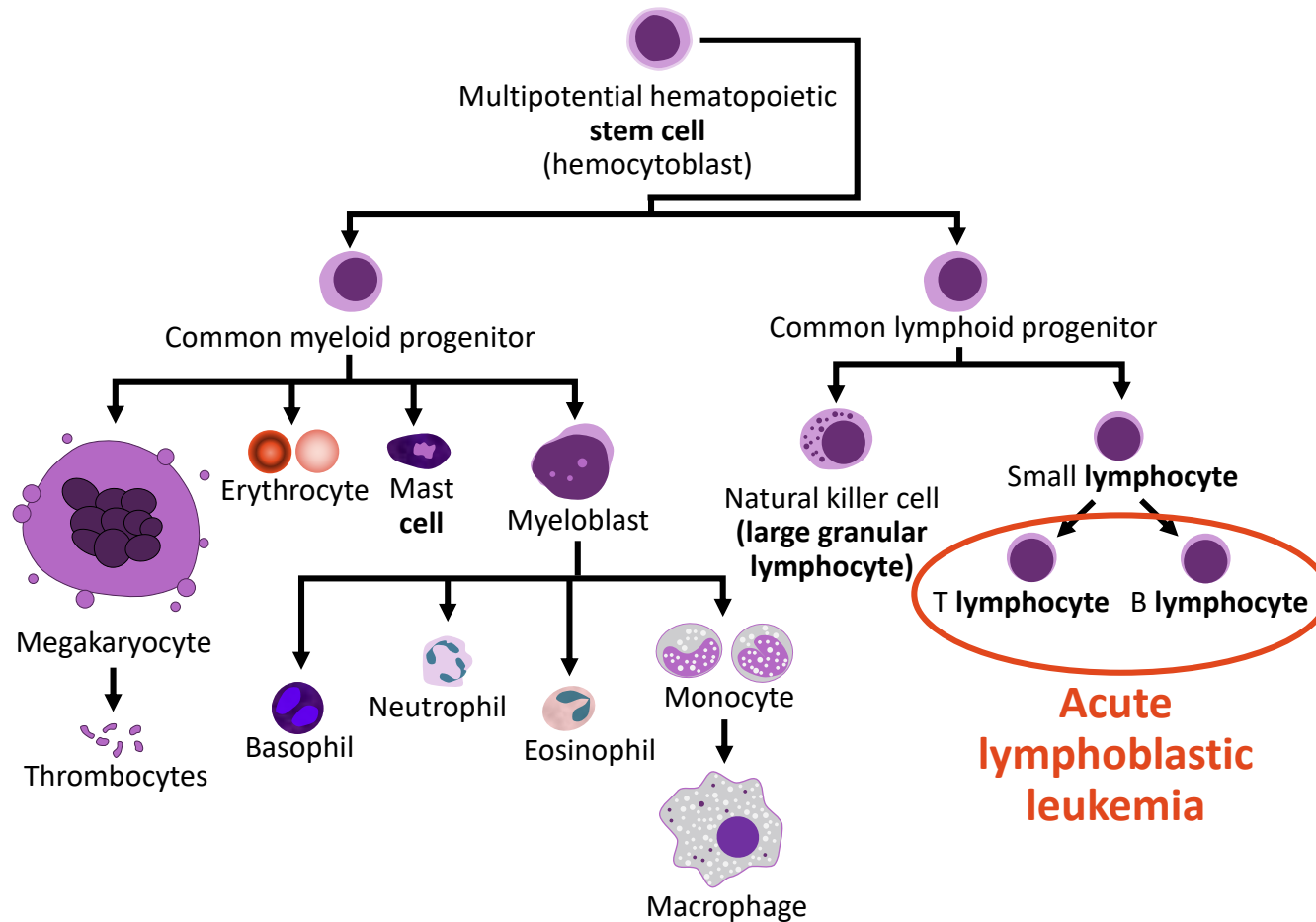


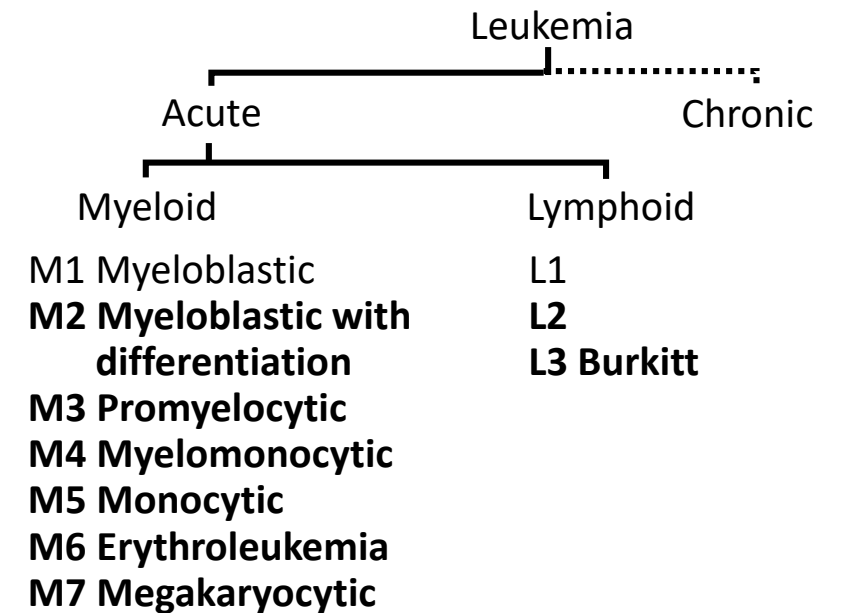
Akut leukémiák

- Belgyógyászati Szakvizsga Előkészítő Tanfolyam
 - 2021.05.17-Június 11.
 - Pécs
 - On-line tanfolyam
-

Hematopoiesis and Acute Leukemias



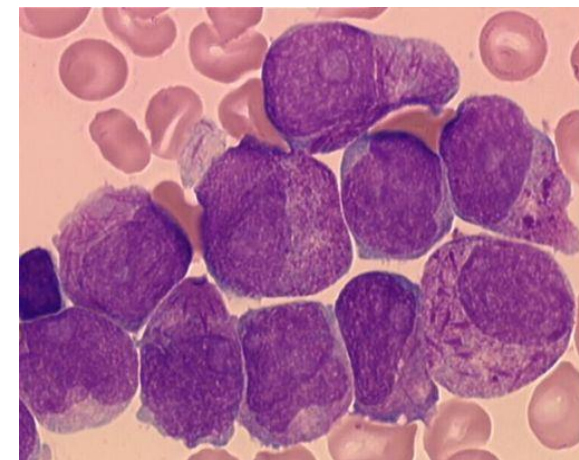
FAB Classification of Leukemias



Left image from Mikael Häggström, derived from original by A. Rad. Permission is granted to copy, distribute and/or modify this image under the terms of the GNU Free Documentation License, Version 1.2, or any later version published by the Free Software Foundation.

AML SEER adatok 2021

- Becsült új AML esetek 2021-ben: 20,240
- Az összes új esetek %-a: 1.1%
- Az összes leukémia %-a: 32%
- AML becsült halálozás 2021-ben: 11,400
- Az összes esetek %-a: 1.9%
- 5-éves túlélés %-a: 29.5% (2011-2017)
- Medián életkor diagnóziskor: 68 years



Bevezetés

- Az AML napjainkban is azon onkohematológiai betegségek egyike, melyek gyógyításában és kezelésében csak szerényebb eredményeket tudtunk felmutatni.
- Az AML-val kapcsolatos ismeretek az utóbbi években a citogenetikának és molekuláris biológiának köszönhetően jelentősen bővültek.
- AML-ben a citogenetika alapján kedvező, intermediér és kedvezőtlen prognózisú betegek különíthetők el. A relapsus veszélye a citogenetikától függően 30%, 50%, illetve 80% körüli.
- A korai terápiás próbálkozásokat követően 1973-ban (Yates és mtsi.) jelent meg az első publikáció egy, a betegség addigi terápiás lehetőségeihez képest átütő sikert jelentő terápiás protokollról, amit ma „7+3”-nak nevezünk. Az elmúlt 5 évtizedben az AML-s betegek kezelése a „7+3” kemoterápiás standard intenzív kezelésből állt.

Az AML terápiás fejlődésének áttekintése: 1973 - 2017

Cytosine Arabinoside (NSC-63878) and Daunorubicin (NSC-83142) Therapy in Acute Nonlymphocytic Leukemia^{1,2,3}

Jerome W. Yates, H. James Wallace, Jr., Rose Ruth Ellison,
and James F. Holland⁴

Brief Reports
and
Preliminary
Communications

Early destruction of leukemic infiltration in the induction phase of treatment may reduce the duration of time most hazardous for infection as well as the total period of necessary hospitalization. Daunorubicin produces rapid bone marrow depression, and when adminis-

intensify the effects of cytosine arabinoside and daunorubicin thereby producing rapid destruction of leukemic cells. Such an effect might attain more remissions and earlier discharges from the hospital.

