



Standard and Novel Therapeutic Hematology Agents for the New Advanced Practice Provider

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Disclosures

- Nothing to disclose

Objectives

- Describe conventional chemotherapy treatment options in acute myeloid leukemia
- Identify targetable mutations for acute myeloid leukemia treatment
- Identify novel agents and drug classes for treatment of CLL
- Discuss conventional treatments for multiple myeloma and identify new drug classes available

	Historical period	Major discoveries in oncology
Ancient discoveries and theories of cancer	3000 B.C.	In Edwin Smith's papyrus the first case of human cancer is described
	1500 B.C.	Ebers' papyrus describes the tumors of the skin, uterus, stomach and rectum
	400 B.C.	Hippocrates proposes the first theory on the development of tumors
	130–200	Galen deepens the theory of Hippocrates, proposing that the excess of black bile causes incurable tumors while the excess of yellow bile causes treatable tumors
	300–400	Oribasius of Baghdad confirms that the tumors are caused by an excess of black bile
No significant progress in the study of tumors*,**	527–565	Aëtius of Amida introduces the treatment of breast tumors by amputation of the entire organ
	625–690	Paul of Aegina describes the tumors of the uterus and the surgical approach for the treatment of the bladder, the thyroid and the polypectomy of the nasal polyps
	860–932	Rhazes di Baghdad describes new treatments for tumors in the "De Chirurgia" manuscript.
	980–1037	Avicenna introduces the removal of tumors of the rectum
	1070–1162	Averroes of Cordoba describes the tumors of the esophagus and rectum and introduces the hysterectomy for the removal of uterine tumors
	1500	Paracelsus questions Hippocrates and Galen theories and hypothesizes that tumors develop due to an accumulation of "salts" in the blood
	1543	Andreas Vesalius published the manuscript "De Humani corporis fabrica" containing anatomical information resulting from post-mortem examinations
	1600	Doctors and surgeons propose that the coagulation and fermentation of blood and/or lymph are the cause of the development of tumors
	1600–1620	Invention of the microscope
	1700	Boerhaave hypothesizes that cancer is most likely induced by elements, present in water or in the ground, which defines viruses. It is theorized that chronic inflammation, injury, trauma and family predispositions can determine the development of tumors
	1760	Morgagni hypothesizes that cancer is related to pathological lesions of a particular organ
	1775	Perciaval Pott defines the association between scrotal cancer and exposure to soot in chimney sweeps
	1858	Rudolf Virchow identifies the origin of tumors in the altered cells
	1896	Wilhelm Conrad Röntgen discovers X-rays
Birth of radiotherapy	1896	Emil H. Grubbé uses X-rays to treat breast cancer
	1898	Marie and Pierre Curie discover the radiation emitted by the Radium
	1899	Marie and Pierre Curie suggest using X-rays to treat tumors
	1920	Birth of radiotherapy

*Hajdu, 2016; **Hajdu, 2017.



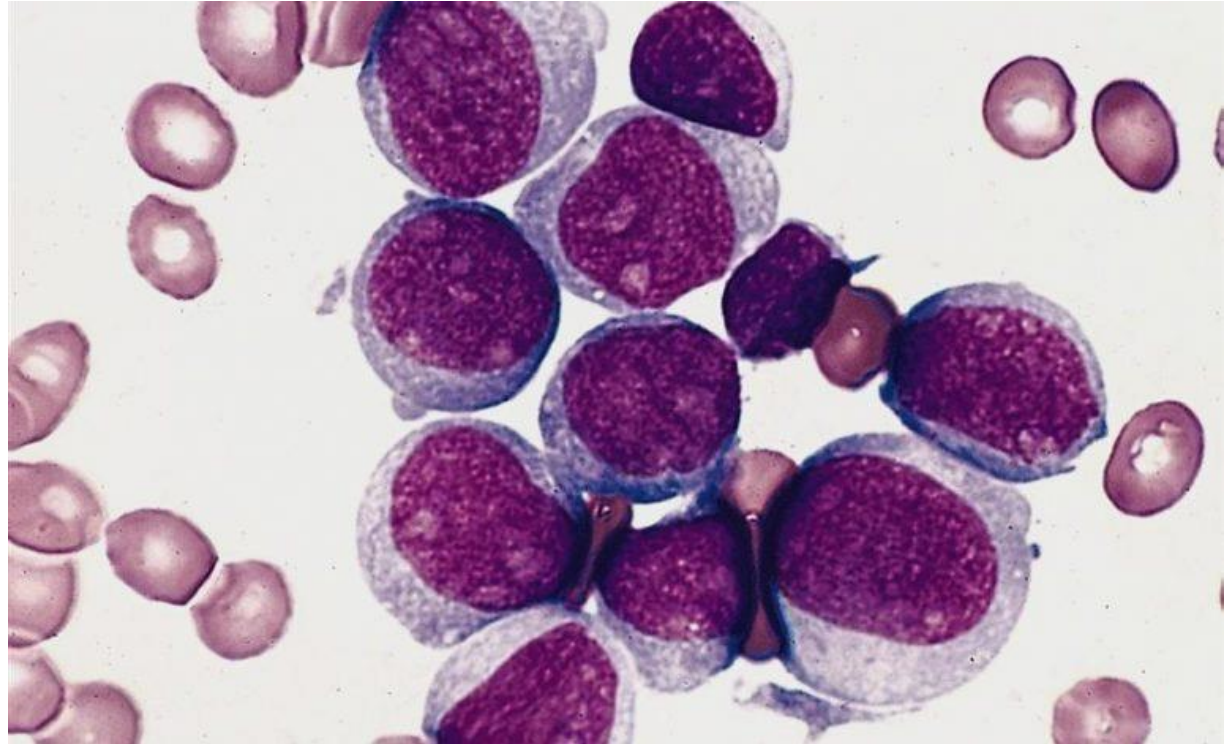
Sidney Farber
Father of Modern Chemotherapy

Cancer Treatment: Drug Therapy

- Chemotherapy
- Biologic Therapy: Immunotherapy
- Biologic Therapy: Targeted/ Directed Therapy
- Hormonal Therapy

“Systemic therapy without specificity is an indiscriminate bomb.”

- Siddhartha Mukherjee, *The Emperor of All Maladies*



Acute Myeloid Leukemia

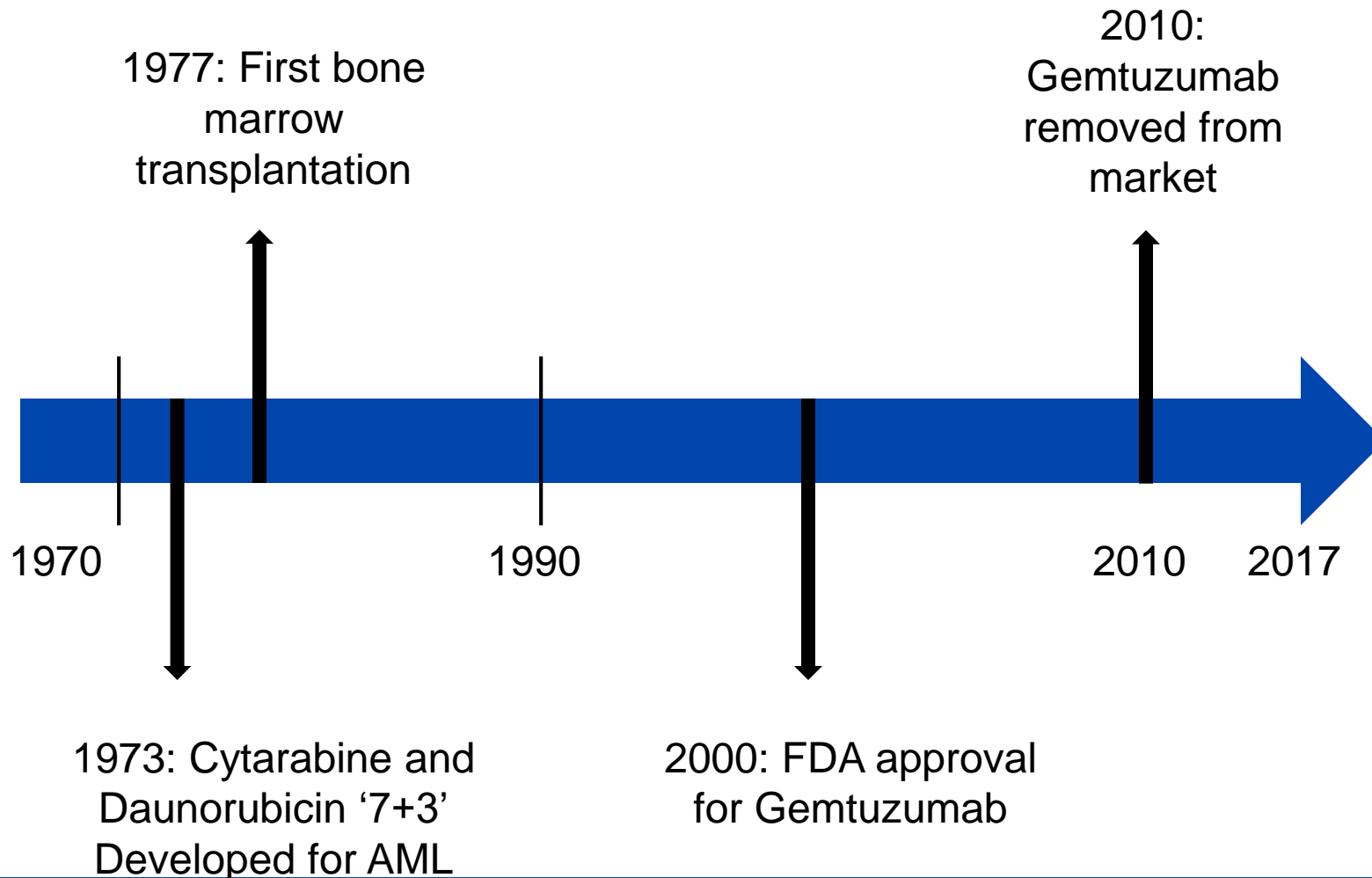
Conventional Therapies in AML

- Traditional cytotoxic therapies
 - Induction: '7+3' Daunorubicin and Cytarabine
 - Daunorubicin 60 or 90 mg/m² for 3 days together with cytarabine 100 mg/m² for 7 days
 - Toxicities: **myelosuppression, infection**
 - Post-remission therapy:
 - Consolidation: Cytarabine
 - Cytarabine twice daily at a 3 g/m² dose on days 1, 3, and 5
 - Allogenic stem cell transplant (HSCT)

