

# Drug Therapy in Multiple Myeloma

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# About McKesson



80 000+ Employees



Operations in 16 Countries



Founded in 1833



15 000+ Canadian Pharmacies



1/3 of all drugs in North America



Fortune 8 Company

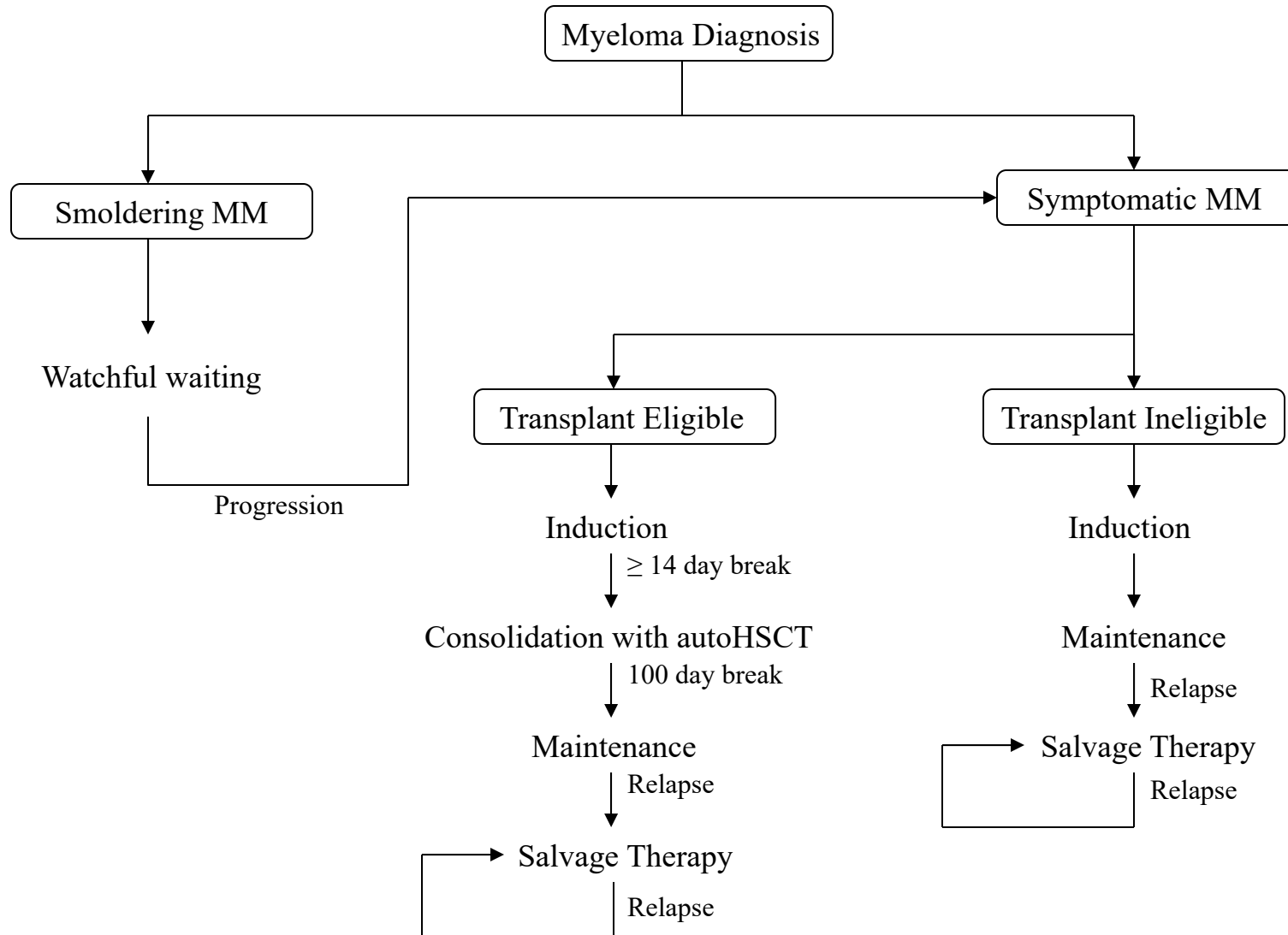


\$29 Billion USD Market Cap



McKesson Specialty Pharmacy

# General Treatment Algorithm for Multiple Myeloma



# Options for Induction Therapy in Transplant Eligible Patients

Protocol	Regimen	CCO	Covered
DEXA	Dexamethasone (high dose)	N	Y
VAD	Vincristine + dexamethasone + doxorubicin	Y	?
BORT	Bortezomib + dexamethasone	N	Y
CyBorD	Bortezomib + dexamethasone + cyclophosphamide	Y	Y
BORTDEXALENA	Bortezomib + dexamethasone + lenalidomide	N	N
	Bortezomib + dexamethasone + doxorubicin	N	N
DEXALENA	Lenalidomide + dexamethasone	N	N
	Daratumumab + bortezomib + dexamethasone + lenalidomide	N	N
	Daratumumab + bortezomib + dexamethasone + thalidomide	N	N
CARFDEXALENA	Carfilzomib + dexamethasone + lenalidomide	N	N
	Cyclophosphamide + dexamethasone + lenalidomide	N	N

Legend:

Commonly used in Ontario

Leading Edge (Not yet publicly covered in Ontario, used in USA)

Not Commonly Used

# Options for Induction Therapy in Transplant Ineligible Patients

Protocol	Regimen	CCO	Covered
BMP	Bortezomib + melphalan + prednisone	Y	Y
DEXALENA	Dexamethasone + lenalidomide	Y	Y
MELPPRED	Melphalan + prednisone	Y	Y
MPT	Melphalan + prednisone + thalidomide ( $\geq 65$ years old)	Y	Y
BORTDEXALENA	Bortezomib + dexamethasone + lenalidomide	Y	N
	Cyclophosphamide + dexamethasone + lenalidomide	N	N
DARADEXALENA	Daratumumab + dexamethasone + lenalidomide	N	N
	Daratumumab + bortezomib + melphalan + prednisone	N	N
CYCLDEXALENA	Cyclophosphamide + dexamethasone + lenalidomide	Y	N
DEXA	Dexamethasone	N	Y
VAD	Vincristine + dexamethasone + doxorubicin	Y	?