Yates, Cancer Chemother Rep. 1973



**First Line: Intensive Remission Induction ChemoRx followed by
Allogeneic SCT**

Relapse



Second Line: Salvage ChemoRx

For Patients Unable to Undergo or Declining Intensive Remission Induction:

Low-intensity Chemotherapy; Palliative Rx

Bevezetés

- Az AML-es betegek kezelési stratégiájának legsarkalatosabb pontja azon döntés, hogy a beteg alkalmas-e intenzív indukciós kemoterápiára.
- A beteg életkorán, kísérőbetegségein, általános állapotán kívül figyelembe kell vennünk az AML ismert prognosztikai faktorait.
- A fiatalabb (50–60 év alatti) betegek túlélése az intenzív kemoterápia (3+7) következtében javult, de kedvezőtlen prognosztikai tényezők esetén csak az allogén HSCT lehet eredményes. A további fejlődés a betegség biológiájának jobb megismerésétől és az ezen alapuló célzott terápiától várható.
- A prognózis a kor, az AML de novo vagy szekunder jellege, a kezdeti blast szám, a terápiára adott válasz mellett elsősorban a leukaemiás sejtek citogenetikai, illetve molekuláris biológiai sajátosságain alapul.
- A tartós túlélés AML-ben 50-60% körüli, azonban 60-65 év felett ma sem haladja meg a 15-20%-ot.

Bevezetés

- A betegek közel 40-50%-ban nem mutatható ki citogenetikai eltérés (normális karyotypus=intermedier prognózisú). Ez a csoport különösen heterogén, az eltérő rizikójú és terápiát igénylő betegek meghatározásában a molekuláris vizsgálatoknak meghatározó szerepük van.
- A kimutatható génmutációk és az ezzel járó molekuláris laesiók fontos szerepet játszanak a leukaemiás sejtek proliferációjában, differenciálódásában, a sejtciklus szabályozásában, az apoptózisban, vagyis a betegség lefolyásában.
- A gyors és megfizethető genom szekvenálás megjelenése elősegítette az AML pathofiziológiájának tudományos megértését.
- Az AML genetikai térképének megismerése kezdetben segítséget nyújtott a betegség klasszifikációjában és prognosztikájában, például, hogy mely betegek profitálnak a legjobban az első remisszióban elvégzett allo-HSCT-ből.

Citogenetikai, molekuláris biológiai jellemzők

- Évek óta ismert a FLT3-ITD, a CEBPA, a NPM-1 mutációja. Az FLT3-ITD mutációja az AML-es betegek közel 30%-ában, az NPM-1-mutáció 30%-ban, a CEBPA gén mutációja mintegy 8-10%-ban fordul elő.
- Az FLT3 és CEBPA fontos szerepet játszik a haemopoesisben és a myeloid progenitorok regulációjában. Az NPM-1 funkciója komplex, a lokalizációtól, az expressziótól függően onkogén és tumorszuppresszor gén sajátosságai lehetnek.
- IDH gén mutációja (cytosol IDH1 és mitochondrialis IDH2) előfordulása AML-ben 15% körüli és gyakoribb a normális citogenetikájú betegekben.
- A DNMT3A génmutáció előfordulása az intermedier csoportban 30% körüli.
- Normális karyotypusú betegekben közel 30%-ban előfordul a RUNX1 gén mutációja, de számos egyéb gén mutációját írták még le (ASXL1, TP53, JAK2-like 1, WT-1, TET2, KMT2A, etc.).

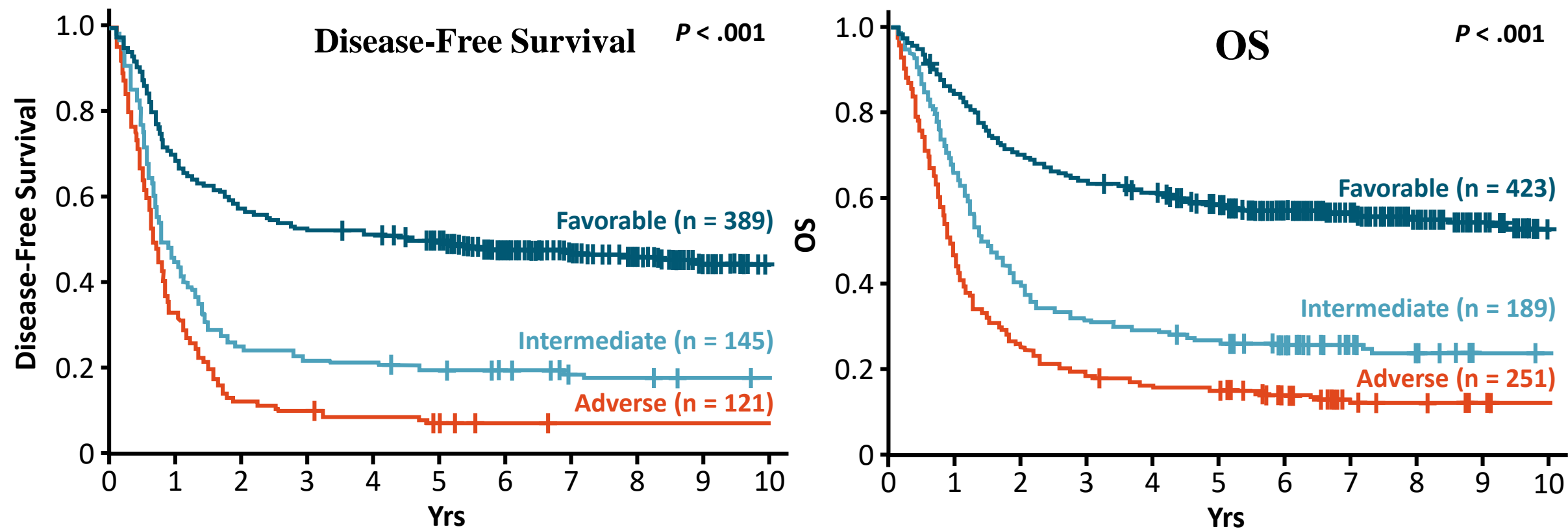
ELN Risk Stratification of AML by Genetics

Risk Category	Genetic Abnormality
Favorable	<p>t(8;21)(q22;q22.1); <i>RUNX1-RUNX1T1</i></p> <p>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i></p> <p>Mutated <i>NPM1</i> without <i>FLT3</i>-ITD or with <i>FLT3</i>-ITD^{low}</p> <p>Biallelic mutated <i>CEBPA</i></p>
Intermediate	<p>Mutated <i>NPM1</i> and <i>FLT3</i>-ITD^{high}</p> <p>Wild-type <i>NPM1</i> without <i>FLT3</i>-ITD or with <i>FLT3</i>-ITD^{low} (without adverse-risk genetic lesions)</p> <p>t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i></p> <p>Cytogenetic abnormalities not classified as favorable or adverse</p>

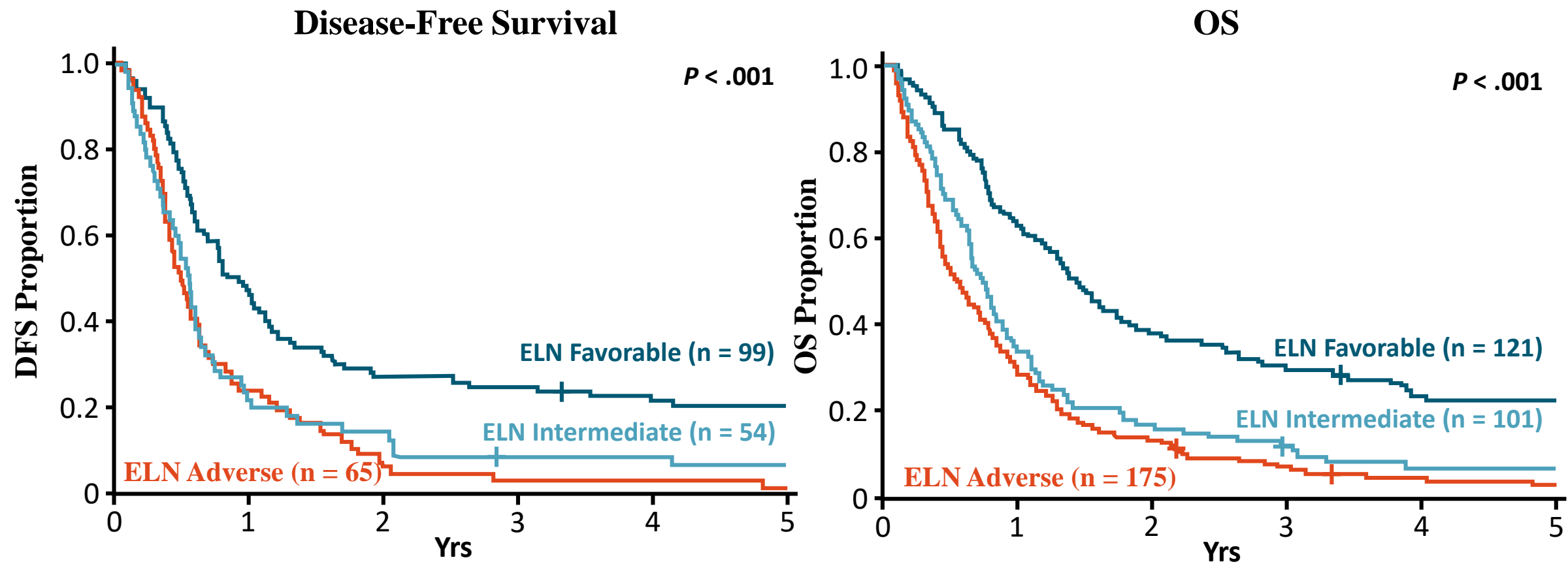
Risk Category	Genetic Abnormality
	<p>t(6;9)(p23;q34.1); <i>DEK-NUP214</i></p> <p>t(v;11q23.3); <i>KMT2A</i> rearranged</p> <p>t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i></p> <p>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2,MECOM(EVI1)</i></p>
Adverse	<p>−5 or del(5q); −7; −17/abn(17p)</p> <p>Complex karyotype, monosomal karyotype </p> <p>Wild-type <i>NPM1</i> and <i>FLT3</i>-ITD^{high}</p> <div style="border: 2px solid red; padding: 5px; display: inline-block;"> <p>Mutated <i>RUNX1</i></p> <p>Mutated <i>ASXL1</i></p> <p>Mutated <i>TP53</i></p> </div> <p style="color: red; font-size: 2em; margin-left: 10px;">?</p>

