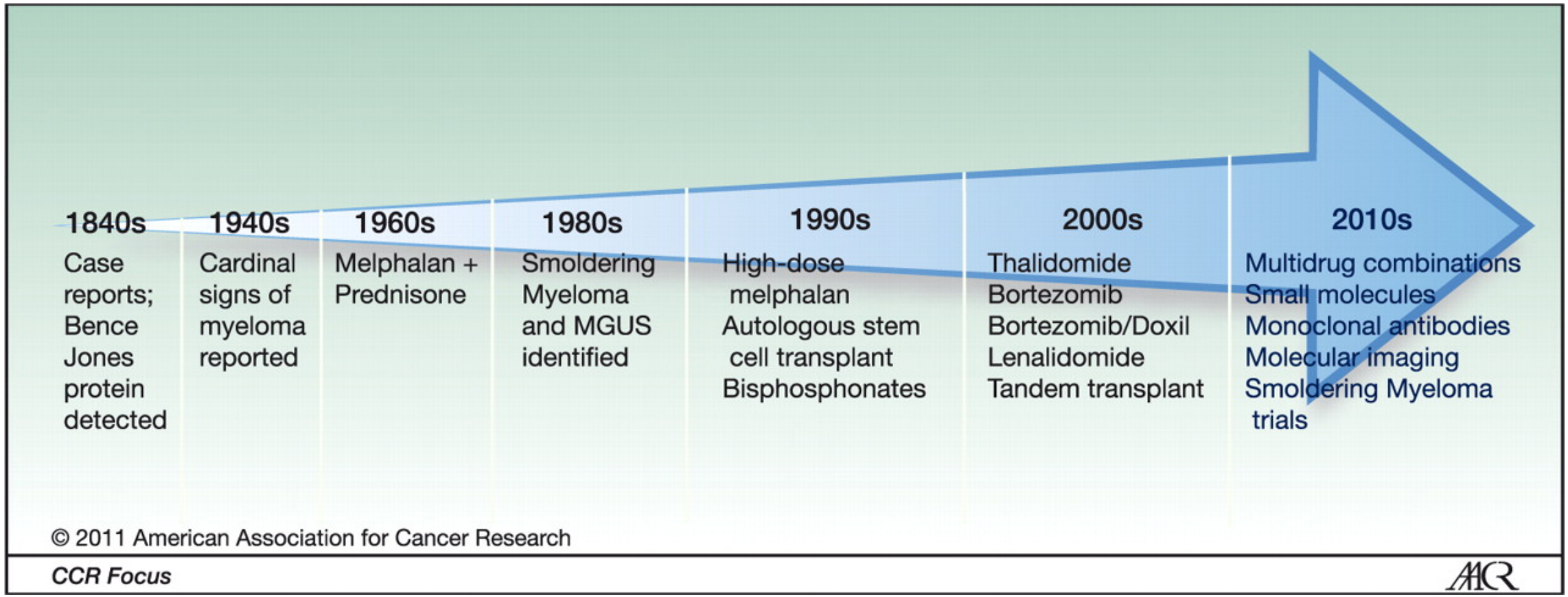
Monoclonal protein: when should I be worried?

- 5% of people aged over 70 will have a detectable monoclonal protein
- The majority will be 'MGUS' with risk of progression to MM approximately 1% per year
- Features that raise concern for myeloma:
  - Hyper**C**alcaemia
  - New **R**enal dysfunction
  - **A**naemia
  - **B**one pain due to lytic lesions
- It is worthwhile screening patients who present with any of these features using **serum electrophoresis *and* serum free light chains**

- When *not* to be worried about myeloma:
  - Polyclonal hypergammaglobulinaemia
  - raised ESR in the absence of a monoclonal protein
  - Mildly elevated light chains with normal ratio (common in CKD)