Legend:

Commonly used in Ontario

Leading Edge (Not yet publicly covered in Ontario, used in USA)

# Options for Maintenance Therapy after Stem Cell Transplant

Protocol	Regimen	CCO	Covered
LENA (MNT)	Lenalidomide	Y	Y
BORT (MNT)	Bortezomib	Y	N
IXAZ	Ixazomib	Y	N

Legend:

Commonly used in Ontario

Not Commonly Used in Ontario

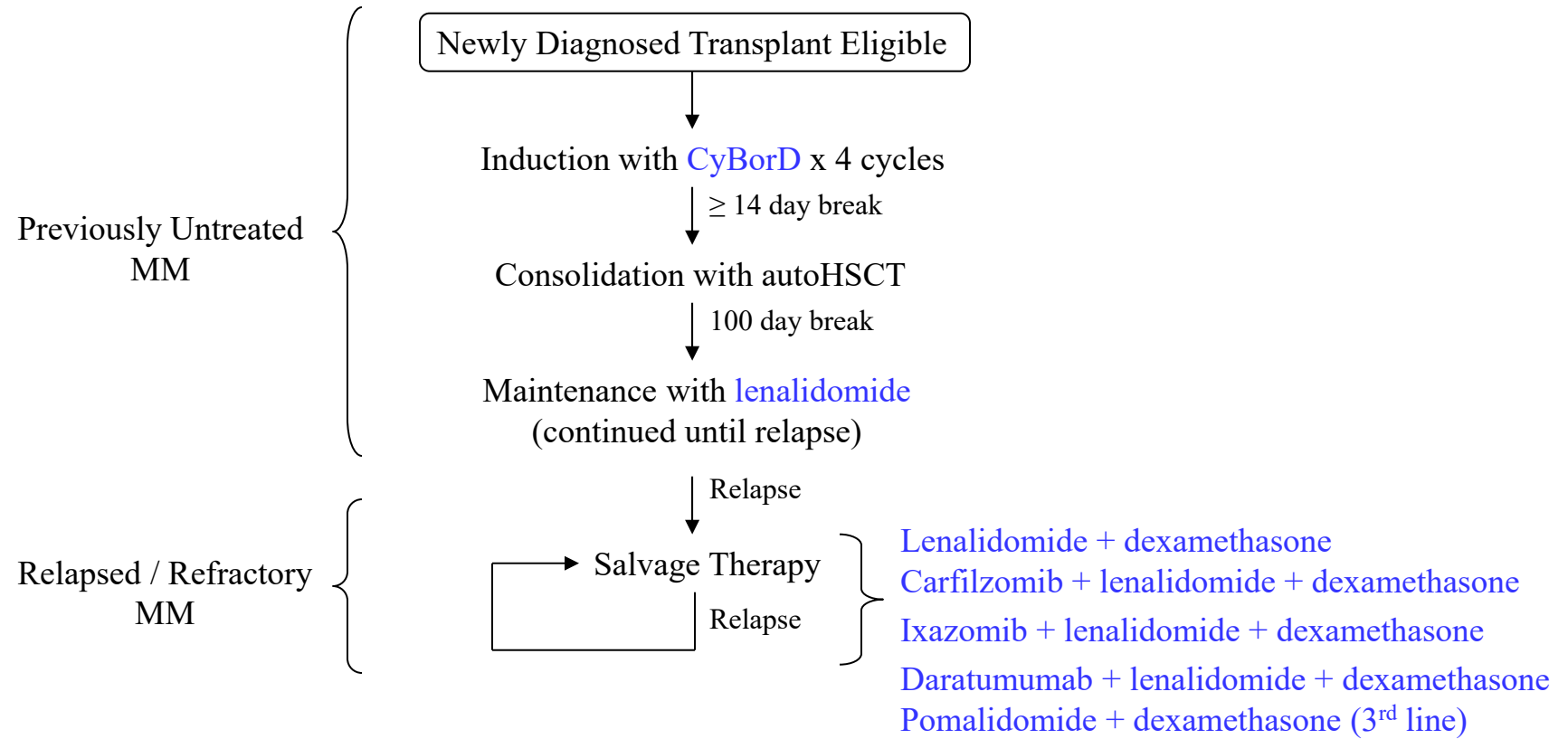
## Options for Relapsed or Refractory MM (Salvage Therapy)

Protocol	Regimen	CCO	Covered
BORT	Bortezomib, bortezomib + dexamethasone	Y	Y
BORTDEXADARA	Bortezomib + dexamethasone + daratumumab	Y	Y
CARFDEXA	Carfilzomib + dexamethasone	Y	Y
CARFDEXALENA	Carfilzomib + dexamethasone + lenalidomide	Y	Y
CyBorP	Cyclophosphamide + bortezomib + prednisone	Y	Y
DARADEXALENA	Daratumumab + dexamethasone + lenalidomide	Y	Y
DEXA(PO)	Dexamethasone	Y	Y
DEXALENA	Dexamethasone + lenalidomide	Y	Y
DEXAPOMA	Dexamethasone + pomalidomide (3 <sup>rd</sup> line only)	Y	Y
BORTDEXAPOMA	Bortezomib + dexamethasone + pomalidomide	Y	N
CARF	Carfilzomib (3 <sup>rd</sup> line)	Y	N
CYCLDEXAPOMA	Cyclophosphamide + dexamethasone + pomalidomide (3 <sup>rd</sup> line only)	Y	N
DARA	Daratumumab (3 <sup>rd</sup> line only)	Y	N
DEXAIXAZLENA	Dexamethasone + ixazomib + lenalidomide	Y	N
THAL	Thalidomide	Y	N
CyBorD	Cyclophosphamide + bortezomib + dexamethasone	N	Y
	Cyclophosphamide + prednisone	N	Y
autoHSCT	Second Stem Cell Transplant (if ≥ 18-24 months from 1 <sup>st</sup> )		

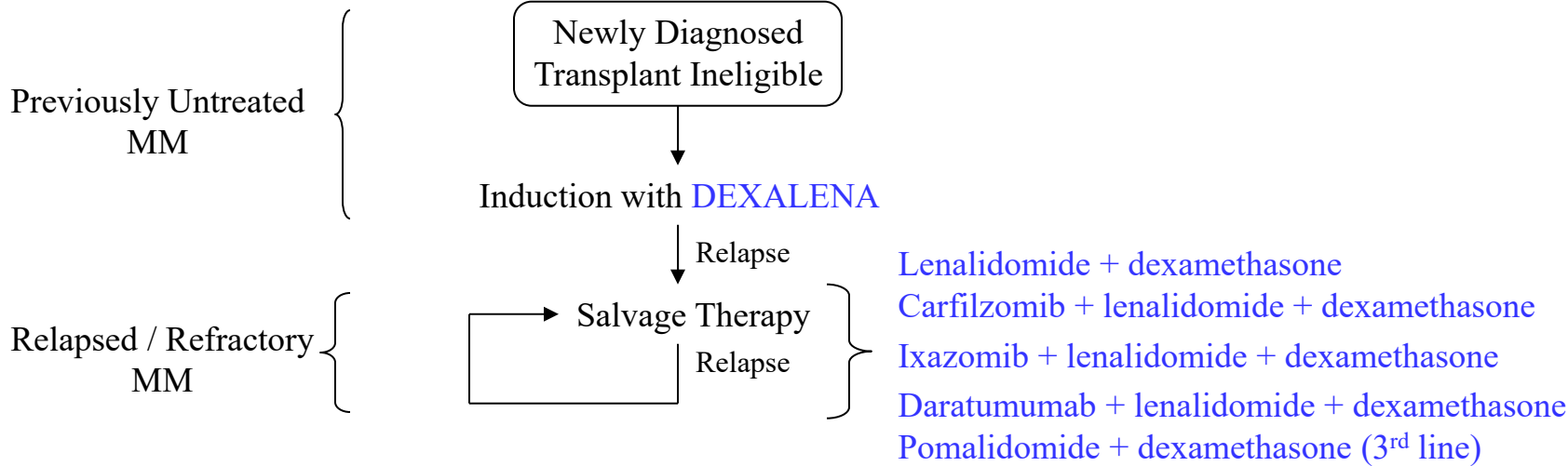
Legend: [Commonly used in Ontario](#)