2017 ELN AML Classification: Survival of Patients < 60 Yrs of Age by Risk Group

- Retrospective analysis of data from CALGB/Alliance clinical trials (N = 863; median age: 45 years)



2017 ELN AML Classification: Survival of Patients ≥ 60 Yrs of Age by Risk Group



Időskori AML (magas rizikójú)

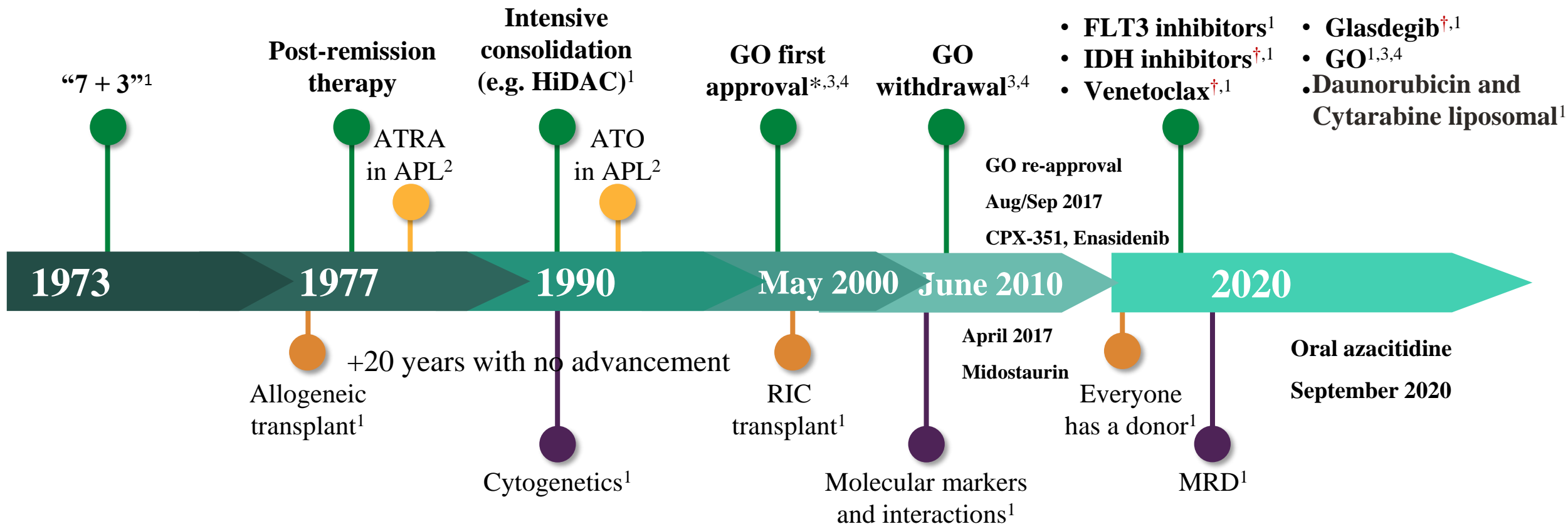
- Az AML-es betegek mintegy 60-70%-a 60 év felett és rossz prognózissal jár.
- A kedvezőtlen prognózist a kor mellett az AML-t gyakran megelőző MDS, az időskori AML-nek a fiataloktól eltérő biológiai sajátosságai (kedvezőtlen citogenetikája, fokozott MDR, etc.), a társuló betegségek magyarázzák.
- Az idősek az intenzív kemoterápiát nagyon rosszul tolerálják, a CR 50% alatti, többnyire rövid tartamú, a tartós túlélők aránya 10% alatt van.
- Az időskorú betegek kezelése ma is megoldatlan, a fiataloktól eltérően nem alakult ki egységes remisszió indukciós és posztremissziós kezelés.
- A gyakorlatban az idős betegek kezelése egyéni és nagy körültekintést igényel.
- Időskorban is lehetőség van allo-HSCT-ra, nem myeloablatív (RIC), ún. „mini” transzplantáció jöhet szóba.

A genetikai és molekuláris eltérések relevanciája AML-ben

- **A betegség pontosabb klasszifikációjában**
- **A prognózis meghatározása homogén betegcsoportokban**
 - Intenzív kezelések
 - Hypomethyláló ágensek (HMA)
- **A kezelési terv meghatározásában**
 - Intenzív vs. kevésbé intenzív kezelés
 - Első vonalbeli célzott kezelések
 - Allogén hematopoetikus őssejt átültetés indikációi
- **Az MRD monitorozásában**

Az AML jelentős fejlődése az elmúlt öt évtizedben

Az AML biológiájának megismerése, az új szerek és az allo-HSCT fejlődésének ütemterve



Adapted from: 1. Rowe JM. *Best Pract Res Clin Haematol* 2019; **32**:101094;

2. Wang ZY & Chen Z. *Blood* 2008; **111**:2505–2515; 3. Ali S, et al. *The Oncologist* 2019; **24**:e171–e179;

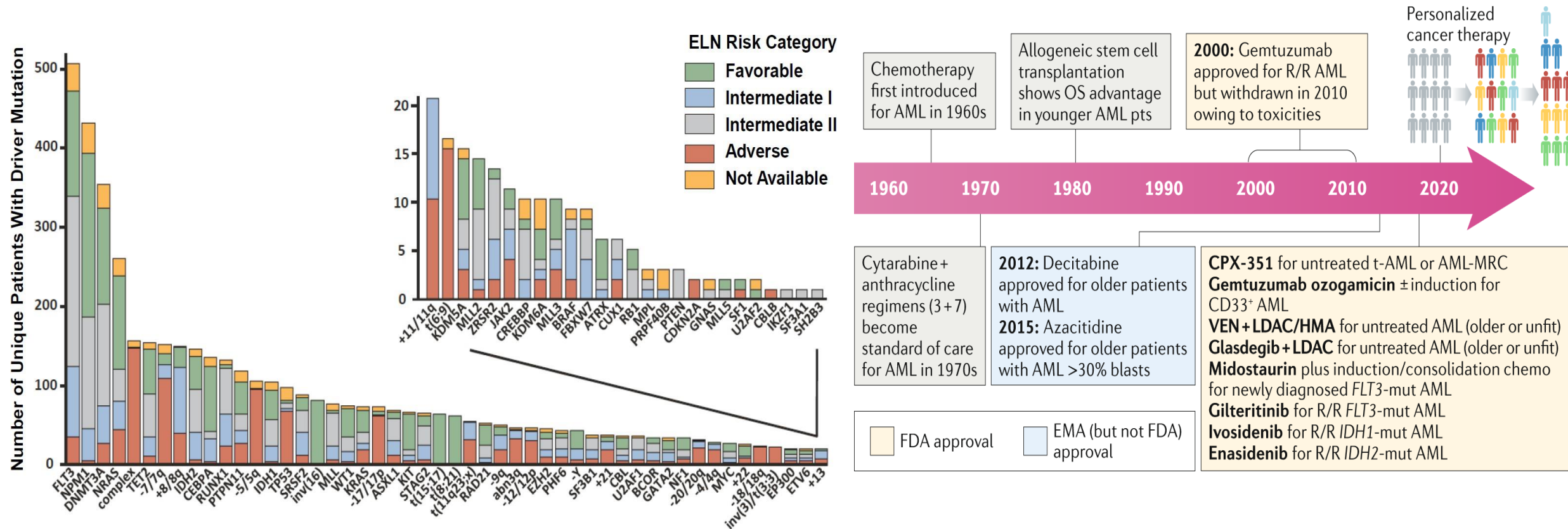
4. FDA News Release. Sept 01, 2017. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-mylotarg-treatment-acute-myeloid-leukemia> (accessed April 2020).