Bone marrow biopsy




1840s
Case reports; Bence Jones protein detected
1940s
Cardinal signs of myeloma reported
1960s
Melphalan + Prednisone
1980s
Smoldering Myeloma and MGUS identified
1990s
High-dose melphalan
Autologous stem cell transplant
Bisphosphonates
2000s
Thalidomide
Bortezomib
Bortezomib/Doxil
Lenalidomide
Tandem transplant
2010s
Multidrug combinations
Small molecules
Monoclonal antibodies
Molecular imaging
Smoldering Myeloma trials
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CCR Focus
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Thalidomide - history

- Broadly marketed in late 1950s as sedative and anti-emetic … in certain regions specifically promoted as highly effective treatment for morning sickness in prengnacy
- By 1961, clearly identified as teratogenic – causing limb deformities and amelia
- Some years later, the teratogenic effects were attributed to inhibition of new vessel formation (… critical to embryonic lengthening of arms, legs, fingers and toes)
- In 1970s : new vessel formation (“angiogenesis”) established as important to the development of solid tumours

… leads to investigation of angiogenesis inhibitors as anti-cancer therapies

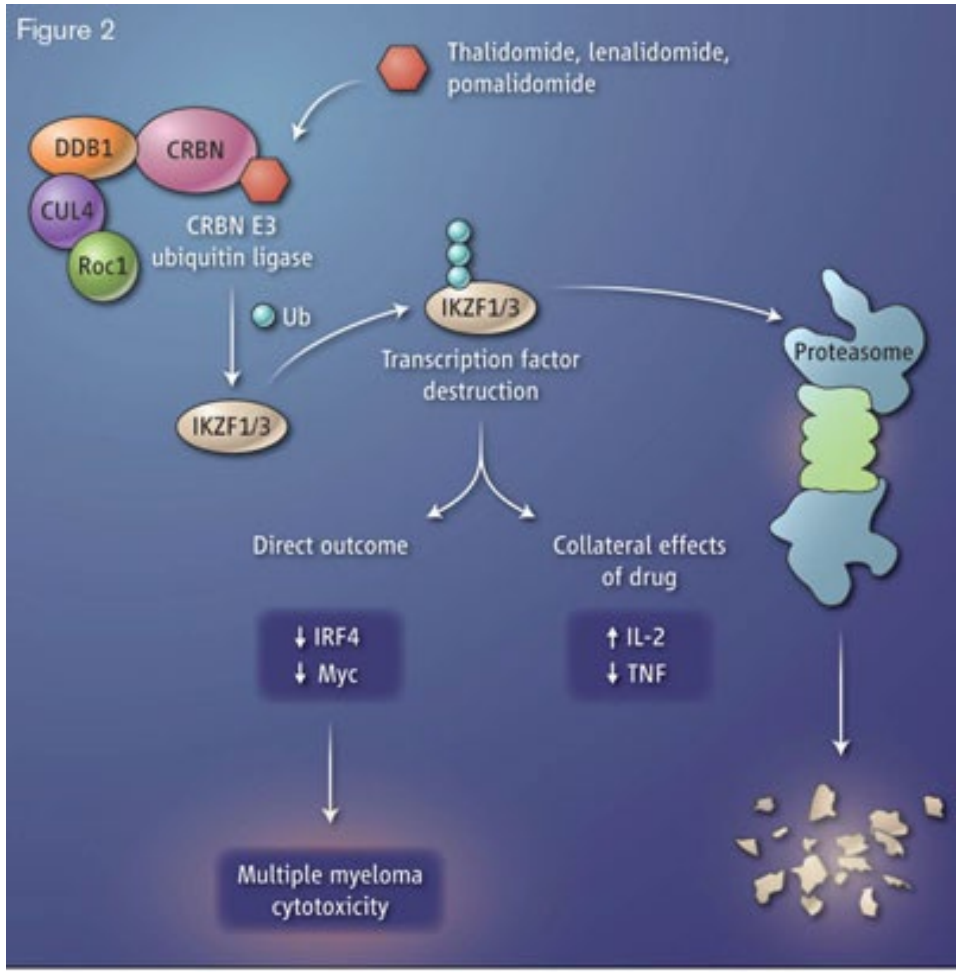
- 1990s Folkman et al hypothesize that growth of blood cancers including myeloma are dependent of angiogenesis
- This leads to sequential clinical trials of thalidomide (= recognised angiogenesis inhibitor) that eventually culminate in several studies in the 1990s demonstrating superior clinical efficacy to “standard of care” therapies in myeloma patients