# Common Treatment Algorithm for Transplant Eligible Patients



# Common Treatment Algorithm for Transplant Ineligible Patients



# Immunomodulatory Drugs (IMiDs)

lenalidomide (Revlimid)



pomalidomide (Pomalyst)

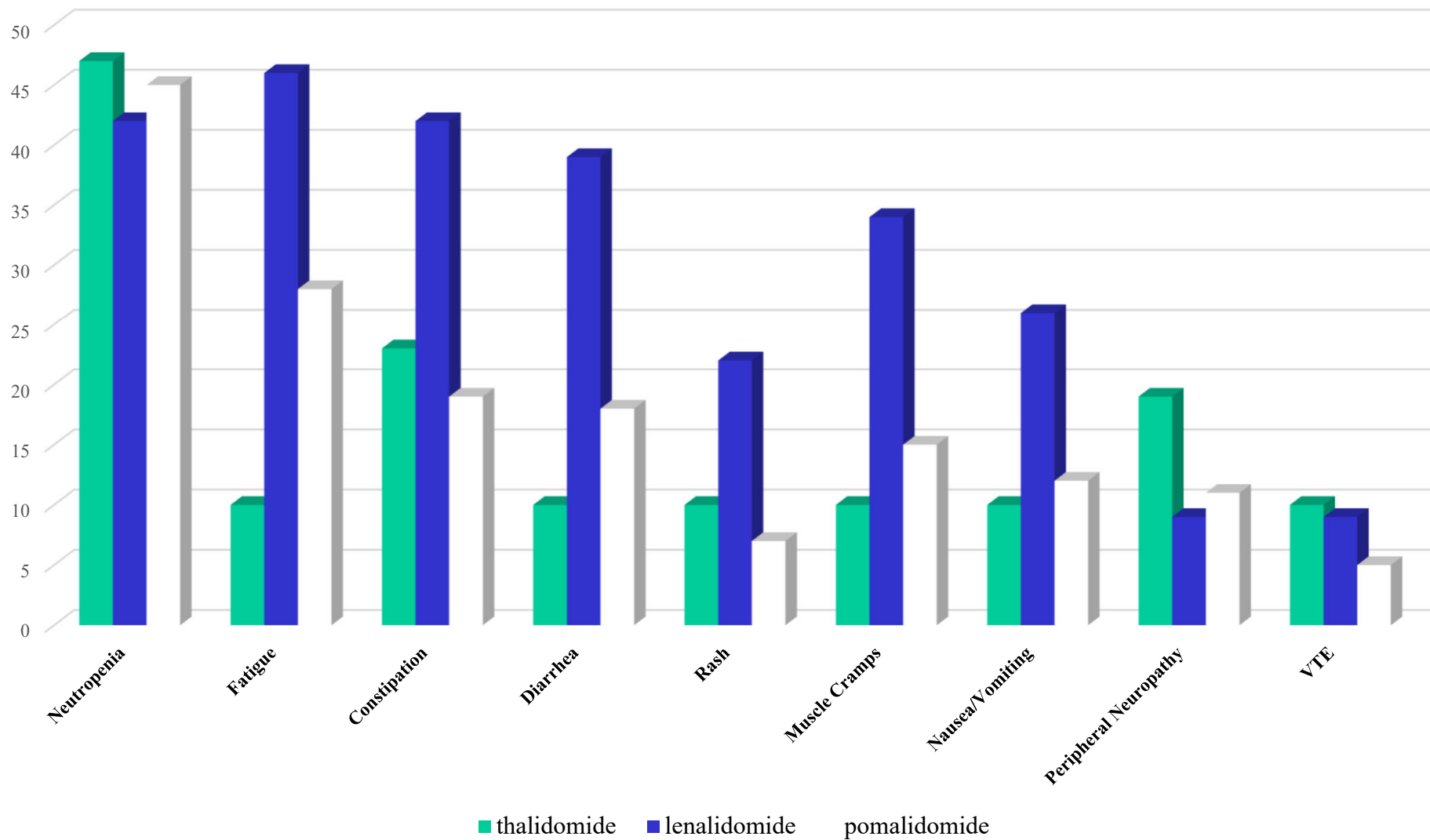


(Capsules shown are not actual size)

thalidomide (Thalomid)