Az AML terápiás vázlat áttekintése: 2017-től napjainkig

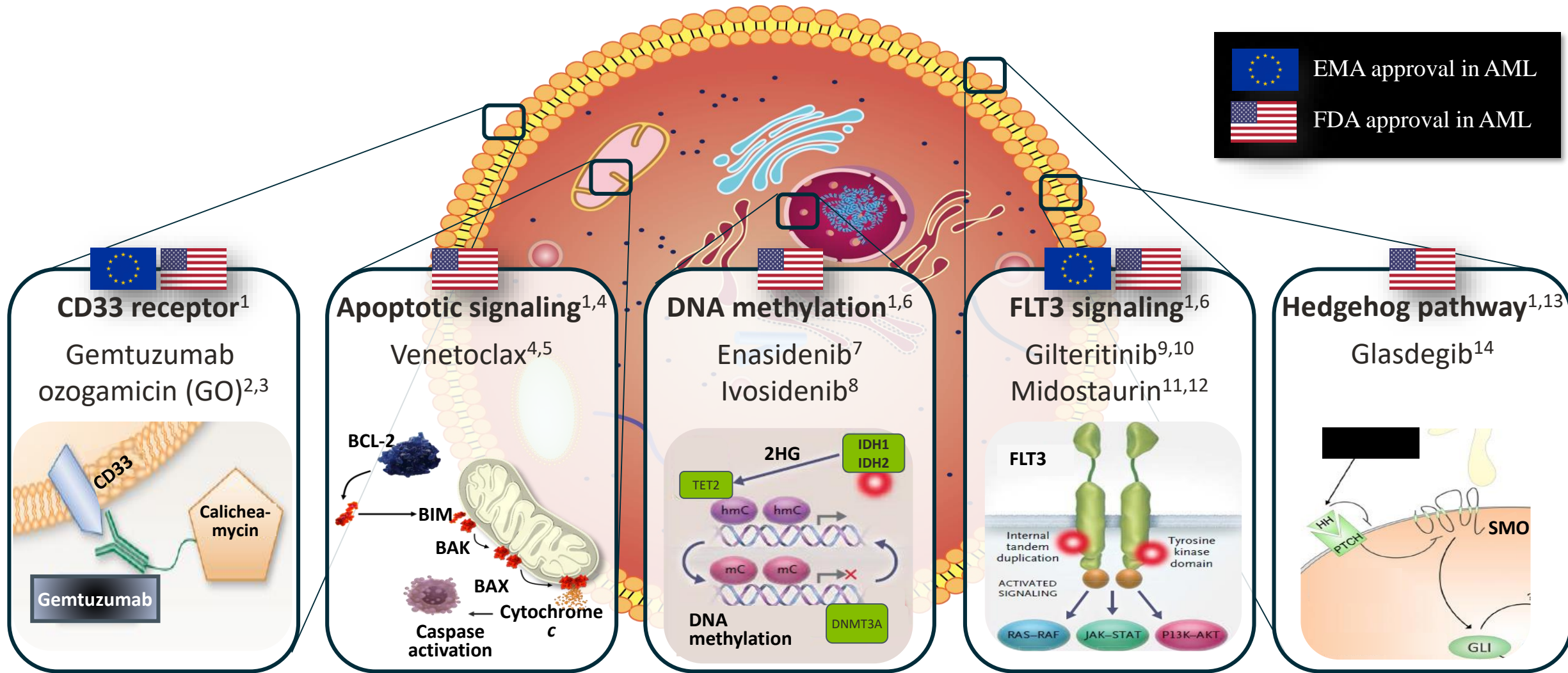
A jelentős változások újszerű, hatékonyabb és általában jobban tolerálható molekulárisan célzott terápiák bevezetésének köszönhetőek.

Az AML genomikai komplexitásának felismerése (Molekuláris heterogenitás).

Furdolópontot ért az AML terápiás fejlődése?



Feltörekvő új szerekek az AML kezelésében

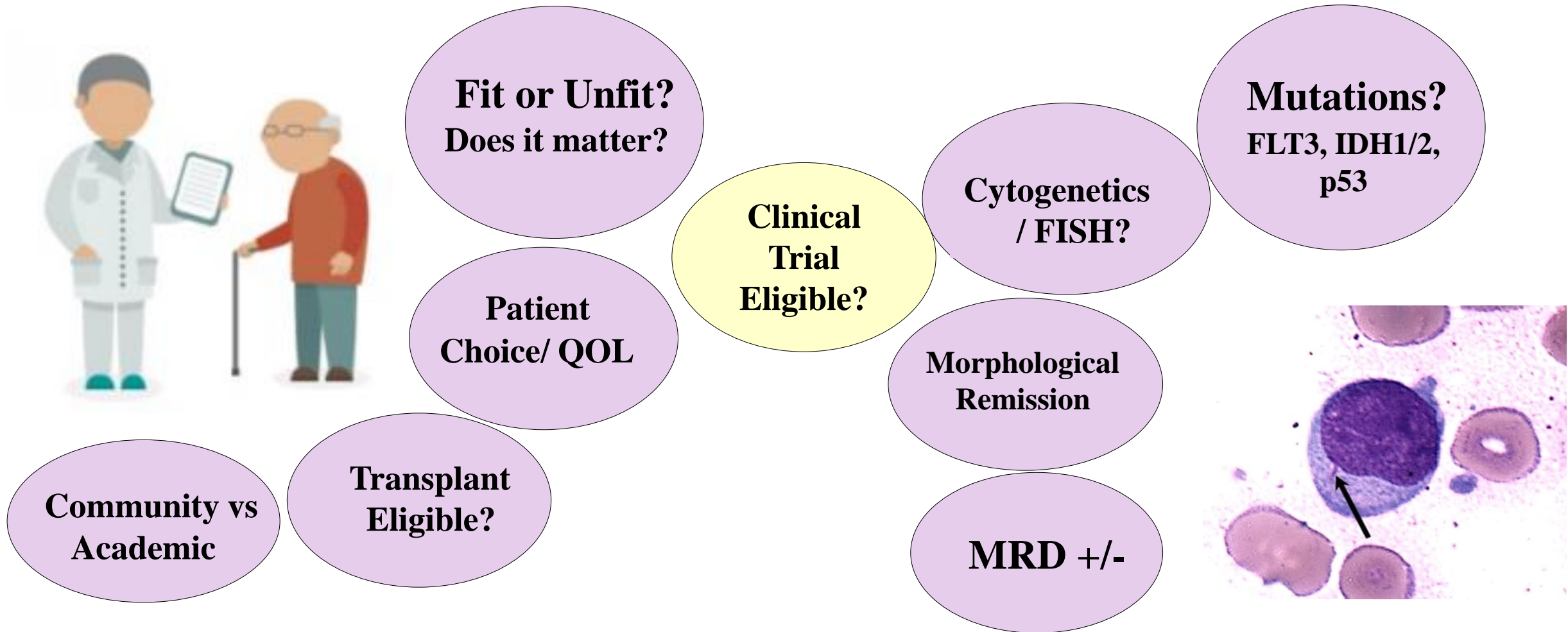


1. Bohl SR, et al. *Int J Mol Sci* 2019; **20**:E1983; 2. Mylotarg® (GO). EMA SmPC (accessed 04/2020); 3. Mylotarg® (GO). US PI (accessed 04/2020); 4. Pollyea DA, et al. *Blood Adv* 2019; **3**:4326–4335; 5. Venclexta® (venetoclax). US PI (accessed 04/2020); 6. Döhner H, et al. *N Engl J Med* 2015; **373**:1136–1152; 7. Idhifa® (enasidenib). US PI (accessed 04/2020); 8. Tibsovo® (ivosidenib). US PI (accessed 04/2020); 9. Xospata® (gilteritinib). EMA SmPC (accessed 04/2020); 10. Xospata® (gilteritinib). US PI (accessed 04/2020); 11. Rydapt® (midostaurin). EMA SmPC (accessed 04/2020); 12. Rydapt® (midostaurin). US PI (accessed 04/2020); 13. Aberger F, et al. *Cell Commun Signal* 2017; **15**:8; 14. Daurismo® (glasdegib). US PI (accessed 04/2020).

Új lehetőségek az AML kezelésében

- Az AML biológiájának megismerésével lehetőség nyílt a betegség kialakulásában szerepet játszó mechanizmusok (molekuláris és epigenetikus eltérések, fúziós proteinek, etc.) befolyásolására („célzott terápia”).
- Az AML-ben, a kemoterápiával és transzplantációval eddig elért eredményeket figyelembe véve, a további haladás az újabb, hatékonyabb és általában jobban tolerálható molekulárisan célzott szerektől várható.