Thalidomide and other “iMIDs” – mechanisms of action

- Suppression of angiogenesis
- Interference with supportive microenvironment
- Alteration of expression of cellular adhesion molecules
- “ Immunomodulation” (IMID)

  Increase cell mediated cytotoxicity

  Increased cytokines eg IL-2
- Inhibition of specific cellular pathways that are know to be aberrantly active in myeloma (eg NFKB)

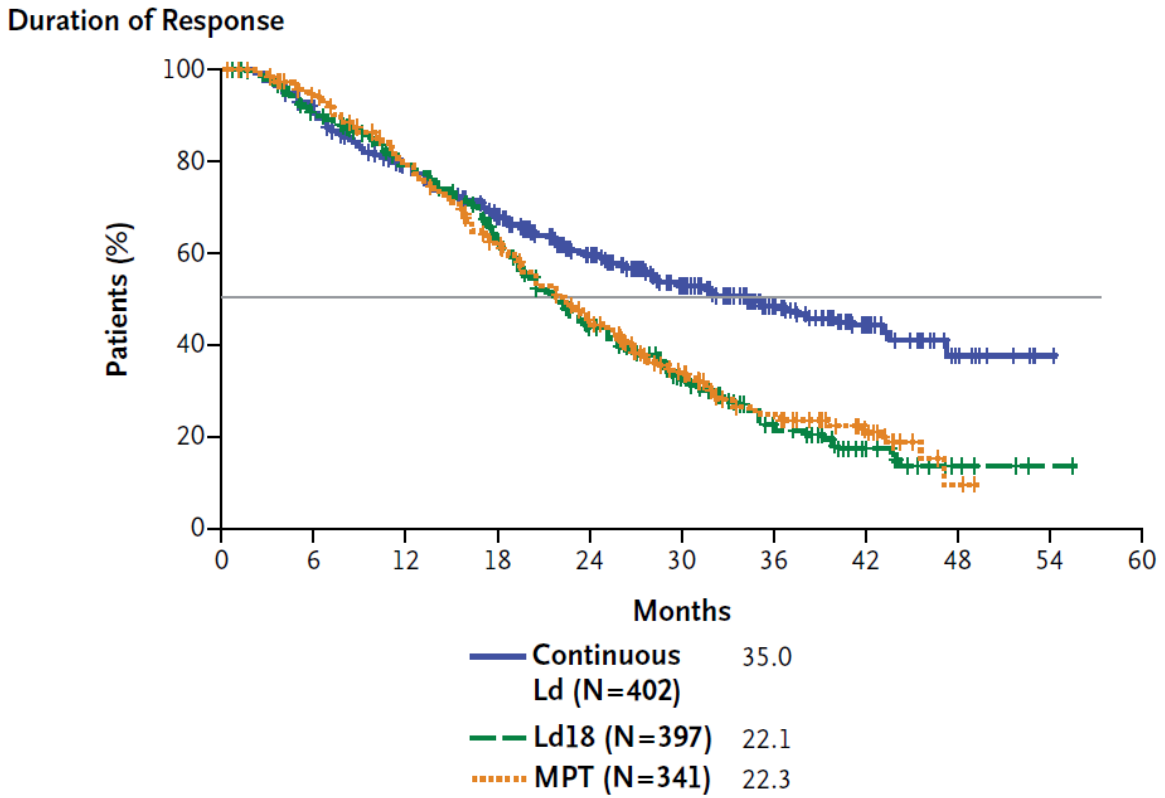


Thalidomide – side effects

- Sedation
  - This is amongst the effects is was originally marketed for in late 1950s
  - Always take dose at night
- Constipation
  - Usually manageable with simple aperients
- Peripheral neuropathy
  - Sensory, length dependent
  - Distal numbness followed by paraesthesia that progresses distal to proximal
  - Time and dose dependent
  - Most common adverse effect that leads to termination of therapy
- Increased risk of venous thromboembolism
  - all patients must at least be on aspirin, and those at “high risk” (immobility, surgery, prior thrombosis) should be considered from LMWH prophylaxis