# Common IMiD Side Effects



# Phocomelia

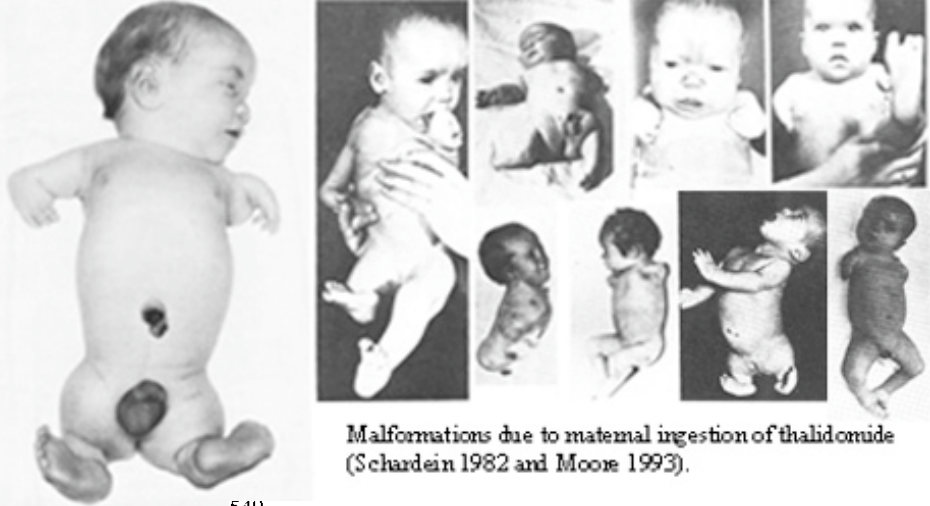
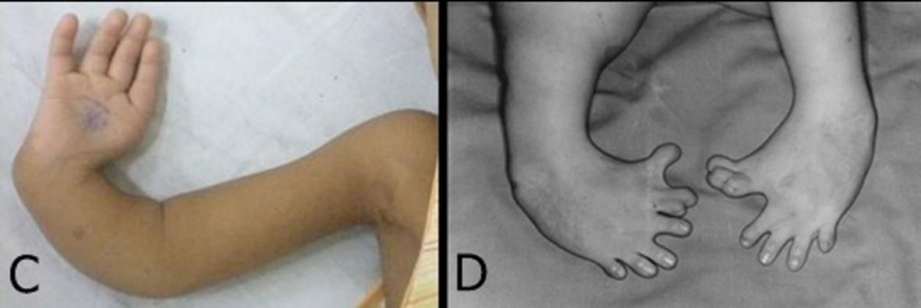
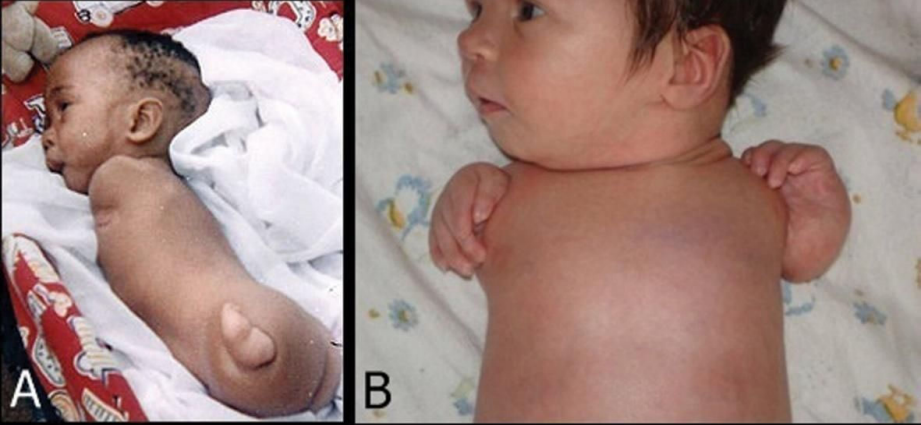
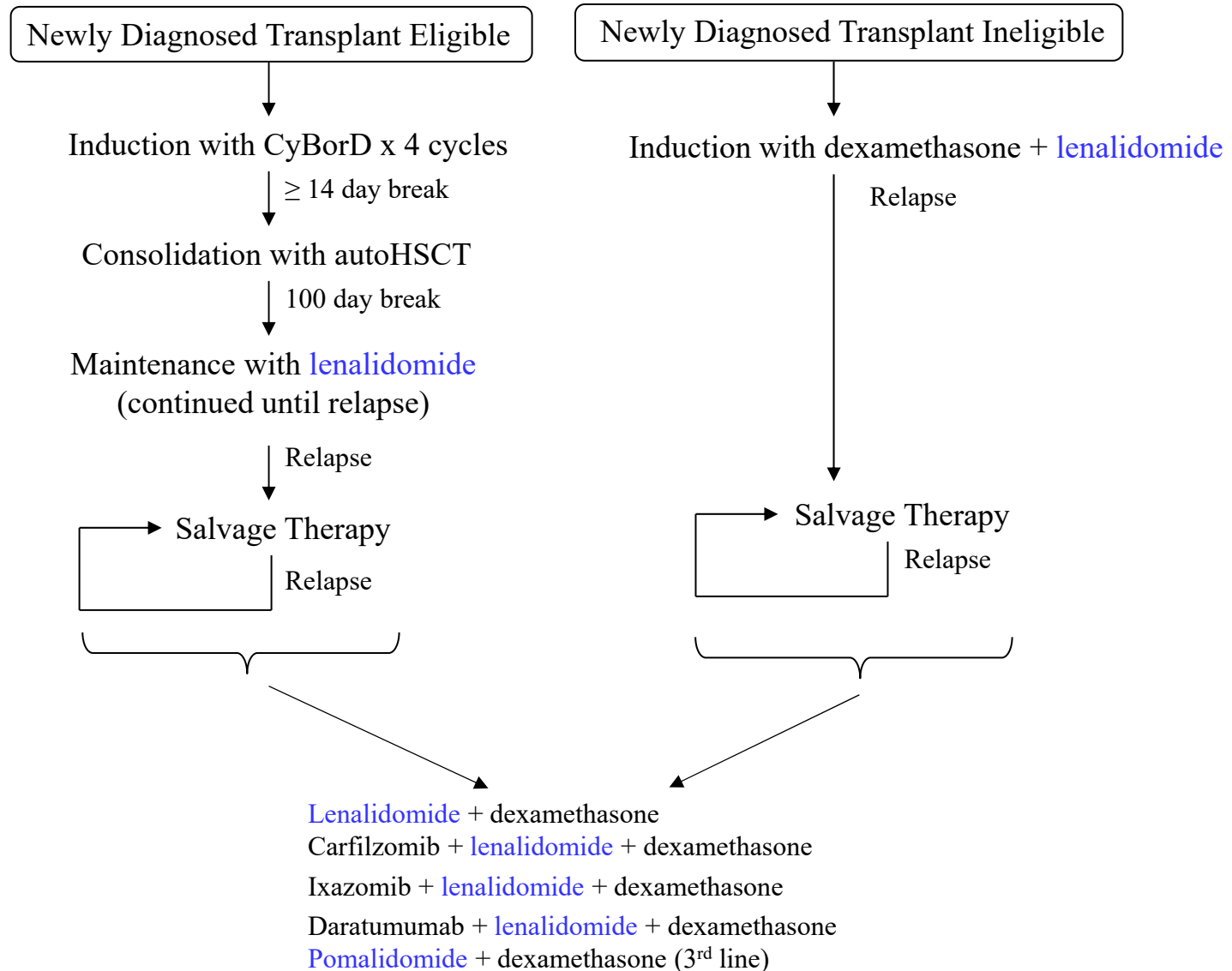


Fig 1 Patient 2 at birth; note phocomelia of both lo

## Differences Between Immunomodulatory Drugs (IMiDs)

	<b>thalidomide</b>	<b>lenalidomide</b>	<b>pomalidomide</b>
U.S. Approval	1998	2006	2013
Canadian Approval	1961	2008	2014
Strengths	50, 100, 200 mg	2.5, 5, 10, 15, 20, 25 mg	1, 2, 3, 4 mg
Monthly Cost	\$970 - \$3 890	\$7 711 - \$9 616	\$11 340
Lifestyle Interactions	Alcohol		Smoking
Drug Interactions	Estrogens, EPO, Neurotoxins (lithium, vincristine, cisplatin, bortezomib), Sedatives, Beta-Blockers, donepezil	Estrogens, EPO, Digoxin	Estrogens, EPO, ciprofloxacin, fluvoxamine, montelukast
Dose Adjustments		Kidney	Liver

# Common Regimens that Use IMiD's



## LENA(MNT)

Indication: Maintenance after stem cell transplant (post autoHSCT)  
Duration of Treatment: Until progression or unacceptable toxicity  
Cycle Length: 28 days (continuously)

<u>lenalidomide</u>	10* mg	PO	Daily
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## DEXALENA

Usage: 1<sup>st</sup> Line for Transplant Ineligible Patients, Treatment of relapsed/refractory MM  
Duration of Treatment: Until progression or unacceptable toxicity  
Cycle Length: 28 days

<u>lenalidomide</u>	25 mg	PO	Days 1 to 21
dexamethasone	40* mg	PO	Days 1, 8, 15, 22*

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## DEXAPOMA

Usage: Treatment of relapsed/refractory MM after failing both bortezomib and lenalidomide  
Duration of Treatment: Until progression or unacceptable toxicity  
Cycle Length: 28 days

<u>pomalidomide</u>	4 mg	PO daily	Days 1 to 21
dexamethasone	40 mg	PO	Days 1, 8, 15 and 22

(Decrease dexamethasone dose to 20 mg Days 1, 8, 15, 22 in patients > 75 years old)



# Proteasome Inhibitors

bortezomib (Velcade)