Conventional Therapies in AML

- Refractory/Salvage regimens
- Objective is to 'bridge' patients to allogenic stem cell transplant.
 - MEC
 - FLAG or FLAG/Ida
 - CLAG-M
 - Carbo/Topotecan
- Treatment of older AML
 - Hypomethylating agents: Azacitadine or Decitabine
 - Low dose infusional cytarabine

FDA Approvals in AML



FDA Approvals in AML

2017

- Gemtuzumab ozogamicin (Mylotarg)
- Liposome-daunorubicin and cytarabine (Vyxeos)
- Enasidenib (Idhifa)
- Midostaurin (Rydapt)

2018

- Gilteritinib (Xospata)
- Glasdegib (Daurismo)
- Ivosidenib (Tibsovo)
- Venetoclax (Venclexta)

Novel Therapies in AML

- **Targeted therapies**
 - Enasidenib
 - Ivosidenib
 - Midostaurin
 - Gilteritinib
 - Glasdegib
 - Venetoclax
- **Therapy-related or MDS related AML**
 - Liposomal daunorubicin and cytarabine
- **Antibody-drug conjugate**
 - Gemtuzumab ozogamicin

Enasidenib

- **Indication:** Relapsed/Refractory (R/R) AML with **IDH2+** mutation
- **Dose:** 100 mg orally once daily until disease progression or unacceptable toxicity
- **Common side effects:** nausea, vomiting, diarrhea, hyperbilirubinemia and decreased appetite.
 - Black box warning for **Differentiation syndrome**
- Multicenter trial in 176 adult patients with RR IDH2+ AML
 - OR rate 40%, 19% achieved CR, with median response duration of 5.6 months.
 - Median OS was 9.3 months, in contrast to ~3 months with standard therapies

Ivosidenib

- **Indication:** Newly dx or R/R **IDH1+** AML in patients 75yrs + or comorbidities that preclude the use of intensive induction chemotherapy
- **Dose:** 500 mg orally once daily
- **Common side effects:** N/V/D, fatigue, edema, arthralgia, abdominal pain, QTc prolongation. Black box warning for **differentiation syndrome**
- Phase 1 open-label, single-arm, multicenter dose-escalation and expansion trial with R/R AML
 - OR was 41%
 - 30% of patients achieved CR or CRh (21% achieved CR)
 - Median time to response = 1.9m; median time to CR or CRh = 2.8m. Median DOR was 8.2m

Source: N Engl J Med. 2018 Jun 21;378(25):2386-2398

Midostaurin

- **Indication:** Newly dx **FLT3+** AML
- **Dose:** 50 mg BID days 8 to 21 of each cycle of induction with 7+3 and consolidation with high-dose cytarabine.
- **Common side effects:** nausea, vomiting, diarrhea
- **RATIFY trial**
 - Combined Midostaurin or placebo with standard induction and consolidation chemotherapy, followed by 12 months of midostaurin or placebo maintenance
 - Significantly improved 4-year OS from 44.3% to 51.4%

Gilteritinib

- **Indication:** Relapsed or refractory AML with a **FLT3+** mutation
- **Dose:** 120mg oral daily
- **Common side effects:** N/V/D, **differentiation syndrome**, pancreatitis, QTc prolongation
- Phase III ADMIRAL trial:
 - OS on Gilteritinib arm was 9.3 months compared to salvage chemotherapy (6 months)
 - Better OR and longer duration of response
 - Improved 1 year survival rates

Source: <https://www.fda.gov/drugs/fda-approves-gilteritinib-relapsed-or-refractory-acute-myeloid-leukemia-aml-flt3-mutation>

Glasdegib

- **Hedgehog pathway inhibitor**
- **Indication:** Newly dx AML in combination with low-dose cytarabine in adults aged 75yrs+, or who have comorbidities
- **Dose:** 100mg oral daily
- **Common side effects:** Cytopenias, fatigue, fever, QTc prolongation, serum creatinine elevation
 - Embryotoxic, fetotoxic, and teratogenic
- Phase 2 BRIGHT 1003 Study
 - Median overall survival was 8.3 months for patients treated with glasdegib plus cytarabine compared with 4.3 months for cytarabine alone.
 - CR for LDAC + glasdegib was 15% vs LDAC alone 2.3%

Source: Blood 2016 128:99

Venetoclax

- **BCL2 inhibitor**
- **Indication:** Newly dx AML, 75 yrs + or with comorbidities; in combination with azacitidine or decitabine or low-dose cytarabine
- **Dose:** Ramp up dosing schedule. Day 1: 100 mg once daily, Day 2: 200 mg once daily, Day 3: 400 mg once daily
- **Common side effects:** N/V/D, cytopenias, infection, fatigue, TLS
- Approval was based on two open-label, non-randomized studies:
 - + azacitidine: 37% achieved CR with a median observed time in remission of 5.5 months
 - + decitabine : 54% achieved CR with a median observed time in remission of 4.7 months
 - + low-dose cytarabine: 21% achieved CR with a median observed time in remission of 6 months

Source: Blood 2019 133:7-17; doi: <https://doi.org/10.1182/blood-2018-08-868752>

Liposomal Daunorubicin and Cytarabine (CPX 315)

- **Indications:** Newly diagnosed **therapy-related** AML (t-AML) or AML with myelodysplasia-related changes
- **Dose:** 100 mg/m² cytarabine + 44 mg daunorubicin mg/m² on days 1, 3, and 5
- **Common Side effects:** Myelosuppression, infection, rash, cardiotoxicity, N/V/D/C , mucositis
- Phase 3 randomized study comparing CPX-315 vs 7+3
 - OR was 48% in CPX-315 group vs 33% in 7+3
 - Median overall survival 9.6 months vs. 5.95 months for patients aged 70-75
 - 34% who received CPX-315 when on to HSCT vs 25% of those with 7+3
- Improves 60-day mortality, remission rate, and OS. More patients going to HSCT

Gemtuzumab ozogamicin

- **Antibody-drug conjugate; CD33**
- **Indication:** CD33+ AML, relapsed refractory or newly diagnosed
- **Dose**
 - **Newly dx**
 - In combination with 7+3: 3mg/m² days 1, 4,7
 - Monotherapy: 6mg/m² on day 1, 3mg/m² day 8
 - **Relapsed/refractory**
 - Monotherapy: 3mg/m² on days 1,4,7
- **Common side effects:** Fever, nausea, vomiting, cytopenias, infection, stomatitis, infusion related reactions
 - Black box warning for **hepatotoxicity and VOD**

Gemtuzumab ozogamicin

- Combination therapy
- Phase 3, multicenter, randomized, open-label study of 271 patients aged 50 to 70 years with newly diagnosed de novo AML1
 - Median, EFS 17.3 months with GO vs. 9.5 months with standard 7+3
 - CR+CRh was 81% compared to 73% with 7+3
 - OS 27.5 months vs 21.8 months

Drug	Mechanism	Indication
Enadsidenib	IDH2+	Relapsed/refractory
Ivosidenib	IDH1+	Newly dx, 75yrs + or comorbidities
Midostaurin	FLT3+	Newly dx, in combination with 7+3
Gilteritinib	FLT3+	Relapsed/refractory
Venetoclax	BCL2 inhibitor	Newly dx, in combination with hypomethylating agent or low-dose cytarabine, 75yrs+ or comorbidities
Gemtuzumab ozogamicin	CD33+; antibody-drug conjugate	Newly dx (combination or monotherapy) Relapsed/refractory (monotherapy)
Liposomal dauno + cytarabine	Liposomal	Newly dx, therapy related or MDS related
Glasdegib	Hedgehog pathway inhibitor	Newly dx, in combination with low-dose cytarabine, 75yrs+ or comorbidities

Questions 1

- A healthy, fit, 67 year old female with past medical history of breast cancer treated with surgical resection and chemotherapy 7 years ago, now presents with pancytopenia and circulating blasts. Bone marrow biopsy confirms acute myeloid leukemia, with 50% blasts. She has normal cytogenetics and normal NGS.

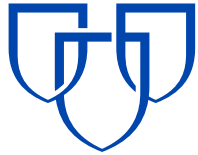


What would be first line treatment?