Lenalidomide (“Revlimid”)

- “More potent “immunomodulation”
- Less neurotoxicity
- PBS-reimbursed for both untreated and relapsed disease
- Effective ‘backbone’ for combination with monoclonal antibodies such as elotuzumab and daratumomab



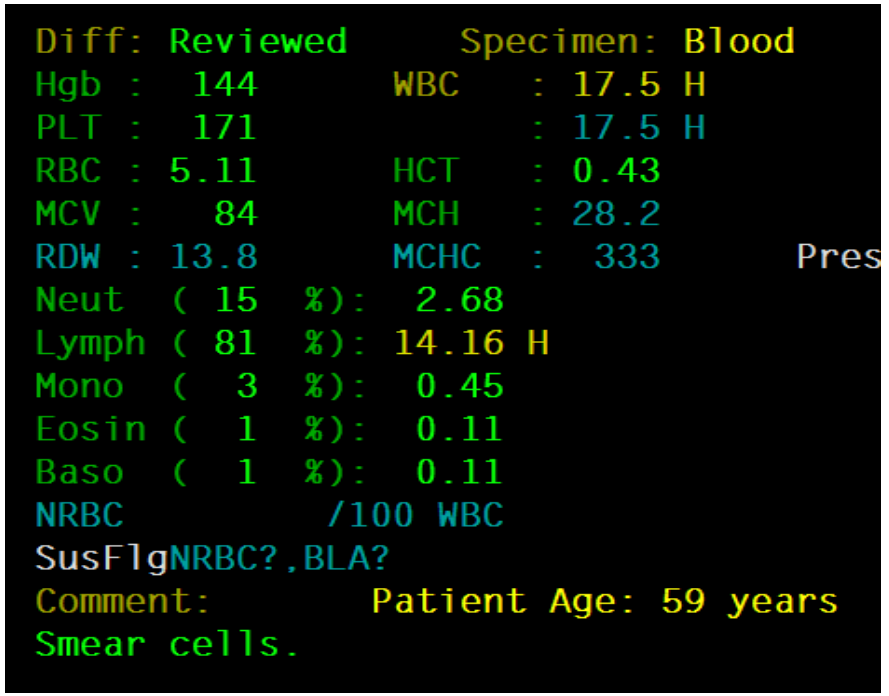
Lenalidomide (Revlimid) – side effects

- Compared to thalidomide
  - MORE cytopenias (esp neutropenia), ? rashes
  - LESS sedation, neuropathy
  - SIMILAR increased risk of venous thromboembolism
    - all patients should at least be on aspirin +/- anticoagulation if risk factors present

  Second primary malignancy risk?
    - Sun avoidance and skin checks are recommended

Case 3

- 59 year old IT technician presents with lethargy
- Mild cervical lymphadenopathy



Flow Cytometric Analysis

Specimen : Blood

Specimen: Peripheral blood

Summary: Consistent with B-CLL

Immunophenotype:
CD5 (weak), CD19, CD20 (weak), CD23 and kappa light chains (weak)

Comment:
An immunoglobulin light chain restricted B-cell population comprised approximately 58% of the total cells. The immunophenotype is consistent with B-CLL. Correlation with other laboratory findings is required.