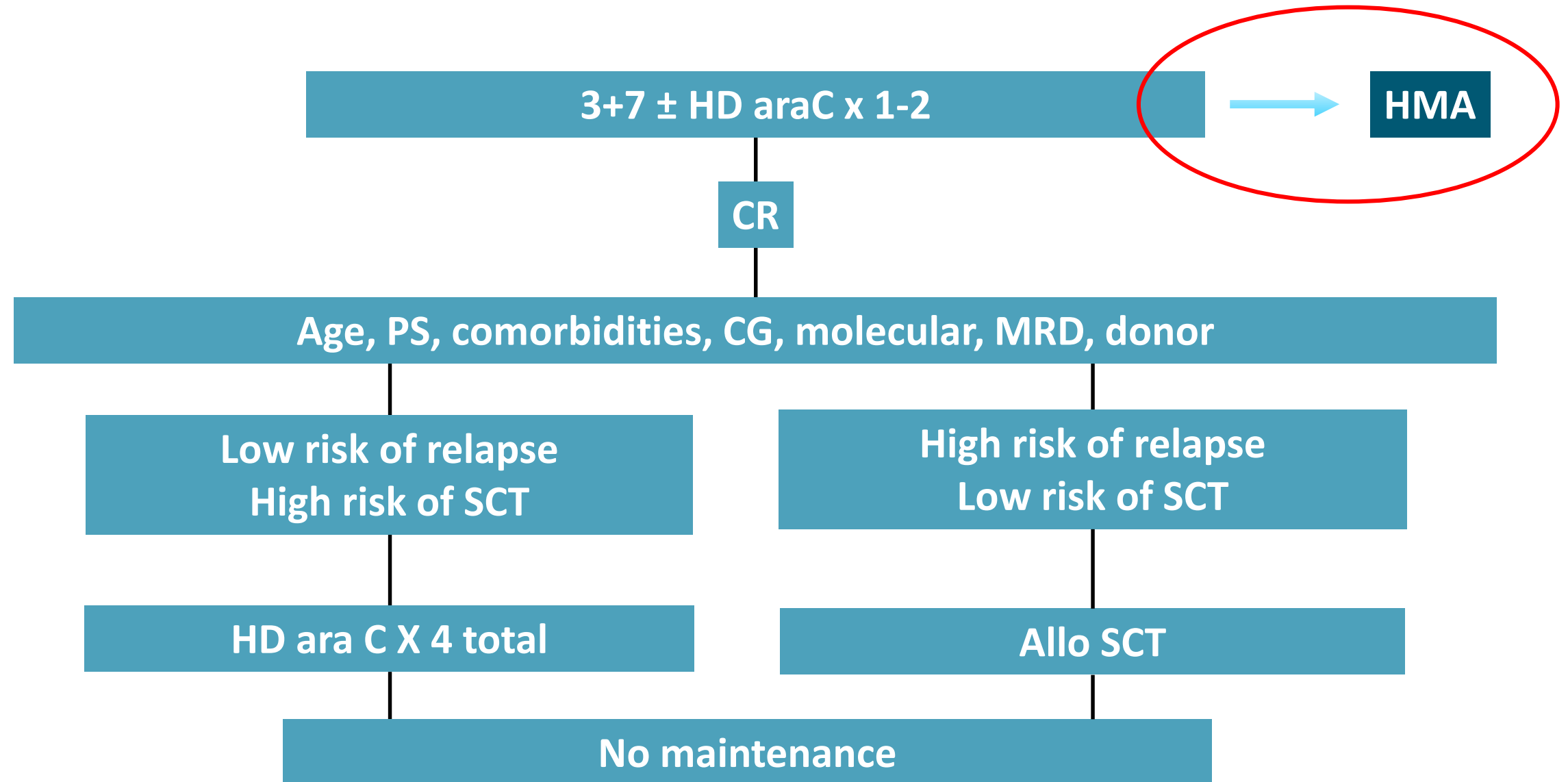
Fontos kérdések az új terápiákkal kapcsolatban



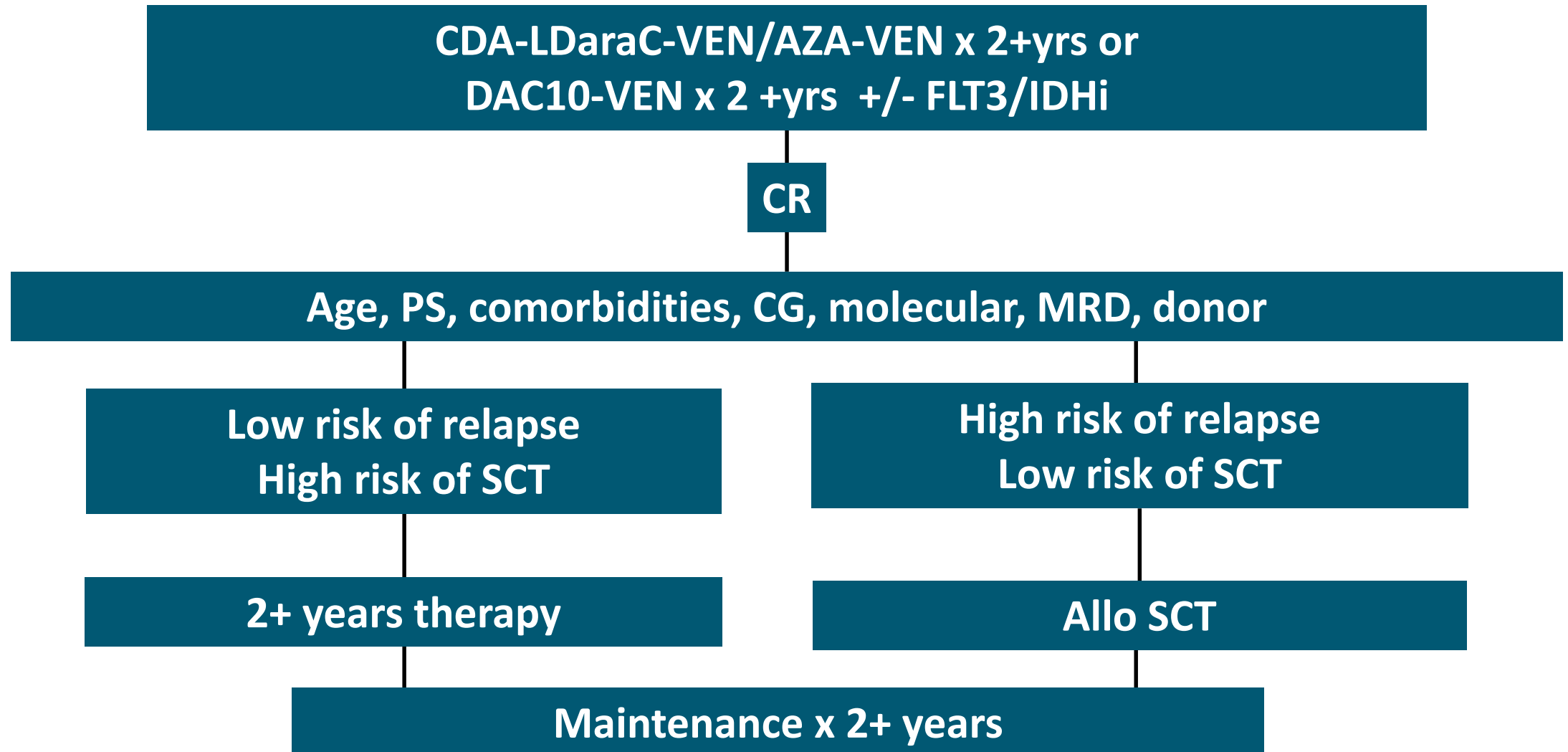
Az AML korszerű kezelése 2018 óta

- 6 fő jellemző
- 1. Cytogenetikai és molekuláris jellemzőkön alapul
- 2. Kevésbé intenzív/agresszív kezelés
- 3. Az MRD jelentősége felértékelődött
- 4. Az allogén HSCT könnyebben elérhető (RIC-alloHSCT, MUD-alloHSCT, Haploidenticus alloHSCT, etc.)
- 5. Idősebb betegek kezelésben paradigma váltás történt
- 6. Az új szereket beillesztették a terápiába