- a. Azacitadine or decitabine + venetoclax
- b. 7+3, daunorubin and cytarabine
- c. Liposomal daunorubicin and cytarabine
- d. Enasidenib
- e. I don't know, you lost me at dinosaurs had cancer



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Acute Lymphoblastic Leukemia/Lymphoma

Conventional Therapies in B Cell-ALL

- No standard approach to front line therapy
- Induction, consolidation, maintenance,
- CNS prophylaxis given at intervals throughout therapy
- Allogeneic stem cell transplant for eligible candidates in CR1, possibly

Conventional Therapies in B Cell-ALL

- Induction backbone
 - Vincristine, corticosteroids and an anthracycline
- Consolidation
 - Similar agents to induction and includes intrathecal chemotherapy for CNS prophylaxis at times.
- Maintenance therapy
 - Daily 6-MP, weekly methotrexate, vincristine and prednisone pulse every 3 months. Maintenance is administered for 2–3 years after induction

ALL in Young Adults

- Pediatric inspired regimens common for adult patients <40yrs
- Younger adults with ALL treated with pediatric regimens have 5 year overall survival rates upward of 70% vs adult regimens closer to 30-40%
- More vincristine, more steroids, more PEG-Asparaginase, more CNS ppx

NCCN: Induction Therapy Options for Ph-Negative ALL

Adult Pts (40 Yrs of Age or Older)	Pediatric-Inspired Protocols for AYA Pts (15-39 Yrs of Age)
CALGB 8811 Larson: daunorubicin, vincristine, prednisone, pegaspargase, cyclophosphamide	GRAALL-2003: daunorubicin, vincristine, prednisone, pegaspargase, cyclophosphamide (pts 60 yrs of age or younger)
Linker 4-drug: daunorubicin, vincristine, prednisone, pegaspargase	CCG-1961: daunorubicin, vincristine, prednisone, pegaspargase (pts 21 yrs of age or younger)
Hyper-CVAD ± rituximab: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose MTX and cytarabine; ± rituximab for CD20+	COG AALL-0434 with nelarabine (for T-ALL): daunorubicin, vincristine, prednisone, pegaspargase; + nelarabine for consolidation regimen (ongoing study)
MRC UKALLXII/ECOG2993: daunorubicin, vincristine, prednisone, pegaspargase (phase I); cyclophosphamide, cytarabine, 6-mercaptopurine (phase II)	DFCI ALL (based on DFCI Protocol 00-01): doxorubicin, vincristine, prednisone, high-dose MTX, pegaspargase (ongoing study in pts younger than 50 yrs of age)
	CALGB 10403: daunorubicin, vincristine, prednisone, pegaspargase (ongoing study in pts < 40 yrs)
	PETHEMA ALL-96: daunorubicin, vincristine, prednisone, pegaspargase, cyclophosphamide (pts younger than 30 yrs of age)
	USC ALL (based on CCG-1882): daunorubicin, vincristine, prednisone, MTX with augmented pegaspargase (pts 18-57 yrs)

Philadelphia Positive ALL

- Philadelphia positive (Ph+) ALL:
 - Tyrosin Kinase Inhibitors (TKIs)
 - Imatinib
 - Dasatinib
 - Ponatinib
- TKIs led to a significant outcome improvement, mainly in terms of better tolerability, and reduction of death during induction rates, if compared with standard chemotherapy-based regimens

Emerging Therapies

- Emerging immunotherapy options
 - Blinatumomab
 - Inotuzumab ozogamicin
 - Tisagenlecleucel

Blinatumomab

- **Bispecific monoclonal antibody to CD19**
- **Indication:** Ph-negative R/R B-ALL
- **Dose:** 9mcg IV continuous infusion x7 days, followed by 28 mcg daily as a continuous infusion on days 8- 28
- **Common side effects:** Black box warning for **cytokine release syndrome (CRS) and neurotoxicity**
- Multi-center, single arm, open label phase 2 study:
 - 43% of patients had CR +CRh in 1st 2 cycles with 82% of those MRD negative
 - Median OS was 6.1 with whos that were MRD negative 11.5m
 - 40% of patients in CR+CRh went on to get HCT

Source: Lancet Oncol. 2015 Jan;16(1):57-66. doi: 10.1016/S1470-2045(14)71170-2. Epub 2014 Dec 16

Blinatumomab

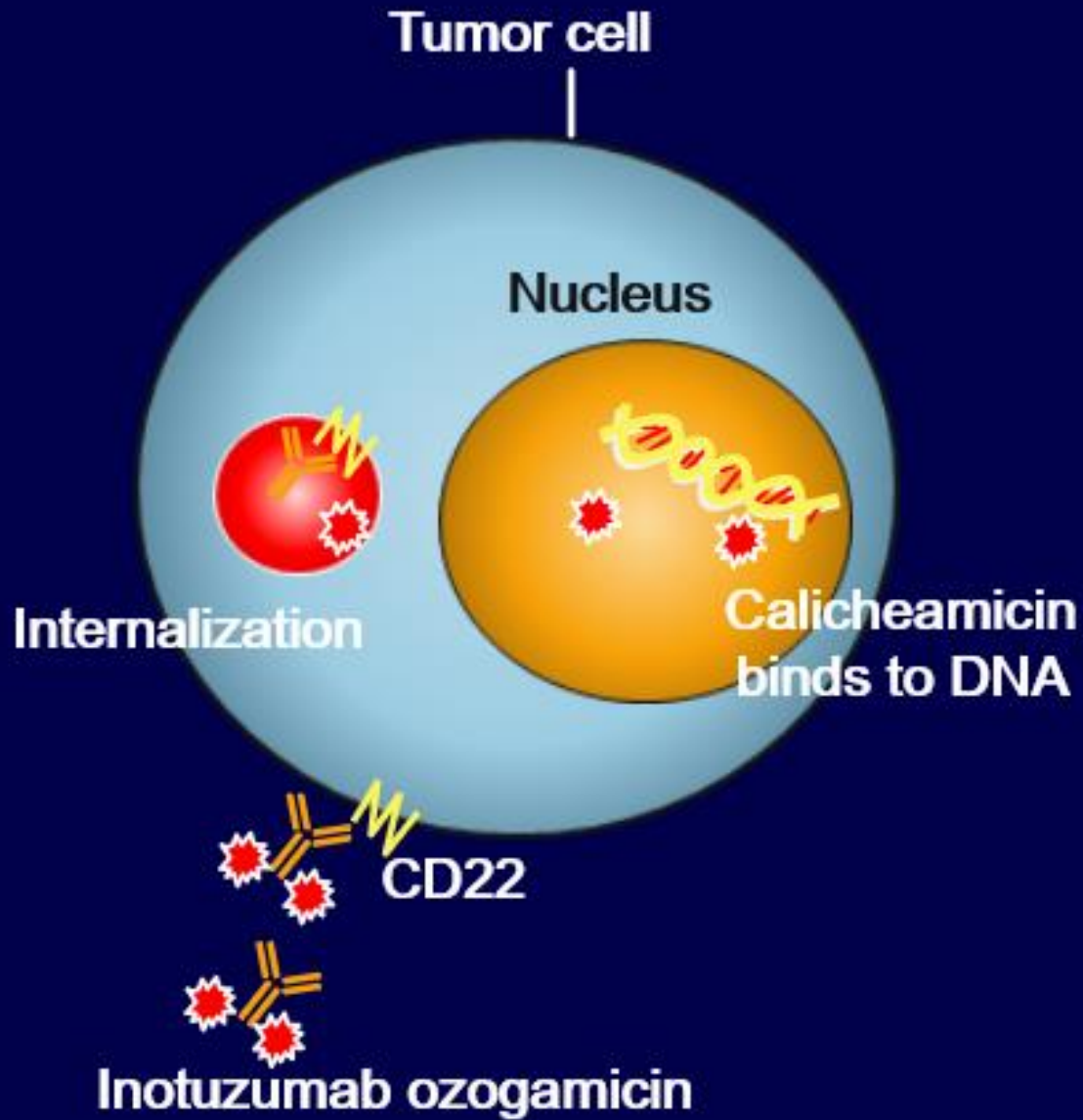
- TOWER study: Phase III Multicenter, randomized, open-label study that compared blinatumomab with standard chemotherapy in adults with relapsed/refractory ALL
- 405 patients enrolled: 271 received blinatumomab and 134 standard chemotherapy of choice
 - OS significant longer in blinatumomab group
 - Median OS was 7.7. months in blinatumomab group vs 4.0 months in chemo group
 - R+CRh was higher in blinatumomab group (44% vs 25%)
 - Longer median duration of remission in blinatumomab group (7.3 vs 4.6 months)
- Approval has also been expanded for MRD+ ALL and Ph+ ALL

Source: N Engl J Med 2017; 376:836-847

Inotuzumab ozogamicin

- **Antibody-drug conjugate**
- **Indications:** adults with R/R CD22+ B-cell ALL
- **Dose:** 0.8 mg/m² on day 1 and 0.5 mg/m² on days 8 and 15 of a 21-day treatment cycle
- **Common side effects:** Infusion reactions, cytopenias. Black box warning **hepatotoxicity and VOD**
- Phase III, multicenter, randomized, open-label study.
 - 80% of patients who received inotuzumab experienced CR vs only 29% on SOC
 - Median duration of CR was 4.6 months for inotuzumab vs 3.1 months on SOC
 - MRD negativity was 78% vs 28%
 - Median OS 7.7 months vs 6.7 months

Source: N Engl J Med. 2016;375(8):740. Epub 2016 Jun 12.