Analysis:
Percentage of cells analysed (gated): 73%
Region gated: Lymphoid

Analysis:
Percentage of cells analysed (gated): 73%
Region gated: Lymphoid

Absolute total B-cell (CD19+) count: 10971/uL

B-CELLS		T-CELLS	
CD10:	<1%	CD3:	22%
CD19:	73%	CD4:	11%
CD20:	73% (weak)	CD8:	11%
CD5+/CD20+:	73%	CD5+/CD20-:	24%
CD23:	60%		
SIg kappa:	73% (weak)		
SIg lambda:	<1%		

MISC.		NK-CELLS	
CD34:	<1%	CD16+/CD3-:	5%
		CD56+/CD3-:	5%

Chronic lymphocytic leukaemia - diagnosis

- Most commonly diagnosed after FBC performed either as “routine” or for “nonspecific” symptoms such as fatigue, sweats
- FBC shows elevated lymphocyte count
  - +/- other cytopenias (anaemia, thrombocytopenia), due to marrow infiltration, splenomegaly and/or immune destruction
- Abnormal circulating lymphocytes are **monoclonal B-cells** that have a characteristic profile of cell surface markers that can be identified by **flow cytometry** (“lymphoid marker studies”)
  - Consider this test if a patient has a persistent lymphocytosis not explained by other conditions (esp infection, inflammatory conditions, smoking)
  - And especially if associated with lymphadenopathy, splenomegaly, or other count abnormalities
- In contrast, reactive lymphocytosis is usually **polyclonal** and predominantly **T-cell**