Therapy of AML: The Old Standard



Potential Standard of Care for Older Patients with AML in 2020+



NCCN Guidelines® Recommendations: AML Age ≥ 60 years

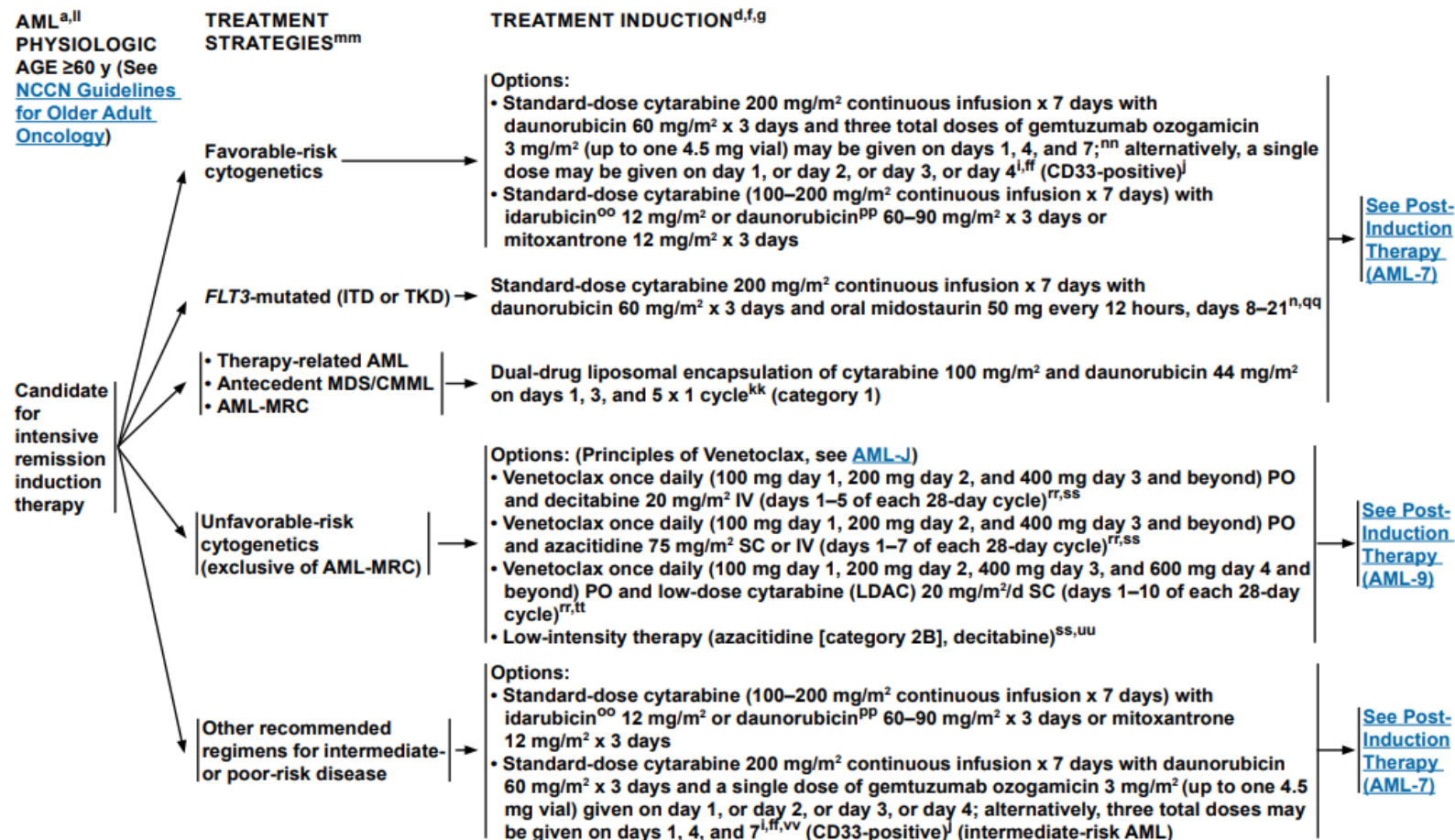


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NCCN Guidelines Version 2.2021

Acute Myeloid Leukemia (Age ≥18 years)

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[See footnotes on AML-5A](#)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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AML-5

NCCN Guidelines® Recommendations: AML Age ≥ 60 years



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AML ^{a,II} PHYSIOLOGIC AGE ≥60 y (See NCCN Guidelines for Older Adult Oncology)	TREATMENT STRATEGIES	TREATMENT INDUCTION ^{d,f,g} Principles of Venetoclax, see AML-J
Not a candidate for intensive remission induction therapy or declines	AML without actionable mutations	<p>Preferred</p> <ul style="list-style-type: none"> • Venetoclax once daily (100 mg day 1, 200 mg day 2, 400 mg day 3 and beyond) PO and azacitidine 75 mg/m² SC or IV (days 1–7 of each 28-day cycle)^{rr,ss} (category 1) • Venetoclax once daily (100 mg day 1, 200 mg day 2, 400 mg day 3 and beyond) PO and decitabine 20 mg/m² IV (days 1–5 of each 28-day cycle)^{rr,ss} <p>Other Recommended</p> <ul style="list-style-type: none"> • Venetoclax once daily (100 mg day 1, 200 mg day 2, 400 mg day 3, and 600 mg day 4 and beyond) PO and LDAC 20 mg/m²/d SC (days 1–10 of each 28-day cycle)^{ss,tt} • Low-intensity therapy (azacitidine, decitabine)^{ss,uu} • Glasdegib (100 mg PO daily on days 1–28) + LDAC 20 mg SC every 12 hours (days 1–10 of each 28-day cycle)^{ww} • Gemtuzumab ozogamicin 6 mg/m² on day 1 and 3 mg/m² on day 8^{xx,yy} (CD33-positive)^l (category 2B) • LDAC (category 3) 20 mg/m²/day SC for 10 consecutive days every 4 weeks^{zz} • Best supportive care (hydroxyurea, transfusion support)
	IDH1 or IDH2 mutation	<p>Preferred</p> <ul style="list-style-type: none"> • Ivosidenib^{aaa,bbb} (IDH1 only) • Enasidenib^{bbb,ccc} (IDH2 only) • Venetoclax-based therapy (same as above in combination with azacitidine,^{rr,ss} or decitabine^{rr,ss}) (category 1 for combination with azacitidine) <p>Other Recommended</p> <ul style="list-style-type: none"> • Low-intensity therapy (azacitidine, decitabine)^{ss,uu} • Venetoclax-based therapy (same as above in combination with LDAC^{tt})
	FLT3 mutation	<p>Preferred</p> <ul style="list-style-type: none"> • Venetoclax-based therapy (same as above in combination with azacitidine,^{rr,ss} or decitabine^{rr,ss}) (category 1 for combination with azacitidine) <p>Other Recommended</p> <ul style="list-style-type: none"> • Low-intensity therapy (azacitidine, decitabine) + sorafenib^{ss,ddd} (FLT3-ITD-positive) • Venetoclax-based therapy (same as above in combination with LDAC^{tt})

See
Post-Induction
Therapy
(AML-9)

[See footnotes on AML-6A](#)

Note: All recommendations are category 2A unless otherwise indicated.
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AML-6

NCCN Guidelines® Recommendations: AML Age ≥ 60 years



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NCCN Guidelines Version 2.2021 Acute Myeloid Leukemia (Age ≥18 years)

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AML ^{a,ii} PHYSIOLOGIC AGE ≥60 y (See NCCN Guidelines for Older Adult Oncology)	TREATMENT STRATEGIES ^{mm}	TREATMENT INDUCTION ^{d,f,g}	
Candidate for intensive remission induction therapy	Favorable-risk cytogenetics	Options: • Standard-dose cytarabine 200 mg/m ² continuous infusion x 7 days with daunorubicin 60 mg/m ² x 3 days and three total doses of gemtuzumab ozogamicin 3 mg/m ² (up to one 4.5 mg vial) may be given on days 1, 4, and 7; ⁿⁿ alternatively, a single dose may be given on day 1, or day 2, or day 3, or day 4; ^{l,ff} (CD33-positive) • Standard-dose cytarabine (100–200 mg/m ² continuous infusion x 7 days) with idarubicin ^{oo} 12 mg/m ² or daunorubicin ^{pp} 60–90 mg/m ² x 3 days or mitoxantrone 12 mg/m ² x 3 days	See Post-Induction Therapy (AML-7)
	FLT3-mutated (ITD or TKD)	Standard-dose cytarabine 200 mg/m ² continuous infusion x 7 days with daunorubicin 60 mg/m ² x 3 days and oral midostaurin 50 mg every 12 hours, days 8–21 ^{n,qq}	
	• Therapy-related AML • Antecedent MDS/CMML • AML-MRC	Dual-drug liposomal encapsulation of cytarabine 100 mg/m ² and daunorubicin 44 mg/m ² on days 1, 3, and 5 x 1 cycle ^{kk} (category 1)	
	Unfavorable-risk cytogenetics (exclusive of AML-MRC)	Options: (Principles of Venetoclax, see AML-4) • Venetoclax once daily (100 mg day 1, 200 mg day 2, and 400 mg day 3 and beyond) PO and decitabine 20 mg/m ² IV (days 1–5 of each 28-day cycle) ^{rr,ss} • Venetoclax once daily (100 mg day 1, 200 mg day 2, and 400 mg day 3 and beyond) PO and azacitidine 75 mg/m ² SC or IV (days 1–7 of each 28-day cycle) ^{rr,ss} • Venetoclax once daily (100 mg day 1, 200 mg day 2, 400 mg day 3, and 600 mg day 4 and beyond) PO and low-dose cytarabine (LDAC) 20 mg/m ² /d SC (days 1–10 of each 28-day cycle) ^{rr,tt} • Low-intensity therapy (azacitidine [category 2B], decitabine) ^{ss,uu}	See Post-Induction Therapy (AML-9)
	Other recommended regimens for intermediate- or poor-risk disease	Options: • Standard-dose cytarabine (100–200 mg/m ² continuous infusion x 7 days) with idarubicin ^{oo} 12 mg/m ² or daunorubicin ^{pp} 60–90 mg/m ² x 3 days or mitoxantrone 12 mg/m ² x 3 days • Standard-dose cytarabine 200 mg/m ² continuous infusion x 7 days with daunorubicin 60 mg/m ² x 3 days and a single dose of gemtuzumab ozogamicin 3 mg/m ² (up to one 4.5 mg vial) given on day 1, or day 2, or day 3, or day 4; alternatively, three total doses may be given on days 1, 4, and 7; ^{l,ff,vv} (CD33-positive) (intermediate-risk AML)	See Post-Induction Therapy (AML-7)

[See footnotes on AML-5A](#)

Note: All recommendations are category 2A unless otherwise indicated.
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Recent FDA Drug Approvals (since 2017) in AML