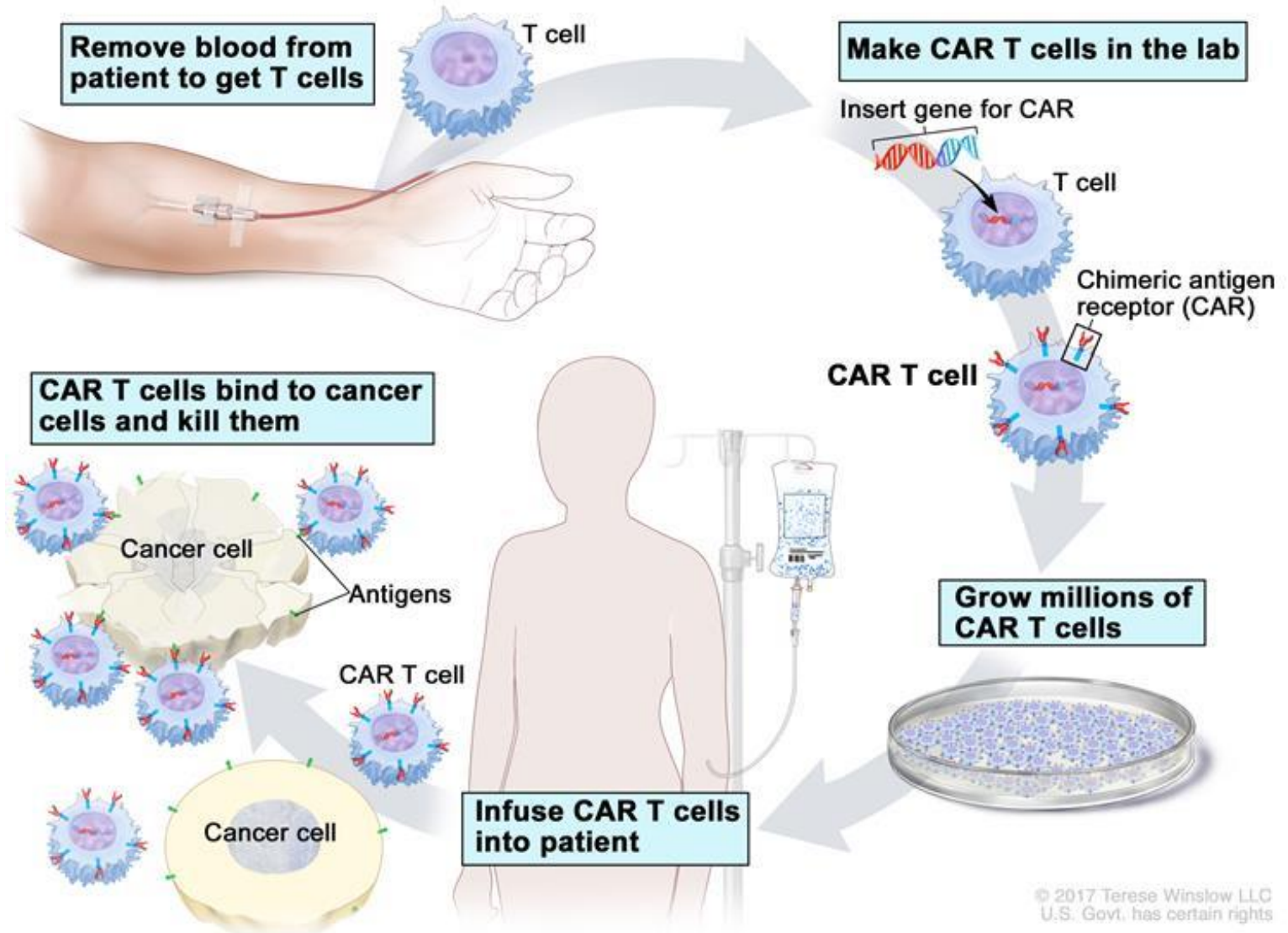


Source: Blood 2018 :blood-2018-05-850461; doi: <https://doi.org/10.1182/blood-2018-05-850461>https://reference.medscape.com/viewarticle/907374_4

CAR-T

- Chimeric Antigen Receptor T (CAR-T) cells
- Form of genetically modified autologous immunotherapy
- Customized treatment using a patient's own T lymphocytes
- Transduced with a gene that encodes a chimeric antigen receptor to direct the patient's T cells against the intended target
- The T cells are genetically modified *ex vivo*, expanded in a production facility, and then infused back into the patient as therapy

CAR T-cell Therapy



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Tisagenlecleucel

- CD19-directed genetically modified autologous T cell immunotherapy
- **Indication:** Relapsed/refractory B-cell ALL in pts <25yo
- Lymphodeplete with fludarabine and cyclophosphamide followed by tisagenlecleucel 2 to 14 days following completion of the chemo regimen
- Black box warnings for **cytokine release and neurotoxicity**
- Phase 2, single-cohort, multicenter study
 - 75 patients received tisagenlecleucel
 - Remission rate within 3 months was 81%
 - All responses were MRD negative
 - OS was 90% at 6 months, 76% at 12 months

Source: N Engl J Med 2018; 378:439-448

In Summary

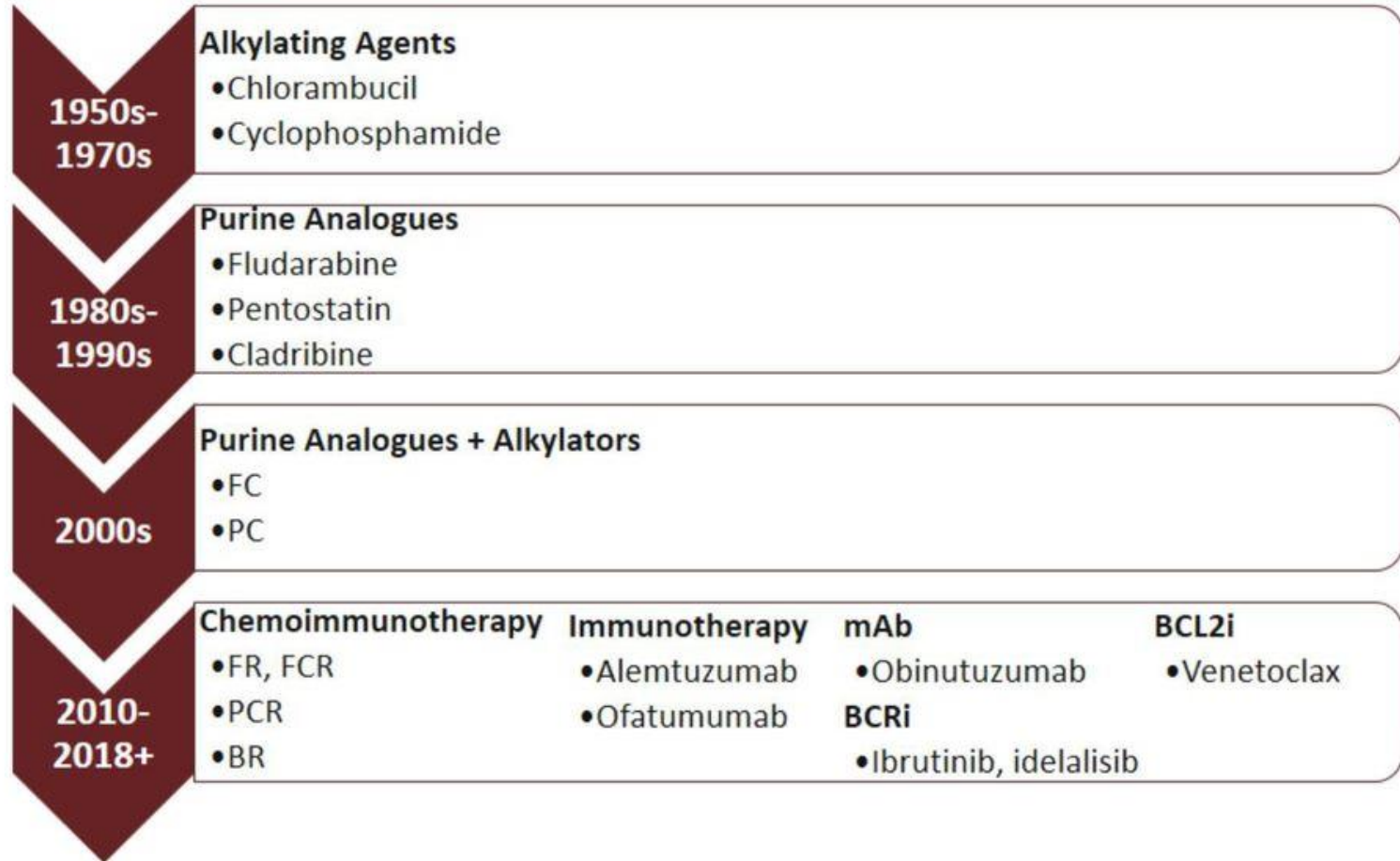
- Pediatric inspired regimens are becoming the standard of care for induction in young adults with ALL
- Novel immunotherapies are effective in relapsed/refractory setting
- Phase III trial to compare Tisagenlecleucel vs Blinatumomab or Inotuzumab for Patients With Relapsed/Refractory B-cell Precursor Acute Lymphoblastic Leukemia (OBERON)

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Chronic Lymphocytic Leukemia

CLL Drug Development Timeline



Rai KR, et al. *Am J Hematol.* 2016;91:330-340.