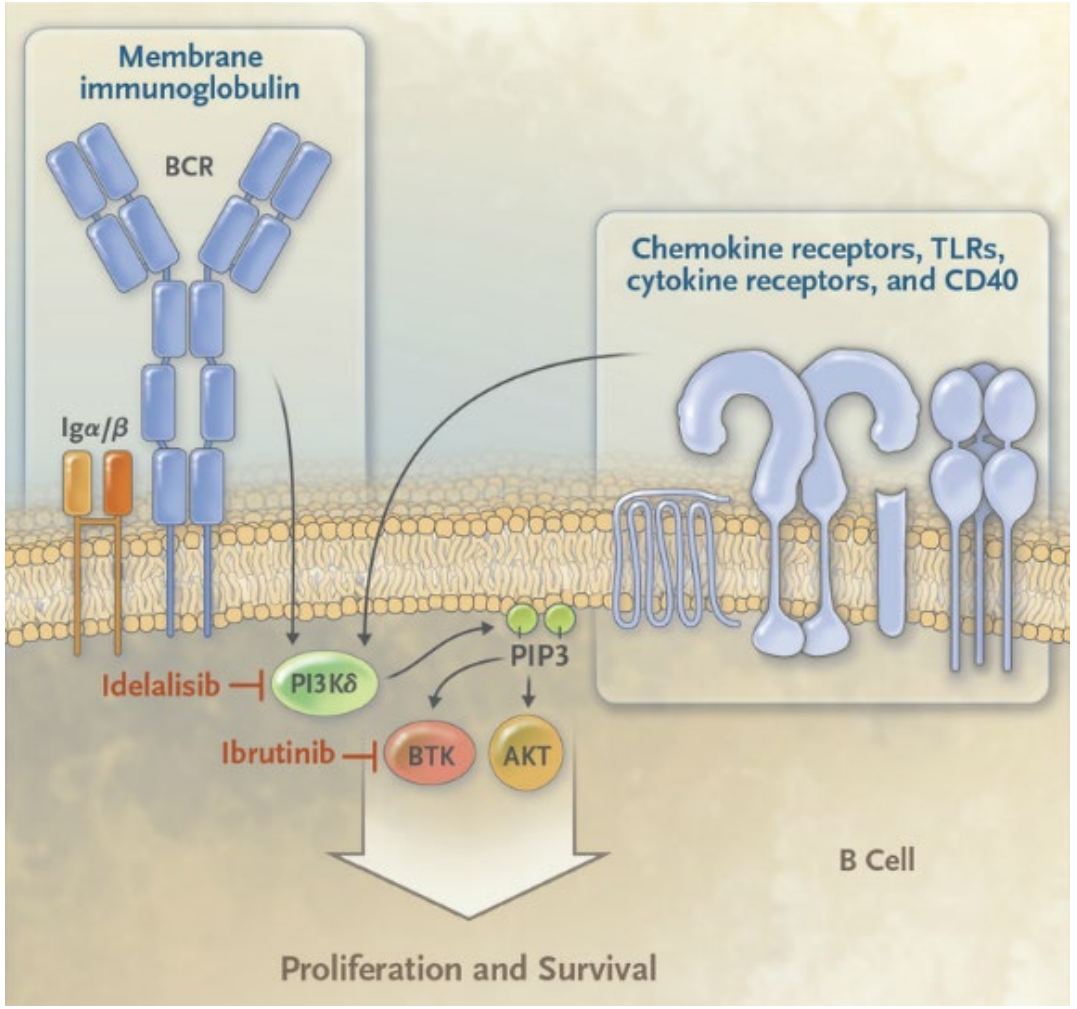
CLL – indications for treatment

- Regarded as incurable = treatment reserved for patients who have “symptomatic” disease
  - Progressive Lymphadenopathy / mass
  - Symptomatic splenomegaly
  - Bone marrow failure -> anaemia, thrombocytopenia
  - Constitutional symptoms (fevers, sweats, weight loss)
- Existing standard treatments combine chemotherapy drugs (fludarabine, chlorambucil) with an anti-CD20 antibody (rituximab, obinutuzumab, ofatumumab)
  - Infection risk (including PCP, shingles, bacterial infections)
  - Skin cancers ++ with fludarabine, rituximab

Novel agents for CLL

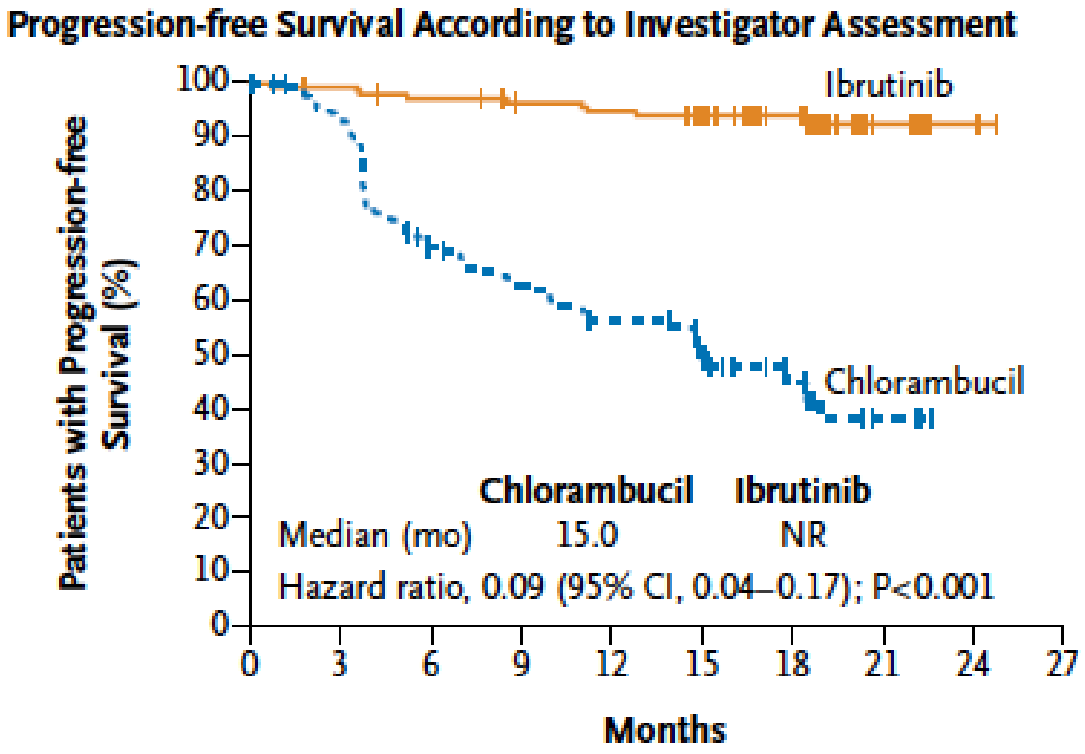
- Ibrutinib: BTK inhibitor
- Idelalisib: PI3Kδ inhibitor