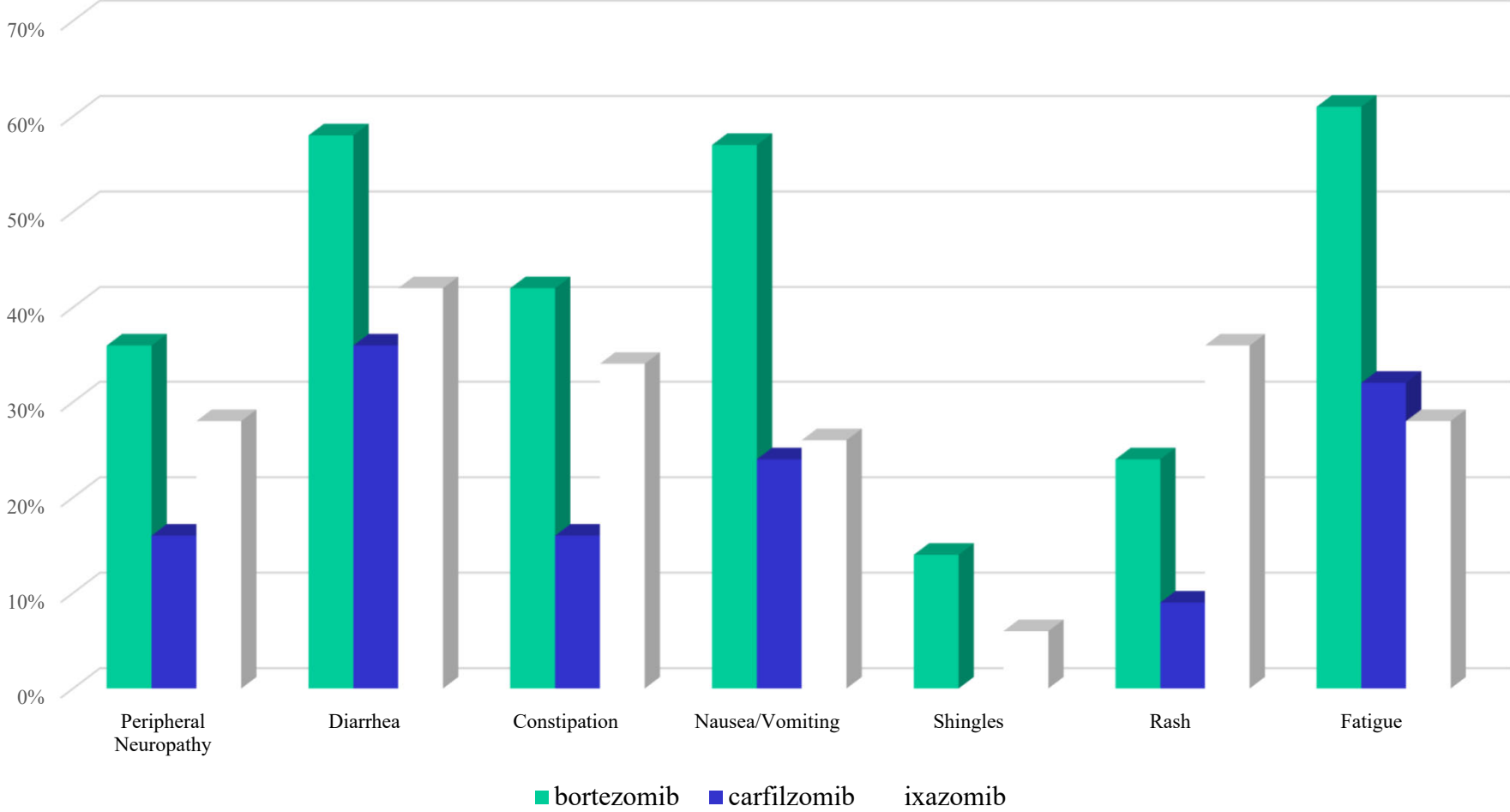
carfilzomib (Kyprolis)



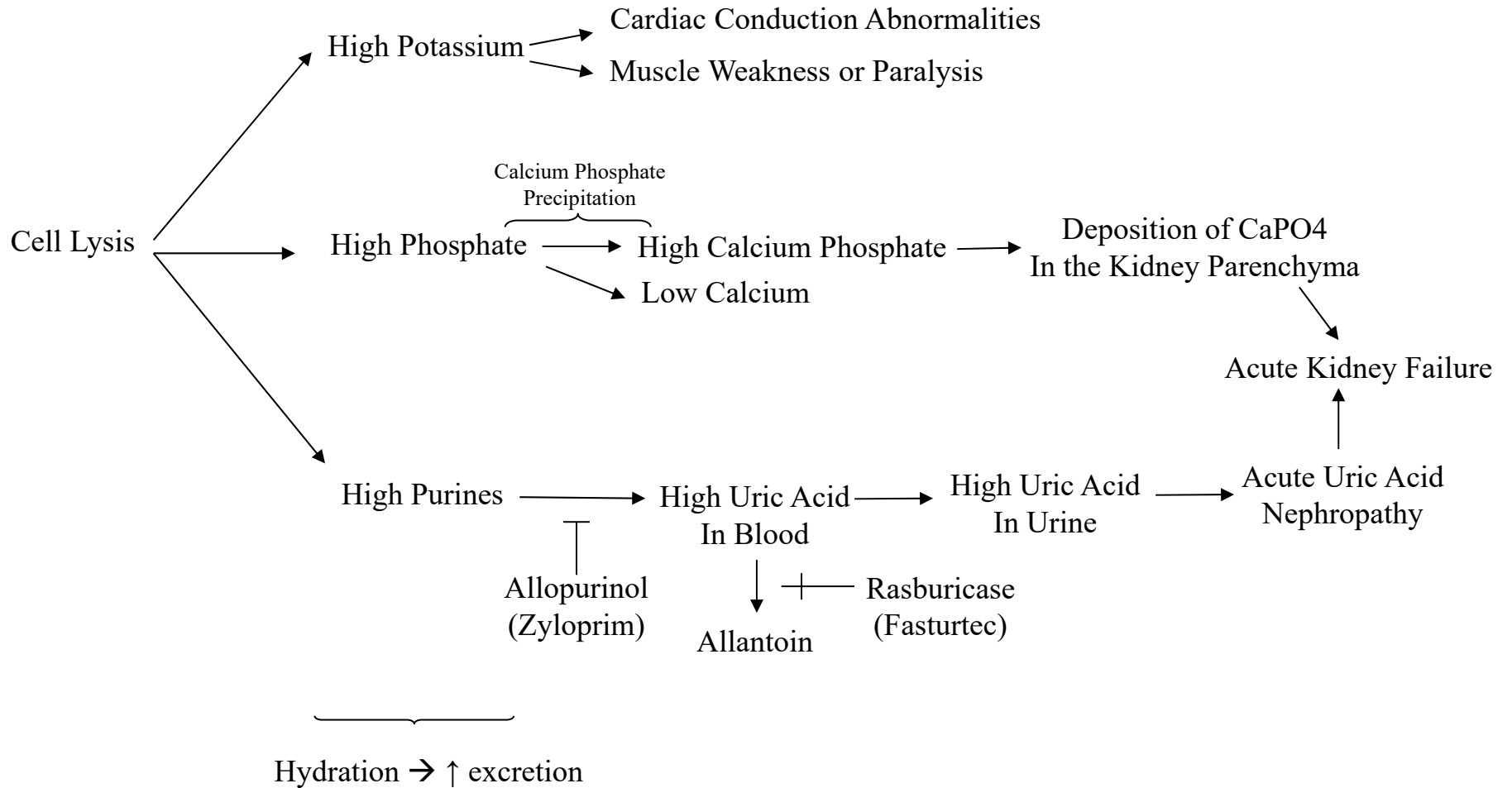
ixazomib (Ninlaro)