Understanding CLL

- Better understanding of disease process and prognostication
 - Immunoglobulin heavy chain (IGHV) mutation status
 - ZAP70
 - FISH
 - CD38

Standard of Care Therapies in CLL

- FCR (fludarabine, cyclophosphamide, and rituximab)
 - Standard of care over the last decade
 - Young, fit patients without del(17p)
- Bendamustine and rituximab
 - Older patients or renal dysfunction
 - Less AEs
- Allogeneic stem cell transplant (HCT)

Novel Therapies in CLL

- Monoclonal antibodies
 - Obinutuzumab, Alemtuzumab, Ofatumumab
- B cell receptor (BCR) signaling pathway
 - Ibrutinib (BTK inhibitor)
 - Idelalisib (PI3K inhibitor)
 - Duvelisib (PI3K inhibitor)
- BCL2 inhibitor– Venetoclax

Obinutuzumab

- **Type II glycoengineered CD20 monoclonal antibody**
- **Indication:** first-line treatment in combination with chlorambucil in previously untreated CLL patients with comorbidities.
- **Dose:** 100 mg on day 1, 900 mg on day 2, 1,000 mg days 8 and 15 in a 28 day cycle. Cycles 2 through 6: 1,000 mg on day 1 every 28 days
- **Common side effects:** infusion related reactions, cytopenias. Black box for PML, hep B reactivation
- Pivotal CLL11 trial
 - Better ORR
 - Higher rate of MRD negativity
 - Time to next treatment significant longer

Source: Engl J Med 2014; 370:1101-1110

Alemtuzumab

- **Humanized monoclonal antibody to CD52**
- **Indication:** Relapsed CLL after tx with alkylating agents and who have failed fludarabine therapy
- **Dose:** 30mg per dose 3 times weekly on alternate days for a total duration of therapy of up to 12 weeks. Must escalate!
- **Common side effects:** Infusion reactions, pancytopenia, infections
- Approval based on CAM 307 trial:
 - ORR was higher for the alemtuzumab arm (83% versus 55)
 - CR rates higher in the alemtuzumab arm (24% versus 2%)
 - Median duration of response was 16.4 months in alemtuzumab arm vs 12.9 months in chlorambucil

Source: Onco Targets Ther. 2010; 3: 53–67.

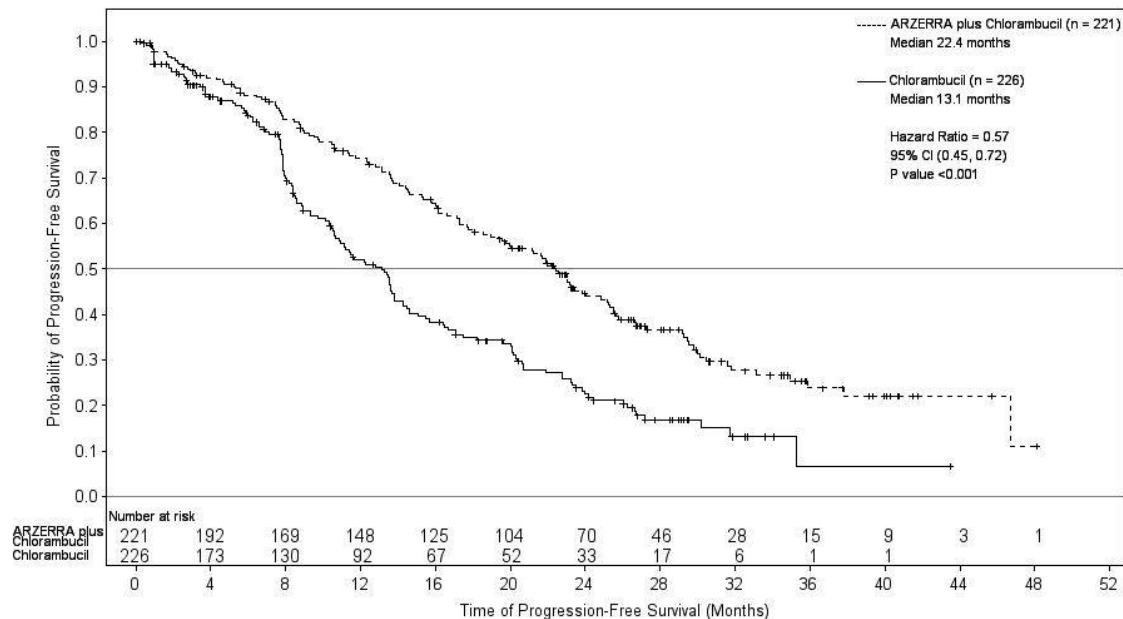
Ofatumumab

- **Novel CD20 monoclonal antibody**
- **Indication:**
 - Previously untreated CLL (in combination with chlorambucil) when fludarabine-based therapy is considered inappropriate
 - Relapsed CLL (in combination with fludarabine and cyclophosphamide).
 - CLL refractory to fludarabine and alemtuzumab
 - Extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL
- **Dose:** Depends on indication
- **Common side effects:** Infusion related reactions, cytopenias. Black box warning for hep B reactivation and PML

COMPLEMENT 1

Untreated CLL; PFS

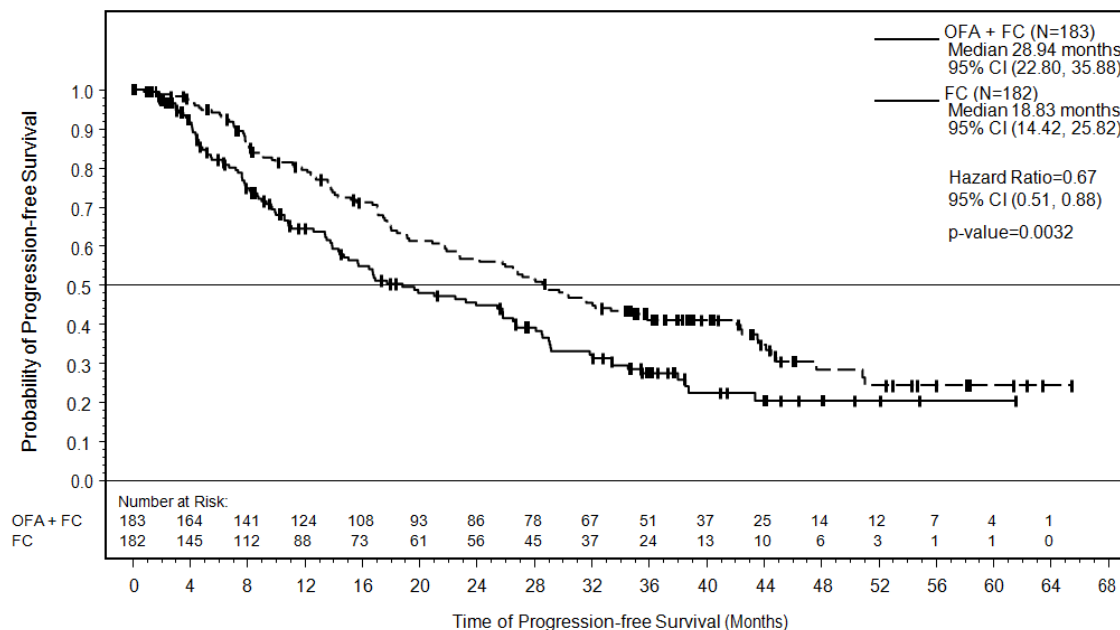
Ofatumumab + chlorambucil vs chlorambucil alone



COMPLEMENT 2

Relapsed CLL; PFS

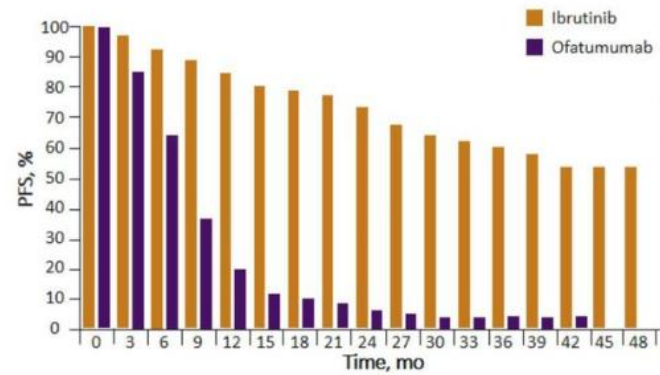
Ofatumumab + FC vs FC alone



Ibrutinib

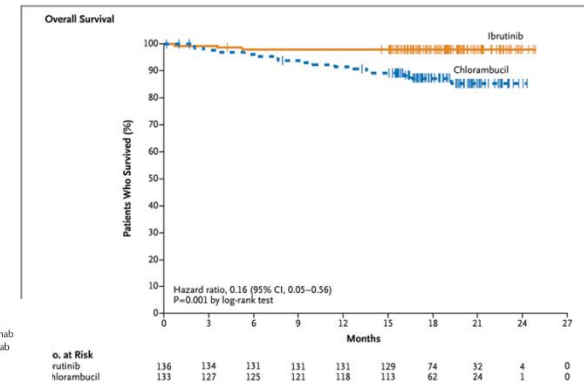
- **Bruton's tyrosine kinase inhibitor**
- **Indication:** Frontline and relapsed CLL; CLL with 17p deletion
 - As monotherapy
 - Combination
- **Dose:** 420mg PO once daily
- **Common side effects:** Bleeding, cytopenias, infection, heart arrhythmias; transient leukocytosis

- RESONATE trial:
 - Ibrutinib monotherapy was more effective than ofatumumab in previously-treated adults

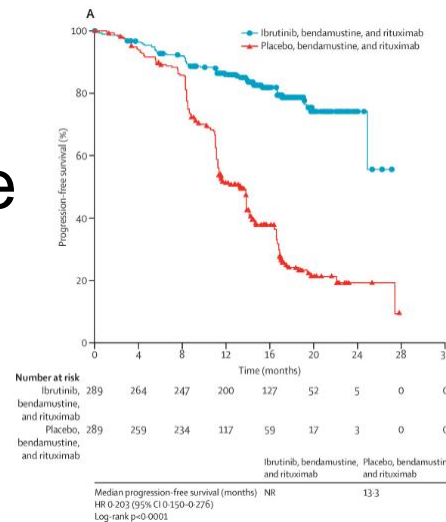


- RESONATE-II trial:
 - Ibrutinib monotherapy was more effective than chlorambucil in the first-line treatment of elderly patients

Byrd JC, et al. *J Clin Oncol.* 2017;35(suppl); Abstract 7510).