- Both agents are active in a range of lymphoid malignancies including CLL, mantle cell and follicular lymphoma
- Impressive activity in high-risk disease (ie 17p deletion and/or fludarabine-refractory)



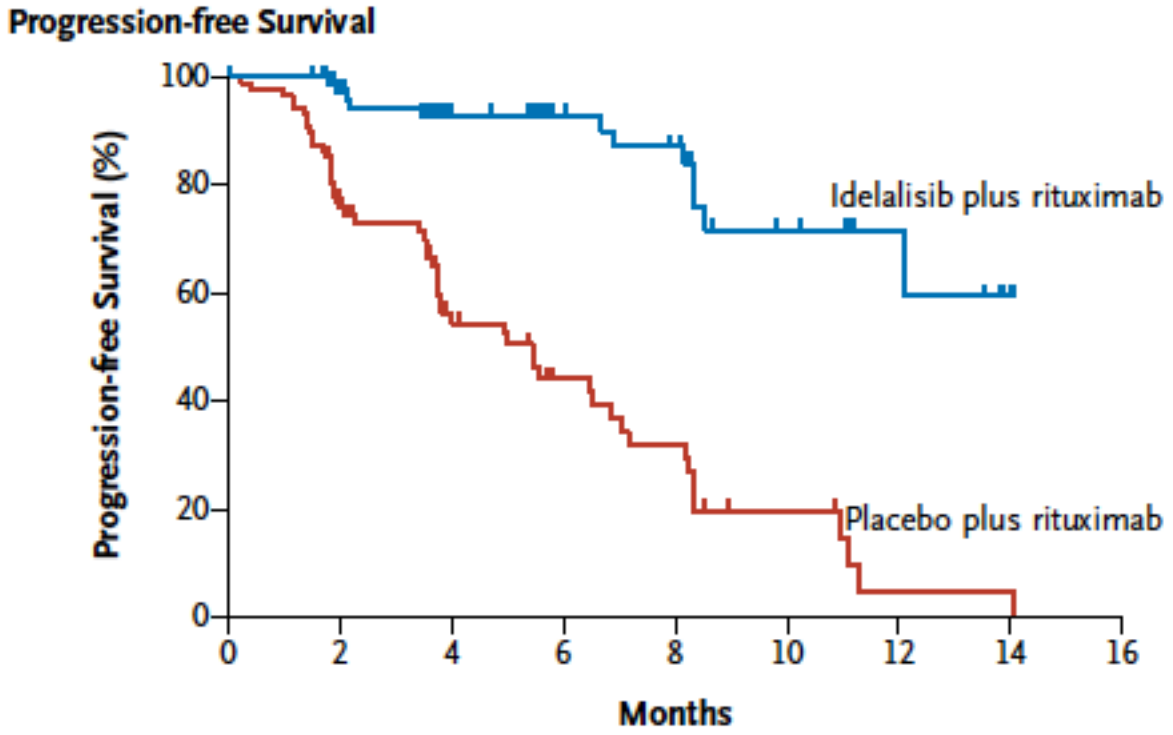
Ibrutinib (“Imbruvica”) –specific issues

- Increased bleeding, especially gastrointestinal
  - Patients on warfarin not allowed to participate in clinic trials
- Atrial fibrillation
- Cytopenias
- Interactions with other drugs via CYP3A4 metabolic pathway



Idelalisib: specific issues

- Pneumonitis
  - Prophlaxis against Pneumocystis (with Bactrim) and monitoring for CMV is strongly recommended
- Colitis
  - Can result in profuse, watery diarrhoea that can be life threatening of not identified
  - Often “late” after commencement of therapy (not infreq > 12 months)
  - Treatment is with steroids +/- drug cessation