# Common Proteasome Inhibitor Side Effects



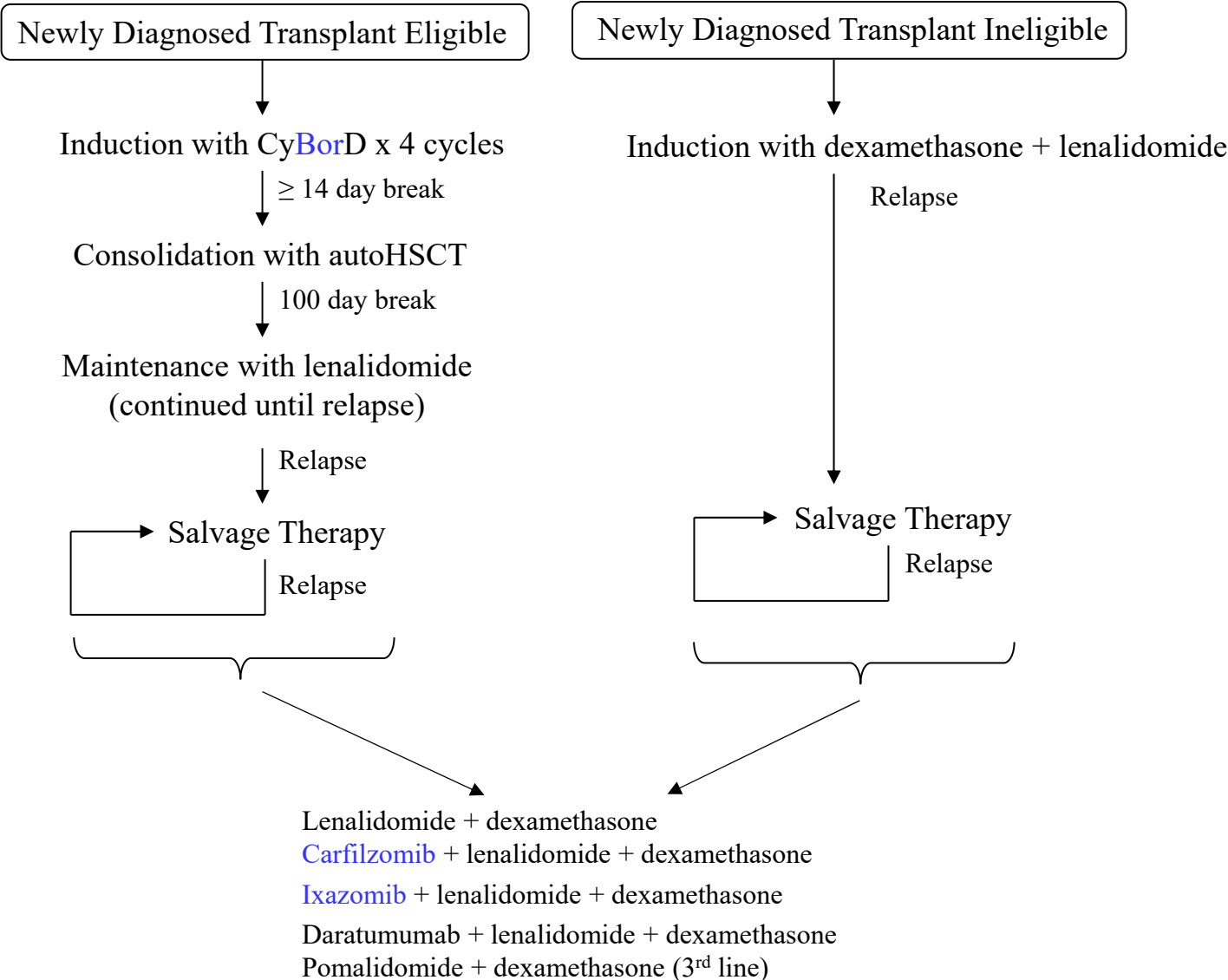
# Tumour Lysis Syndrome (TLS)



## Differences Between Proteasome Inhibitors

	<b>Bortezomib</b>	<b>Carfilzomib</b>	<b>Ixazomib</b>
U.S. Approval	2003	2012	2015
Canadian Approval	2005	2016	2016
Administration	SC or IV	IV	Oral
Manufacturer	Janssen Inc.	Amgen	Takeda Canada Inc.
Strengths	3.5 mg/vial	60 mg/vial	2.3, 3, 4 mg
Cost	\$1973/vial (brand)	\$1618/vial	\$9 383/month
Unique Side Effects	Injection site reactions (sc)	Cardiotoxicity, Pulmonary Toxicity, PRES, renal failure, IRR's, TLS	Eye Disorders
Drug Interactions	CYP3A4 Substrate (avoid strong inducers such as rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort, caution with strong inhibitors such as ketoconazole and ritonavir) Vitamin C, Green Tea	Oral Contraceptives, digoxin	Phenytoin, carbamazepine, St. John's Wort
Dose Adjustments	Liver	Liver	Liver, Kidney

# Common Regimens that Use Proteasome Inhibitors



# CyBorD

Indication: Induction for transplant eligible patients  
Duration of Treatment: 4 cycles  
Cycle Length: 28 days

## ONCE WEEKLY TREATMENT: cycle length 28 days

Drug	Dose	BCCA Administration Guideline
bortezomib	1.5 mg/m <sup>2</sup> (may start with 1.3 mg/m <sup>2</sup> ) on days 1, 8, 15, 22 of each cycle	SC*, ** (abdomen or thigh)***  <b>OR</b>  IV push over 3-5 seconds
<b><u>If using:</u></b> cyclophosphamide	300 mg/m <sup>2</sup> /day on days 1, 8, 15, 22****	PO
dexamethasone	Cycle 1 & 2: 40 mg on days 1-4, 9-12, 17-20  Cycle 3 & 4: 40 mg on days 1, 8, 15, 22	PO, in the morning with food

$$BSA = \sqrt{\frac{W \times H}{3600}}$$

# CARFDEXALENA

Usage: Treatment of relapsed/refractory MM after failing 1-3 prior lines of therapy

Duration of Treatment: Until progression or unacceptable toxicity

Cycle Length: 28 days

Why: Median PFS of 26.3 months vs. 17.6 months on LENADEXA, n=792 (Stewart, 2015)

All Cycles:

dexamethasone	40* mg /day	IV / PO	Days 1, 8, 15, 22
<u>lenalidomide</u>	25** mg /day	PO	Days 1 to 21

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Cycle 1:

<u>carfilzomib</u>	20 mg /m <sup>2</sup>	IV	Days 1, 2
<u>carfilzomib</u>	27 mg /m <sup>2</sup>	IV	Days 8, 9, 15, 16

Cycles 2 to 12:

<u>carfilzomib</u>	27 mg /m <sup>2</sup>	IV	Days 1, 2, 8, 9, 15, 16
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Cycles 13 to 18#:

<u>carfilzomib</u>	27 mg /m <sup>2</sup>	IV	Days 1, 2, 15, 16
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Cycle 19 onwards#: No more carfilzomib

# DEXAIXAZLENA

Usage: Treatment of relapsed/refractory MM after failing at least one prior therapy

Duration of Treatment: Until progression or unacceptable toxicity

Cycle Length: 28 days

Why: Median PFS of 20.6 months vs. 14.7 months on LENADEXA, n=722 (Moreau, April 2016)

[ixazomib](#)