- HELIOS trial:
 - Ibrutinib, bendamustine and rituximab was more effective in previously-treated adults than bendamustine plus rituximab



Source: Blood 2019 :blood-2018-08-870238; doi: <https://doi.org/10.1182/blood-2018-08-870238>

Idelalisib

- Small molecule, BCRi, **phosphoinositide 3-kinase delta inhibitor (P3KI)**
- **Indication:** In combination with rituximab for relapsed CLL
- **Dose:** 150mg PO twice daily
- **Common side effects:** **Black box warning:** hepatotoxicity, diarrhea/colitis, infection, pneumonitis, intestinal perforation
- Phase III trial comparing idelalisib + rituximab vs rituximab alone
 - Better overall response, longer PFS, longer OS in idelalisib arm vs rituximab alone

Duvelisib

- Small molecule inhibitor of **phosphoinositide 3-kinase (PI3K)**
- **Indications:** Relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) or follicular lymphoma
- **Dose:** 25mg PO twice daily
- **Common side effects:** **Black box warning:** infections, diarrhea/colitis, rash, pneumonitis
- Phase III DUO Trial:
 - Improved PFS, better overall response with duvelisib vs ofatumumab

Venetoclax

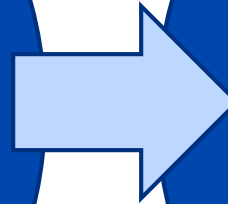
- **BCL2 inhibitor**
- **Indication:** In combination with obinutuzumab for frontline therapy in CLL
 - Monotherapy in relapsed CLL in patients with 17p deletion in combination
 - Combination with rituximab in relapsed CLL
- **Dose:** weekly ramp up over 5 weeks: 20mg, 50mg, 100mg, 200mg, 400mg
- **Common side effects:** cytopenias, infection, **TLS**, nausea/diarrhea

Venetoclax

- Phase 2, single-arm, multicenter study, of high-risk (17p del), relapsed CLL
 - 80% ORR
 - Venetoclax monotherapy is active and well tolerated in patients with relapsed or refractory del(17p)
- CLL14 trial: phase III trial of venetoclax + obinotuxumab vs obinutuzumab + chlorambucil
 - Higher ORR, longer PFS in venetoclax-obinutuzumab
- MURANO trial: Venetoclax + Rituximab vs bendamustine + rituximab
 - Improved 2 year PFS and OS

Then to Now

Steroids
Chlorambucil
Cyclophosphamide
Fludarabine
FCR



BCR signaling kinase
inhibitors
Novel mAbs
Anti-Bcl2 agents
Exportin inhibitor
(CART) cell therapy

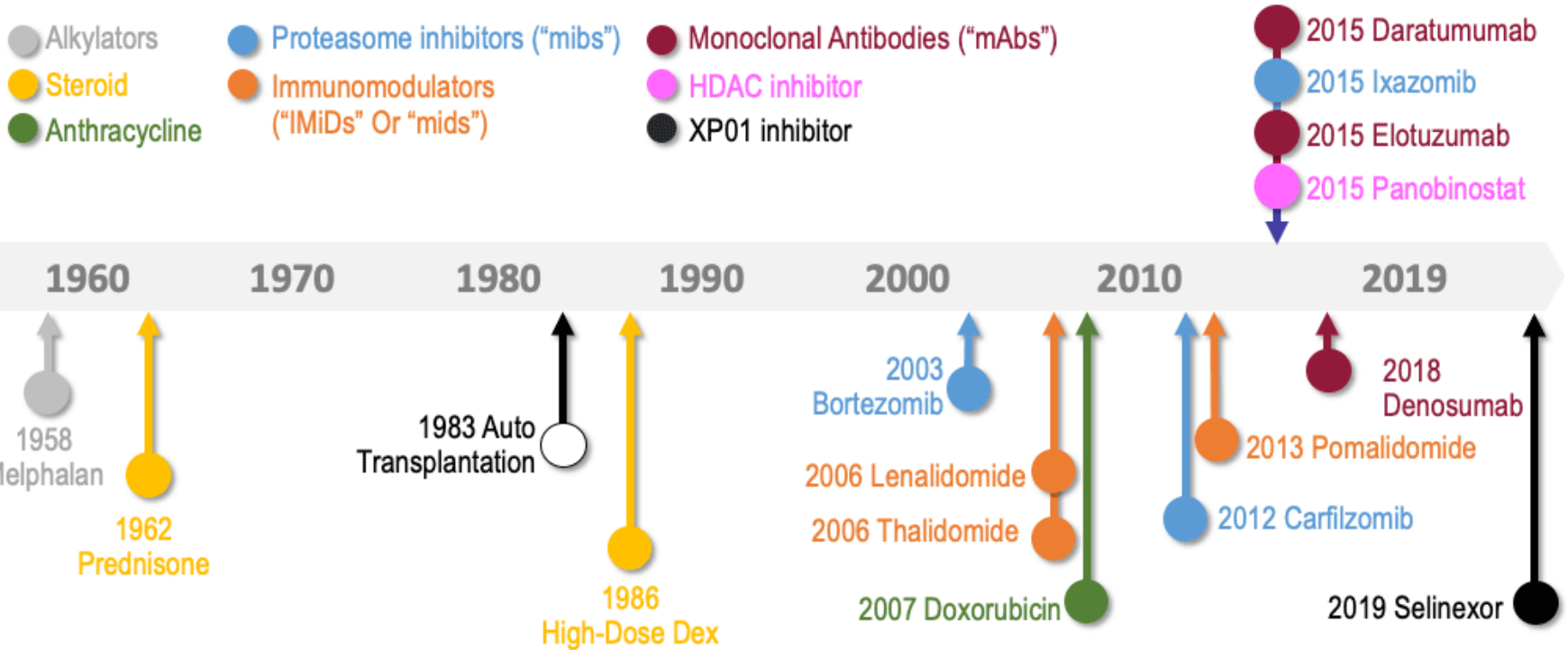


Multiple Myeloma

Conventional Therapies in MM

- 15 years ago, dismal prognosis for MM
- Treatment options and clinical outcomes have changed dramatically
- Alkylators (Melphalan) and corticosteroids were mainstay of treatment
- High dose chemotherapy followed by autologous stem cell transplant (ASCT) for select patients

Myeloma Drug Development



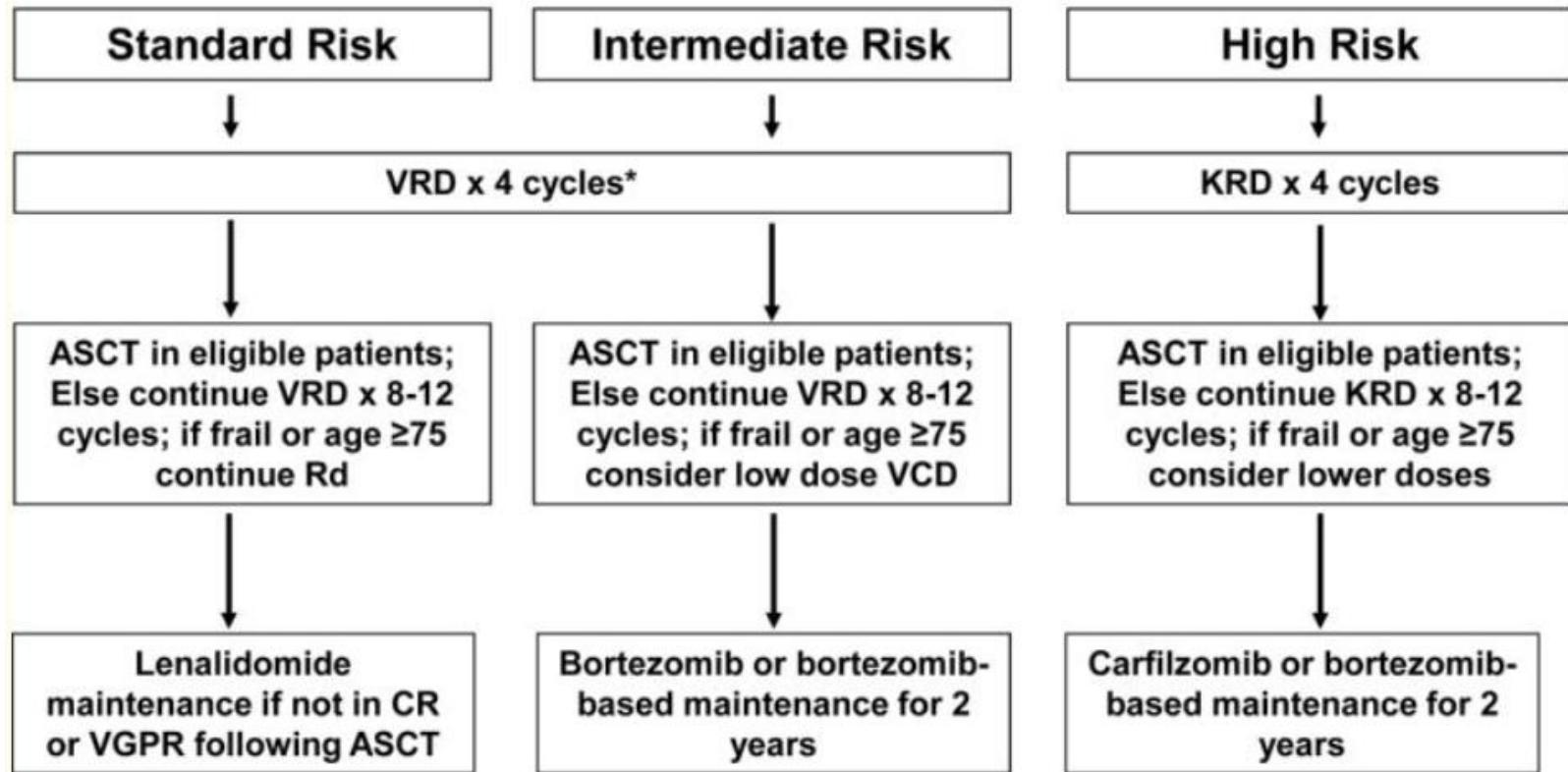
Auto = autologous; Dex= dexamethasone.