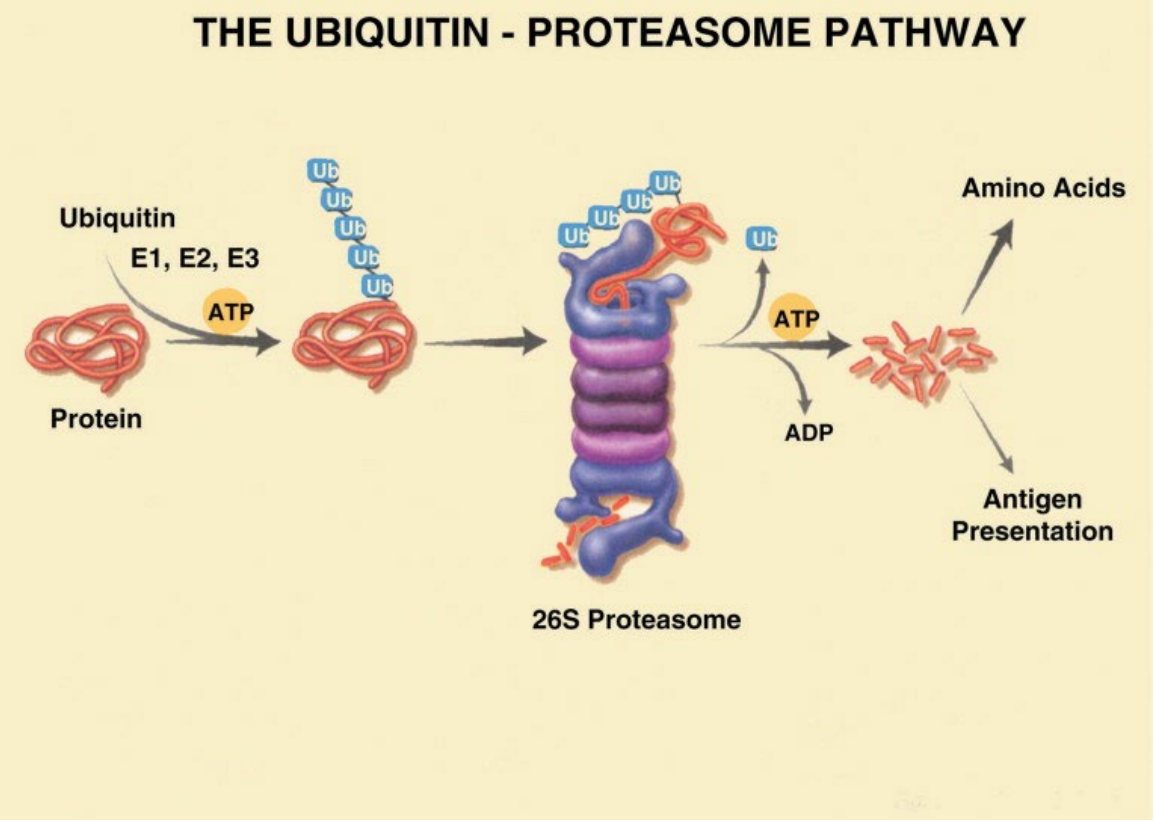
Conclusion

- Increasing number of orally-active therapies for common haematological malignancies, many with unique/distinct side-effect profiles
- Role of primary care practitioners in co-managing these patients is expanding:
  - Blood test monitoring
  - Adverse event surveillance
  - Preventative health issues
  - Cardiovascular risk factor management
- As always, don’t hesitate to contact the haematologist if you’re unsure or need advice

Proteasome inhibitors

- Unique mechanism of action
- Bortezomib:
  - Subcutaneous, once-twice weekly
  - Well-tolerated
  - Less neurotoxicity than IV administration
- Carfilzomib:
  - Second generation
  - Intravenous, 2 days/week
  - 5% risk of cardiac dysfunction

VZV prophylaxis with valaciclovir is recommended due to reactivation rates ~16% in clinical trials



Monoclonal antibodies

- Various agents in development
  - Anti-CD38: daratumumab, isatuximab
  - Anti-SLAMF7: elotuzumab
- The “Mabthera of myeloma”
- Most effective when used in combination with lenalidomide or bortezomib backbone
- All require IV administration and have significant risk of infusion reactions