Treatment (approval date)	Description	Indication
Midostaurin (April 2017)	Multikinase FLT3 inhibitor	Newly diagnosed <i>FLT3</i> -mutated (as detected by FDA-approved test) AML, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Gemtuzumab ozogamycin (September 2017)	Anti-CD33 antibody–drug conjugate	Adults with newly diagnosed CD33-positive AML; refractory-relapsed CD33-positive AML in patients ≥ 2 years of age
CPX-351 (August 2017)	Liposomal cytarabine and daunorubicin at a fixed 5:1 molar ratio	Newly diagnosed therapy-related AML, secondary AML or AML with myelodysplasia-related changes
Glasdegib (November 2018)	Hedgehog pathway inhibitor	Newly diagnosed AML aged ≥ 75 years or with co-morbidities that preclude the use of intensive induction chemotherapy (in combination with low-dose cytarabine)
Venetoclax (November 2018)	BCL-2 inhibitor	In combination with azacitidine or decitabine, or low-dose cytarabine in newly diagnosed AML aged ≥ 75 years or with co-morbidities that preclude the use of intensive induction chemotherapy
Enasidenib (August 2017)	IDH2 inhibitor	Relapsed or refractory <i>IDH2</i> -mutated AML (as detected by FDA-approved test)
Ivosidenib (July 2018) (May 2019)	IDH1 inhibitor	1. Relapsed or refractory <i>IDH1</i> -mutated (susceptible mutation, as detected by FDA-approved test) AML. 2. First line treatment of <i>IDH1</i> -mutated AML (as detected by FDA-approved test), patients ≥ 75 years old or ineligible to receive intensive chemotherapy.
Gilteritinib (November 2018)	FLT3 inhibitor	Patients with relapsed or refractory <i>FLT3</i> -mutated AML (as detected by FDA-approved test)
CC-486 (September 2020)	Oral azacitidine hypomethylating agent (30% absorption) approved at 300 mg daily \times 14 every month	Continued treatment of adult patients with AML who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and who are not able to complete intensive curative therapy
Oral Decitabine-cedazuridine (July 2020)	Oral hypomethylating agent (100% absorption)	Alternative to parenteral HMAs decitabine for the treatment of adults with MDS (pretreated/untreated; de novo/secondary) or CMML

Summary of combination of targeted-therapy trials in IDH1/2-mutant newly diagnosed AML

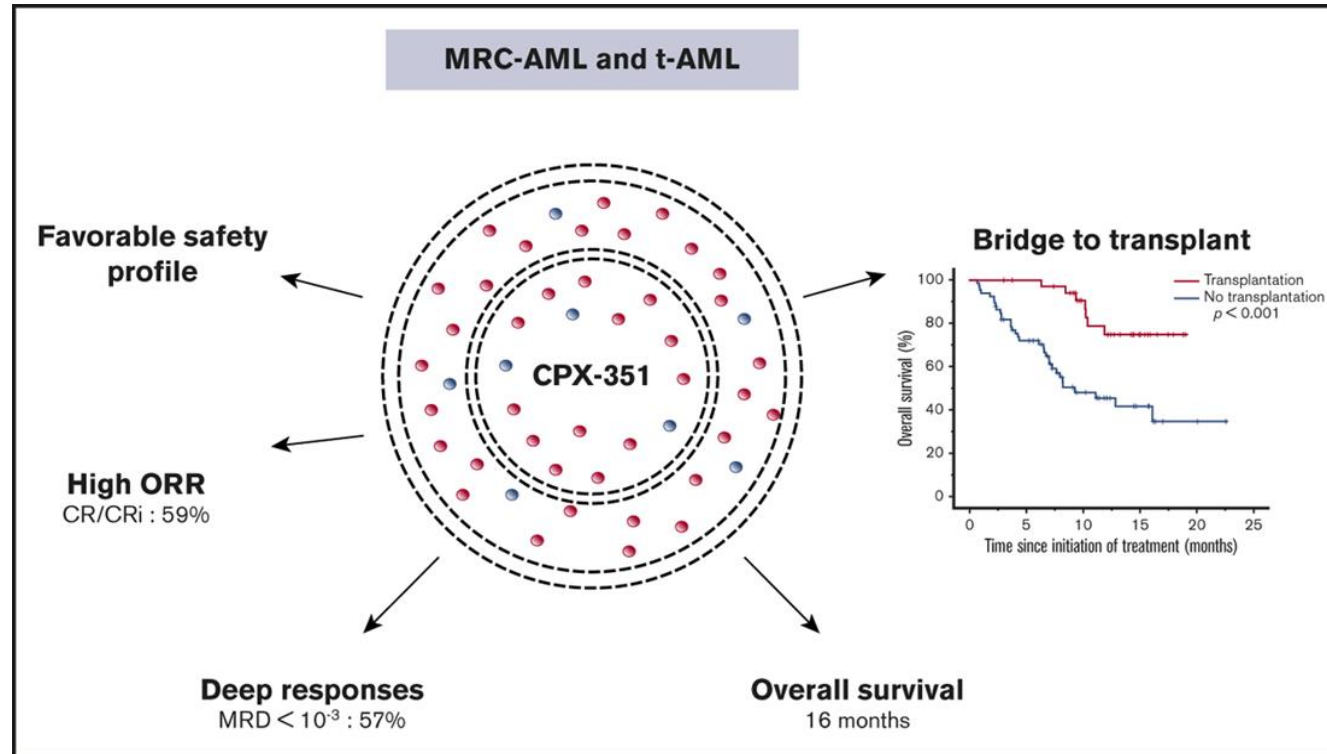
Regimens	Phase	Patient Number	CR/CRi rate, %	Time to CR or response (median), months	OS (median), months
HMA + venetoclax	Ib	35	71	2.1	24.4
AZA + venetoclax	III	46	75.4	N/A	N/A
AZA + venetoclax	Pooled data from two trials	79	72	1.0	24.5
LDAC + venetoclax (HMA naïve)	Ib/II III	18	72	1.4	19.4
AZA + ivosidenib	Ib	23	69.6	3.7	N/A
AZA + enasidenib	II	68	68	5	22.0
Venetoclax + ivosidenib	Ib/II	12	83	NA	NA
AZA + venetoclax + ivosidenib	Ib/II	6	67	NA	NA

New standards of care in AML

- 1. Phase III QUAZAR AML-001: Oral Azacitidine (ONUREG®) as Maintenance Therapy in First-Remission AML (improved OS & RFS)
- 2. SORMAIN: OS with Sorafenib Maintenance After Allogeneic HCT in *FLT3*+ AML (improved OS & RFS)
- 3. Vosaroxin: First-in-Class Anticancer Quinolone Derivative (VALOR Phase III trial): Intercalates DNA and inhibits topoisomerase II. Stable quinolone core (no metabolites, free radicals, or ROS, low likelihood for off-target organ damage and cardiotoxicity, evades common mechanisms of drug resistance, not a substrate for P-glycoprotein, and activity independent of *TP53* status): improved CR rate: 31.9% vs 13.8% ($P < .0001$), and improved OS
- 4. Liposomal Cytarabine and Daunorubicin (CPX-351=VYXEOS®): Phase III CPX-351 vs Standard 7+3 chemotherapy in Older Patients With Newly Diagnosed tAML or sAML (improved OS and EFS especially in 70-75 Yrs of Age patients)

New standards of care in AML

■ CPX-351 (Vyxeos®)



The overall response rate after induction by CPX-351 was 59%, and MRD <10⁻³ was achieved in 57% of CR/CRi patients.

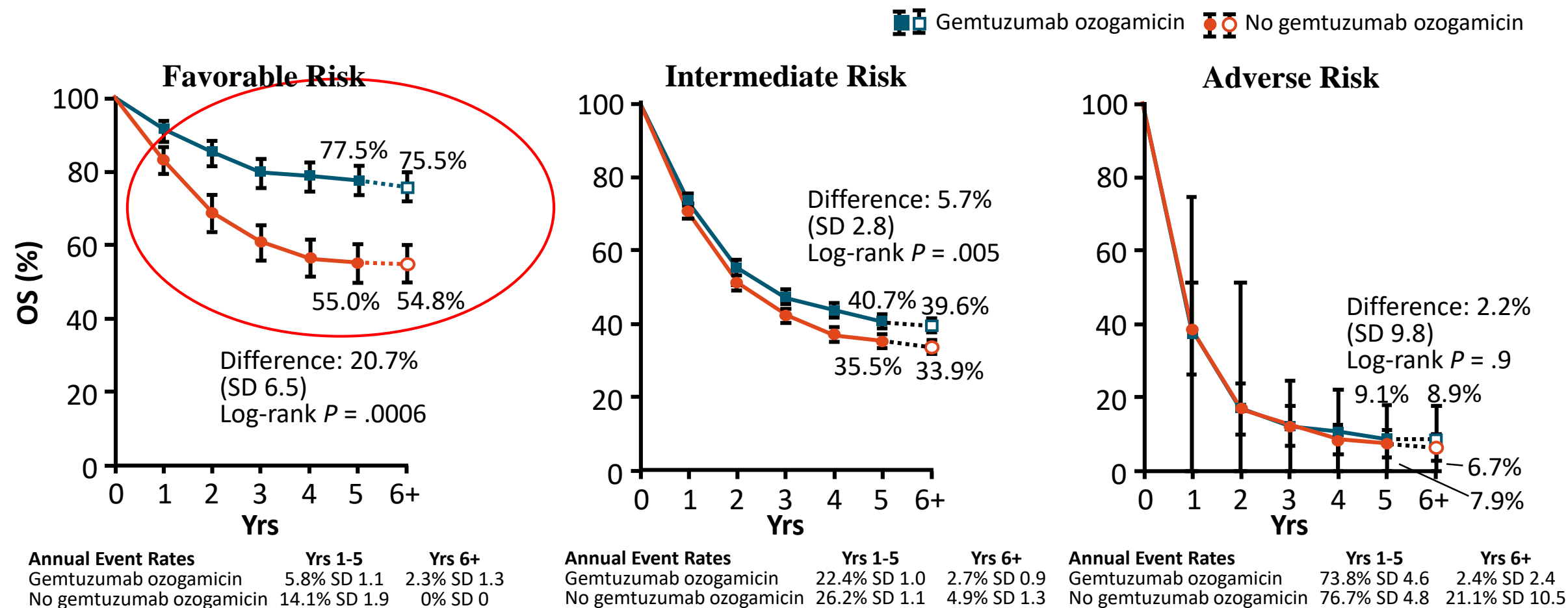
CPX-351 improves the poor prognosis associated with some unfavorable mutations defined in the 2017 ELN risk stratification.