Tariman, J. *Nurs Clin North Am.* 2017;52(1):65-81. DRUGS@FDA.gov

Approach to Newly Diagnosed Myeloma

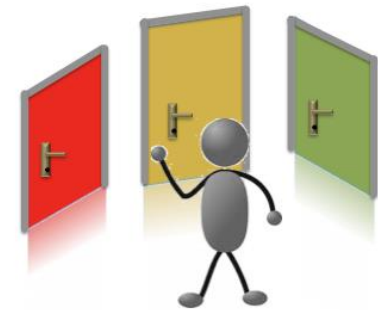
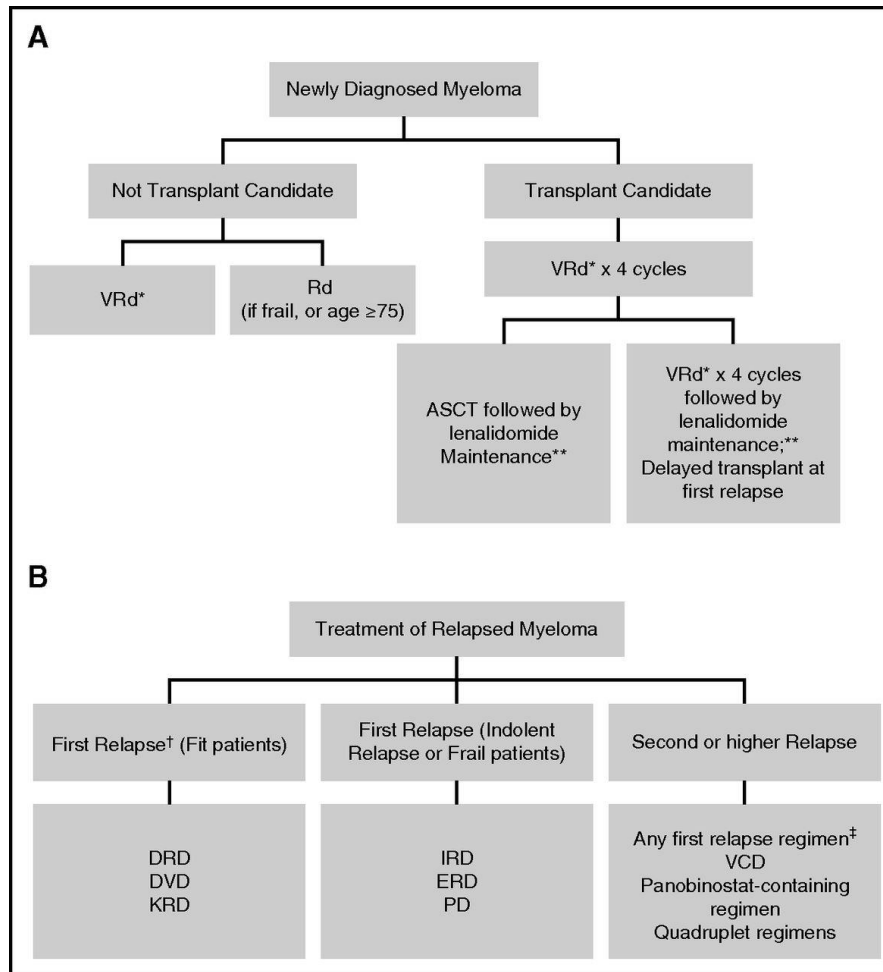
- Non-transplant candidate
 - Triplet regimen consisting of steroid + proteasome inhibitors (mibs) + immunomodulator (IMiDs)
 - For 12 to 18 months or until progression
- Transplant candidate
 - Induction, ASCT, maintenance
 - Induction Therapy: Triplet regimen x 3-4 cycles
 - High dose chemotherapy (melphalan) with ASCT
 - Maintenance: Treatment for 1-2 years.
 - Lenalidomide is the drug of choice for maintenance
 - May also consider bortezomib-based maintenance for patients with intermediate- and high-risk disease

Approach to Newly Diagnosed Myeloma



Source: Rajkumar SV, Kumar S. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin Proc. 2016;91(1):101–119. doi:10.1016/j.mayocp.2015.11.007

Approach to Newly Diagnosed Myeloma



Source: Blood 2018 :blood-2018-05-850461; doi: <https://doi.org/10.1182/blood-2018-05-850461> https://reference.medscape.com/viewarticle/907374_4

Relapsed/Refractory Multiple Myeloma

- Almost all patients with myeloma relapse after initial therapy, at a median duration of 4 years after ASCT plus maintenance, or ~2.5 years without ASCT
- Main factors that influence the selection of a specific regimen
 - When did the relapse occurs? On or off therapy?
 - The nature of response and tolerability of the prior regimen
 - Number of prior lines of therapy
 - Aggressiveness of the relapse
 - Physical condition of the patient

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson's specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient's care. This algorithm should not be used to treat pregnant women.

APPENDIX B: Treatment

<p>Induction Therapy for Stem Cell Transplant Candidates:</p> <p>Preferred treatments:</p> <ul style="list-style-type: none"> • Carfilzomib/lenalidomide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone <p>Others:</p> <ul style="list-style-type: none"> • Carfilzomib/dexamethasone • Bortezomib/dexamethasone • Lenalidomide/dexamethasone <p>Special considerations:</p> <ul style="list-style-type: none"> • If neuropathy, consider lenalidomide/dexamethasone containing therapy or carfilzomib containing regimen • If renal impairment: <ul style="list-style-type: none"> ◦ Dose reduce lenalidomide according to guidelines ◦ Use carfilzomib with caution; close renal monitoring is warranted • Check 2D echocardiogram or equivalent prior to use of carfilzomib to ensure adequate baseline ejection fraction (EF) • If diabetic, consider low-dose dexamethasone-based combination therapy and consultation to Endocrinology—Diabetes for diabetes management 	<p>Primary Treatment for Non-Stem Cell Transplant Candidates:</p> <ul style="list-style-type: none"> • Consider treatments indicated for stem cell transplant candidates plus ixazomib/lenalidomide/dexamethasone <p>Consolidation/Maintenance Therapy:</p> <ul style="list-style-type: none"> • Carfilzomib/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Lenalidomide • Ixazomib • Bortezomib <p>Salvage Therapy:</p> <ul style="list-style-type: none"> • Bendamustine/bortezomib/dexamethasone • Bendamustine/lenalidomide/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Bortezomib/lenalidomide/dexamethasone • Bortezomib/liposomal doxorubicin/dexamethasone • Carfilzomib/bendamustine/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone • Carfilzomib (twice weekly)/dexamethasone • Carfilzomib (weekly)/dexamethasone • Carfilzomib/lenalidomide/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab • Daratumumab/bortezomib/dexamethasone • Daratumumab/lenalidomide/dexamethasone • Daratumumab/pomalidomide¹/dexamethasone • Elotuzumab/bortezomib/dexamethasone • Elotuzumab/lenalidomide/dexamethasone • Ixazomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Ixazomib/pomalidomide¹/dexamethasone • Lenalidomide/dexamethasone • Panobinostat/bortezomib/dexamethasone • Panobinostat/carfilzomib • Panobinostat/lenalidomide/dexamethasone • Pomalidomide¹/bortezomib/dexamethasone • Pomalidomide¹/carfilzomib/dexamethasone • Pomalidomide¹/cyclophosphamide/dexamethasone • Pomalidomide¹/dexamethasone • Pomalidomide¹/elotuzumab/dexamethasone <p>Consider in aggressive disease:</p> <ul style="list-style-type: none"> • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) with or without bortezomib (VID-PACE) • Modified hyperfractionated cyclophosphamide/bortezomib/doxorubicin/dexamethasone • Proteasome inhibitor and immunomodulator combination for high risk disease
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¹ Two prior therapies should include proteasome inhibitor and lenalidomide agent and have disease progression on or within 60 days of last therapy

Novel Multiple Myeloma Agents

Proteasome inhibitor

Bortezomib
Carfilzomib
Ixazomib
Oprozomib

Immunomodulatory agent

Thalidomide
Lenalidomide
Pomalidomide

Histone-deacetylase inhibitor

Panobinostat

Monoclonal antibody

Daratumumab (anti-CD38)
Elotuzumab (anti-CS1)

Kinesin spindle protein inhibitor

Filanesib

PI3K-AKT-mTOR inhibitor

Afuresertib

Nuclear protein exportin 1

Selinexor

Novel Therapies in Multiple Myeloma

- Panobinostat
- Elotuzumab
- Daratumumab
- Ixazomib
- Selinexor



Panobinostat

- Histone deacetylase (HDAC) inhibitor
- **Indication:** In combination with boretizomide + dex for relapsed/refractory disease after at least two prior standard therapies
- **Dose:** 20 mg orally twice weekly 3 weeks on, one week off
- **Common side effects:** Diarrhea, thrombocytopenia, fatigue
- PANORAMA1 trial: Panobinostat + bortezomib/dex vs placebo + bortezomib/dex

Elotuzumab

- **Monoclonal antibody against CS1, a subunit of CD2**
- **Indication:** In combination with:
 - Lenalidomide + dex after 1-3 therapies
 - Pomalidomide + dex after at least 2 prior therapies
- **Dose:** 10 mg/kg intravenously weekly × 8 weeks, and then every 2 weeks
- **Common side effects:** Infusion related reactions, fatigue, infections
- ELOQUENT-2 trial: phase III, randomized, open-label study that evaluated elotuzumab + Rd vs Rd alone
- ELOQUENT-3 trial: phase III, randomized, open-label study that evaluated elotuzumab + Pd vs Pd alone