4 mg

PO

once a week on Days  
1, 8, and 15

(available as 2.3 mg, 3 mg, and 4 mg capsules)

[lenalidomide](#)<sup>1</sup>

25 mg

PO

once daily on Days 1  
to 21

(available as 5 mg, 10 mg, 15 mg, and 25 mg capsules)

dexamethasone

40 mg

PO

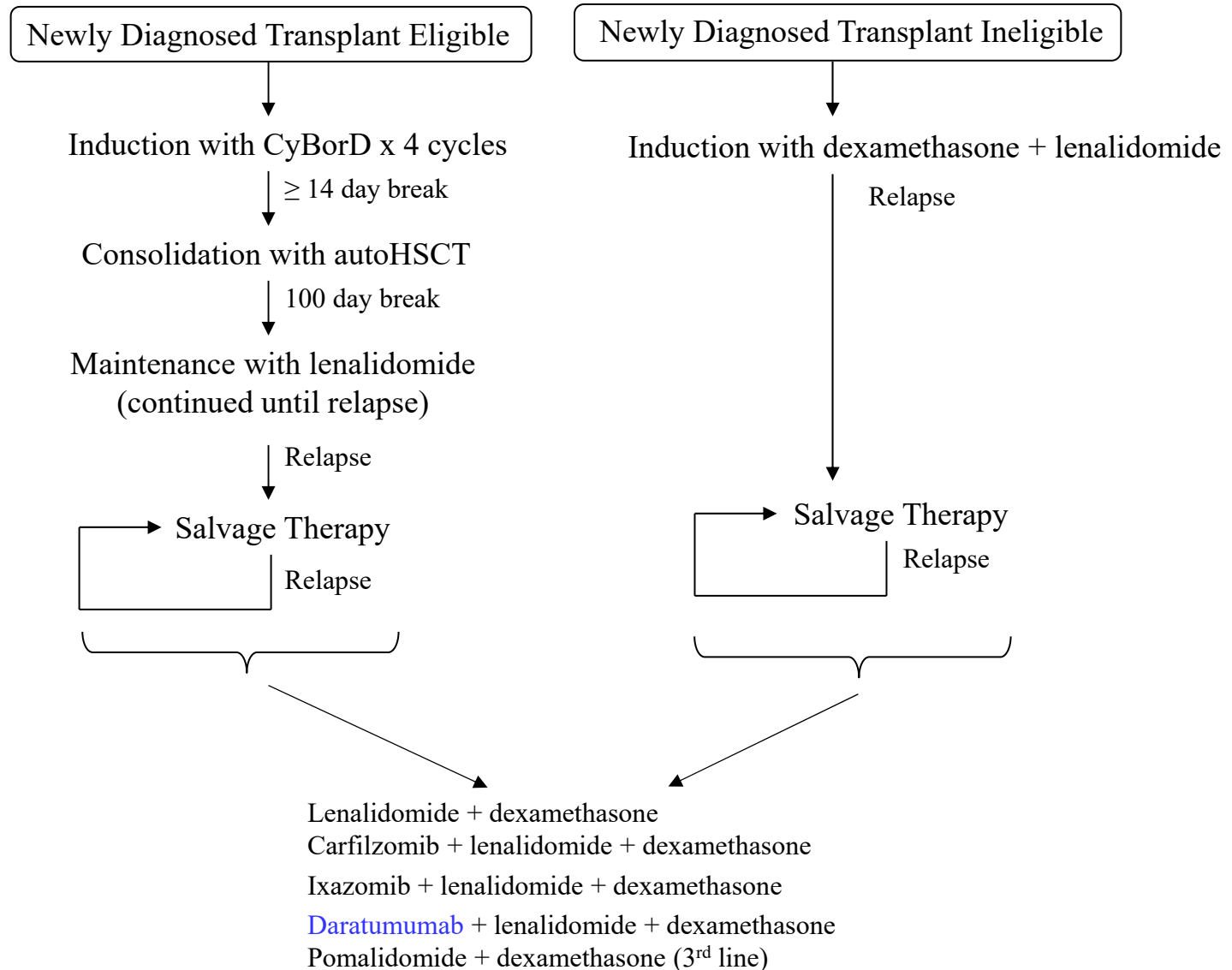
once a week on Days  
1, 8, 15, and 22



# Biologic: Daratumumab (Darzalex)



# Common Regimens that Use Daratumumab



# DARADEXALENA

Usage: Treatment of relapsed/refractory MM after failing at least one prior therapy (and who did not fail on lenalidomide)

Duration of Treatment: Until progression or unacceptable toxicity

Cycle Length: 28 days

## Cycles 1 to 2:

<a href="#">daratumumab</a> <sup>1</sup>	16 mg /kg	IV	Days 1, 8, 15, 22
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## Cycles 3 to 6:

<a href="#">daratumumab</a> <sup>1</sup>	16 mg /kg	IV	Days 1 and 15
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## Cycle 7 and beyond:

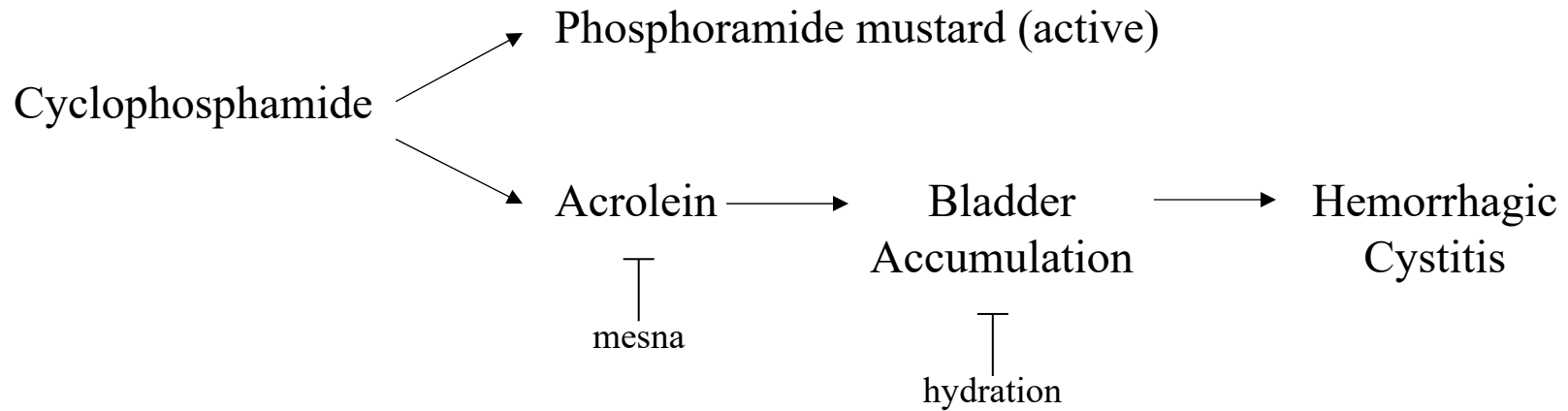
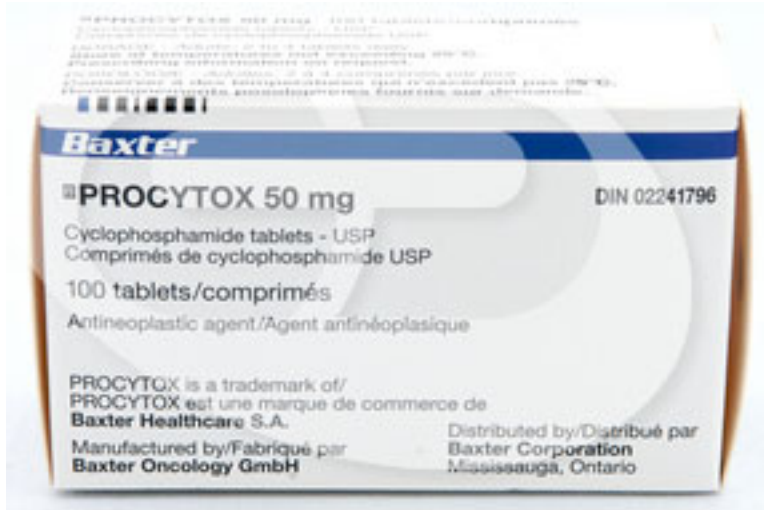
<a href="#">daratumumab</a> <sup>1</sup>	16 mg /kg	IV	Day 1
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## During all cycles:

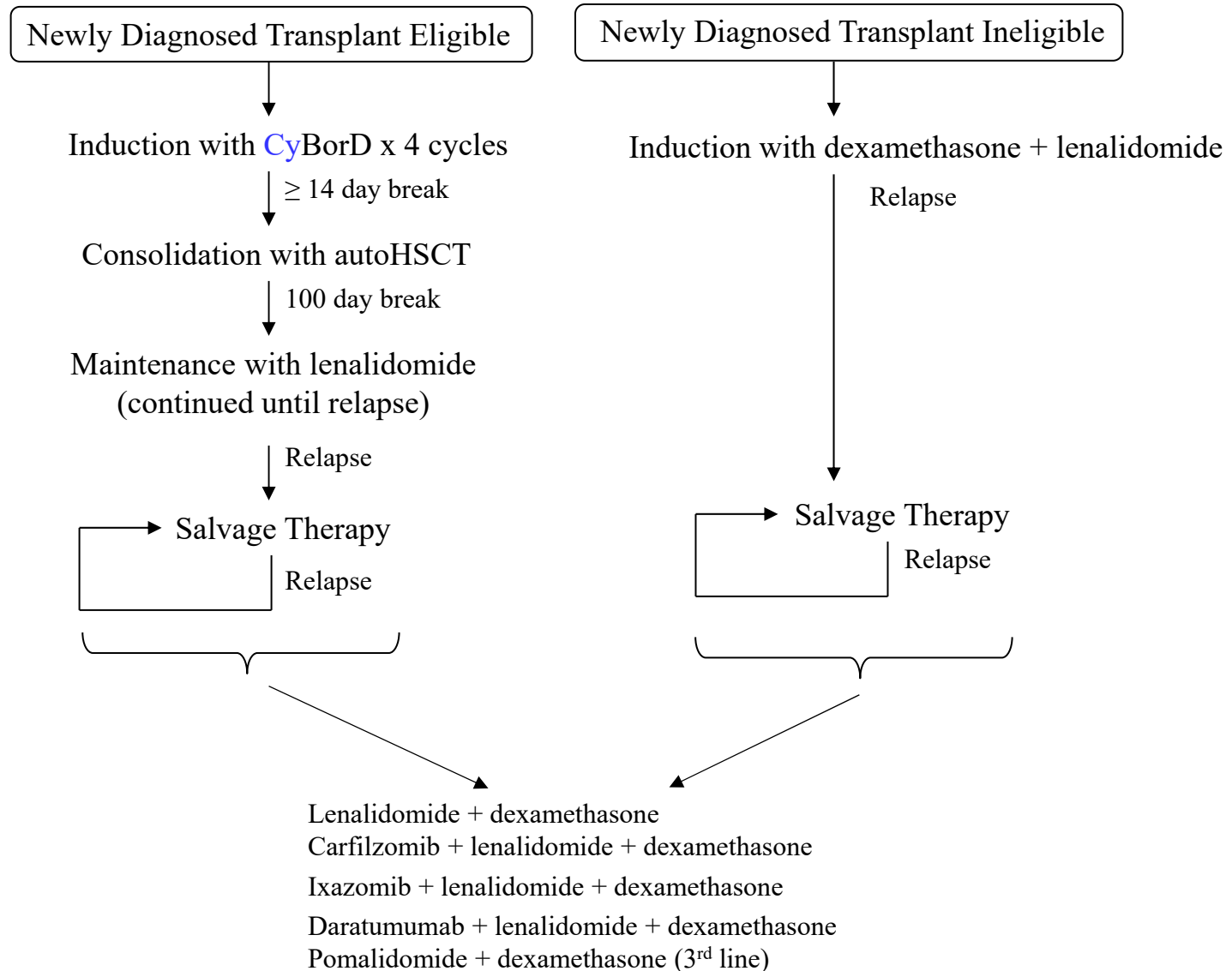
dexamethasone <sup>2</sup>	40* mg 20 mg before infusion and 20 mg day after infusion	PO	Days 1, 8, 15 and 22
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<a href="#">lenalidomide</a> <sup>3</sup>	25 mg	PO	Days 1 to 21
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# Cyclophosphamide (Procytox)



# Common Regimens that Use Cyclophosphamide



## Dexamethasone (Decadron)



# Supportive Medications

# Acetylsalicylic Acid (ASA, Aspirin)



Felix Hoffmann

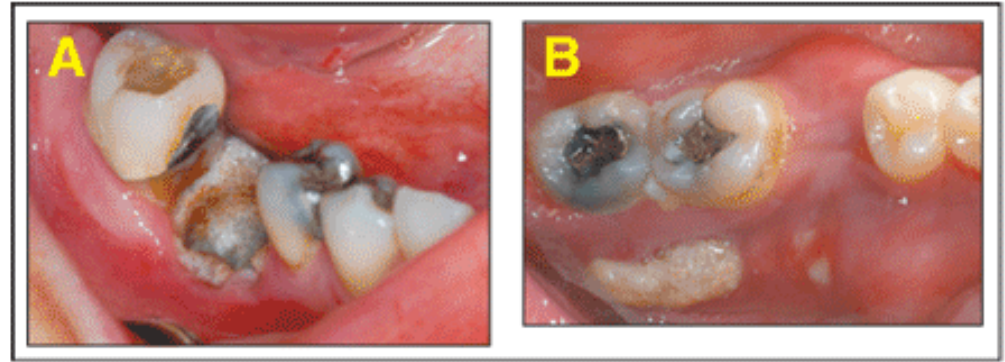




# Acyclovir (Zovirax)



# Pamidronate, Zoledronic Acid (Zometa) and Denosumab (Xgeva)



**Figure 1: Osteonecrosis of the Jaw Presents As Exposed Necrotic Bone—** It is seen in both the maxilla and mandible. Most cases are initiated by a dental extraction (A) but some occur spontaneously (B). The most common areas of spontaneous osteonecrosis of the jaw are areas where the mucosa is thin, such as the lingual posterior mandible.





# Drug Information



Government  
of Canada

Gouvernement  
du Canada

## Health Canada Drug Product Database

<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>

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Cancer Care Ontario

<https://www.cancercareontario.ca/en>



<http://www.bccancer.bc.ca/>