Daratumumab

- **Monoclonal antibody to CD38**
- **Indication:** Many*
- **Dose:** 16 mg/kg intravenously weekly × 8 weeks, every 2 weeks × 16 weeks, then once monthly
- **Common side effects:** Infusion related reactions, fatigue, anemia, nausea
- **Special considerations:**
 - Can interfere with blood compatibility testing
 - Can cause false positives on SPEP

FDA Approved Indications for Daratumumab

INDICATION	REGIMEN	STUDY
Newly diagnosed transplant ineligible	Dara + VMP (bortezomib + melphalan + prednisone)	ALCYONE
	Dara + Rd (lenalidomide + dex)	MAIA
After 1 prior therapy	Dara + Rd (lenalidomide + dex)	POLLUX
	Dara + Vd (bortezomib + dex)	CASTOR
After 2 prior therapies	Dara + Pd (pomalidomide + dex)	EQUULEUS
After 3 prior therapies	Daratumumab monotherapy	SIRIUS

Source: International Myeloma Foundation

Ixazomib

- **Oral proteasome inhibitor**
- **Indication:** In combination with lenalidomide and dexamethasone for patients with multiple myeloma following progression on at least one prior therapy
- **Dose:** 4 mg once weekly on days 1, 8, and 15 of a 28-day treatment cycle
- **Common side effects:** neuropathy, cytopenias, GI toxicities, edema
- **TOURMALINE-MM1**
 - Median PFS 20.6 months vs. 14.7 months
 - ORR was 78% vs 72%
 - Median time to response was 1.1 vs 1.9 months
 - Median duration of response was 20.5 months and 15.0 months

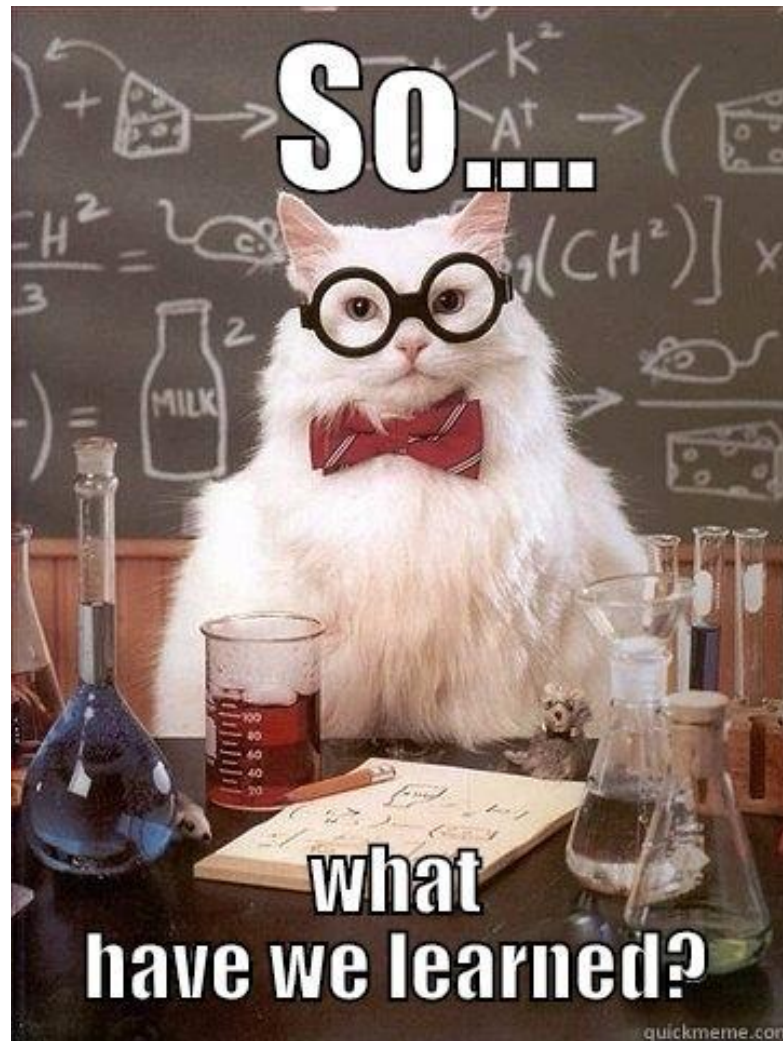
Selinexor

- First-in-class oral selective **XPO1 inhibitor**
- **Indication:** Combination with dexamethasone for adults with relapsed or refractory multiple myeloma
- **Dose:** 80 mg in combination with dexamethasone taken orally on days 1 and 3 of each week
- **Common side effects:** thrombocytopenia, GI toxicities, neuro toxicities
- STORM trial: multicenter, single arm study analyzing Selinexor + dex in patients with relapsed/refractory disease
 - 122 patients treated with Selinexor + dexamethasone
 - ORR was 25.3%
 - The median response duration was 3.8 months

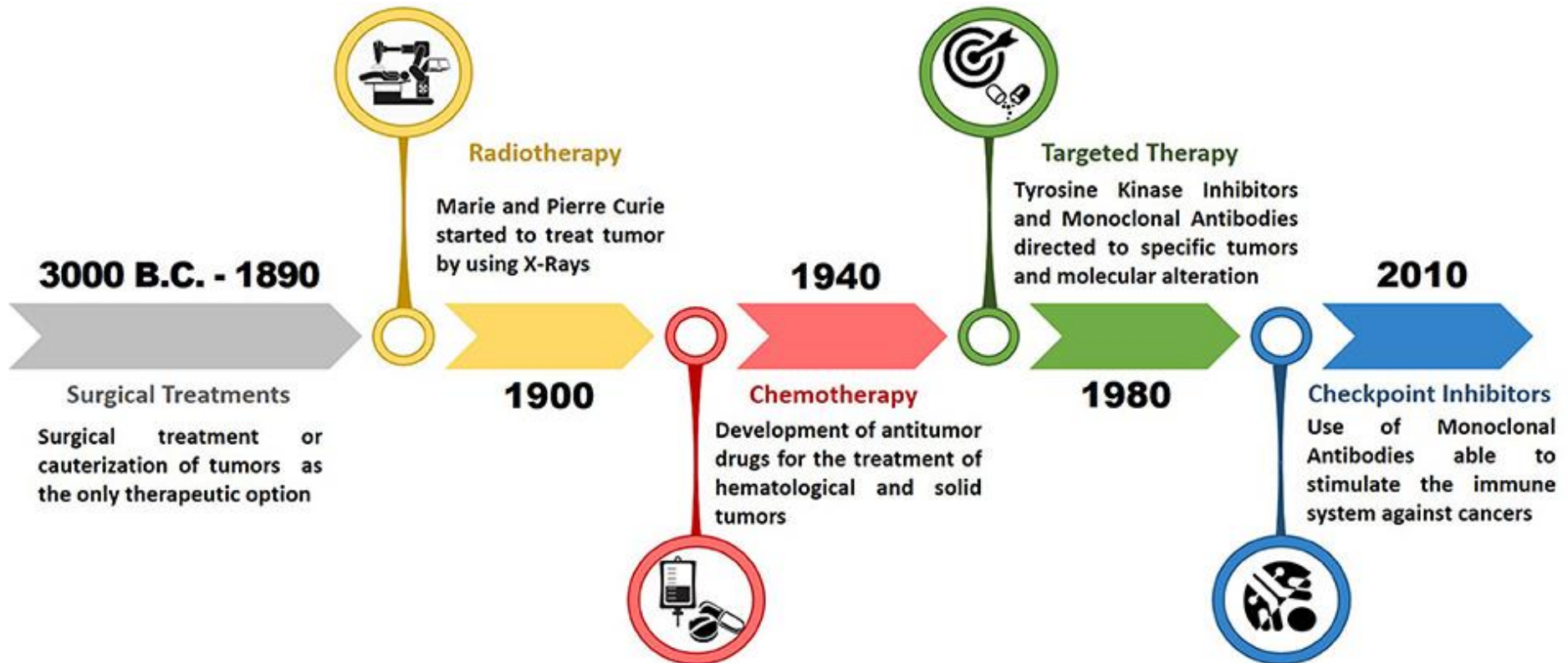
Source: <https://www.hematology.org/Clinicians/Drugs/FDA/>

Which drug below is approved for newly diagnosed CD38+ multiple myeloma?

- A. Daratumumab
- B. Elotuzumab
- C. Panobinostat
- D. Idelisib



Timeline of Modern Oncology



Source: Falzone, Luca & Salomone, Salvatore & Libra, Massimo. (2018). Evolution of Cancer Pharmacological Treatments at the Turn of the Third Millennium. *Frontiers in Pharmacology*. 9. 10.3389/fphar.2018.01300.

In Summary

- Conventional cytotoxic chemotherapies suffer from a narrow therapeutic index and significant toxicities
- In hematologic malignancies, patients who are older, with comorbidities, or who have relapsed disease are often limited in their treatment options. Historically, a majority of these individuals do not receive treatment and face a poor prognosis.
- Over the last decade we have seen growth in biologic therapies such as monoclonal antibodies and antibody-drug conjugates, checkpoint inhibitors, targeted therapies, adoptive T-cell approaches and cancer vaccines, etc.
- Patients are having durable responses and less toxicities, with more individualized approaches to treatment.

Considerations for Novel Therapies

- Unique side effect profiles
- Financial toxicity of long term targeted therapies?
 - Almost every approved cancer drug in the last few years costs more than \$100 000 per year in the United States



Questions & Discussion

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