The efficacy and safety of CPX-351 in high-risk AML (t-AML and MRC-AML). CPX-351 is a treatment of choice for patients aged ≥60 years.

New standards of care in AML

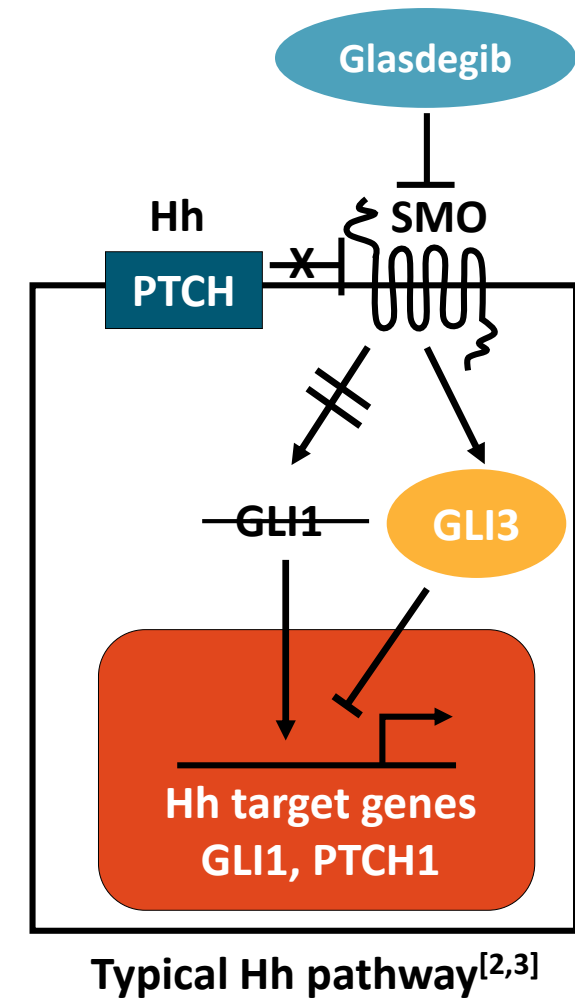
- 5. RATIFY phase III: Frontline 7+3 Chemotherapy ± Midostaurin in *FLT3*-Mutated AML Patients (median OS improved with CR rate of 59% vs. 54%)
- 6. QuANTUM-R Phase III Study Design: *FLT3* Inhibitor Quizartinib in R/R AML (median OS improved 27% vs. 20%)
- 7. Phase III ADMIRAL Study: Gilteritinib in *FLT3*-Mutant R/R AML (median OS improved 9.3 mons vs. 5.6 with 1-yr survival rate of 37% vs. 17%) and conversion to transfusion independence occurred in 31%
- 8. Gemtuzumab Ozogamicin: Reapproved for Adults With ND or R/R CD33-Positive AML (Phase III ALFA-0701: First-line combination, Phase III EORTC-GIMEMA AML-19: First-line monotherapy, and phase II MyloFrance-1: R/R disease)

Gemtuzumab Ozogamicin in AML Induction Therapy: Meta-analysis of 5 Randomized Trials



New standards of care in AML: Targeting Hedgehog Pathway Signaling in AML

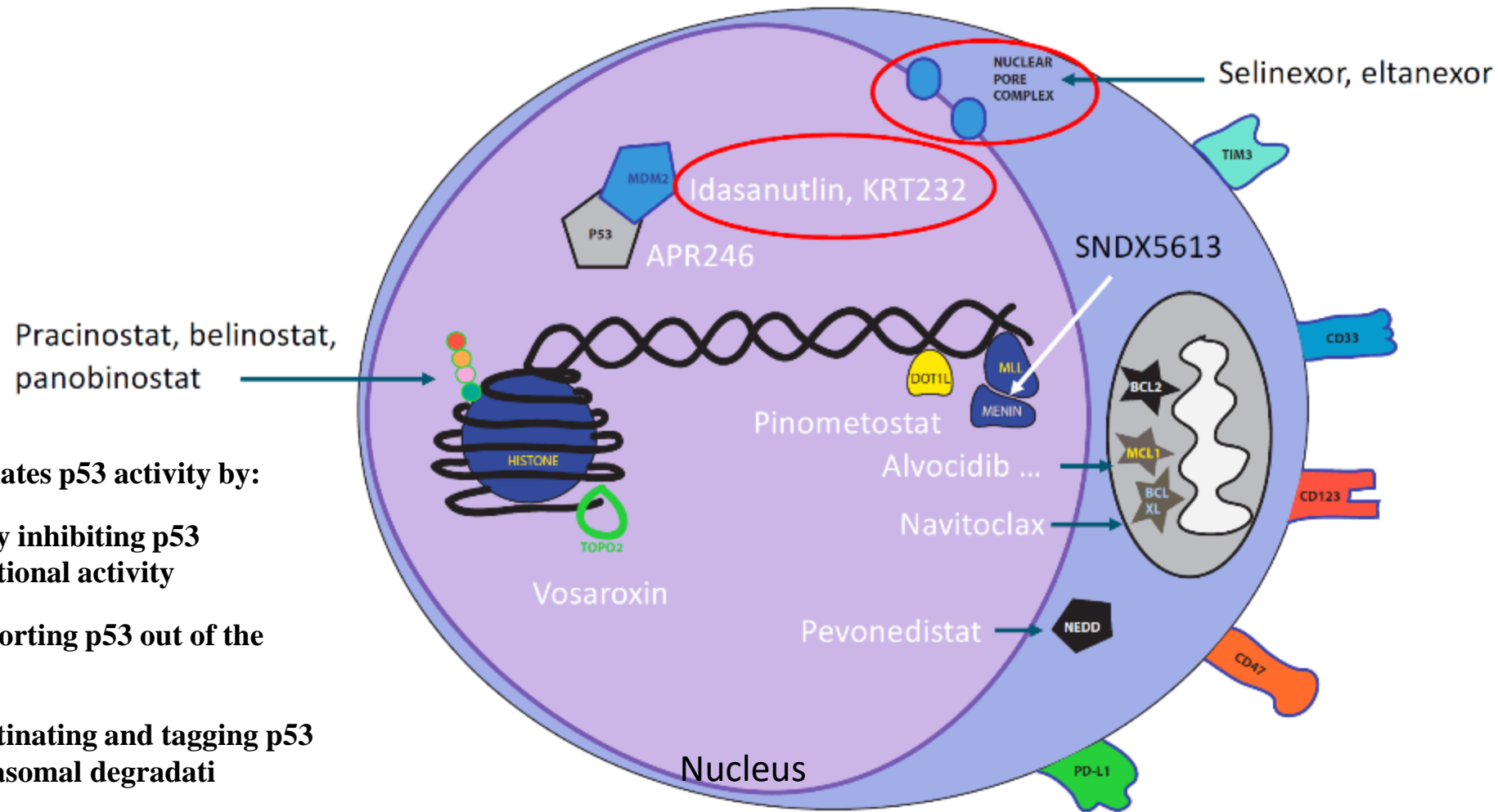
- 9. Aberrant Hedgehog (HH) pathway signaling critical for leukemia stem cell survival and expansion^[1]
- Overexpression of HH pathway components observed in chemotherapy-resistant myeloid leukemia cells
- Inhibition of HH pathway enhanced sensitivity to chemotherapy
- Glasdegib is a potent, selective oral inhibitor of HH signaling pathway through binding to Smoothened (SMO)
- Glasdegib: selective, potent oral inhibitor of transmembrane protein smoothened (SMO), a component of the sonic hedgehog (Hh) signaling pathway and resulted in **improvement of OS and CR rate**
- Overcomes therapy resistance in LSC and bulk AML cells
- Other agents: Sonidegib, Vismodegib



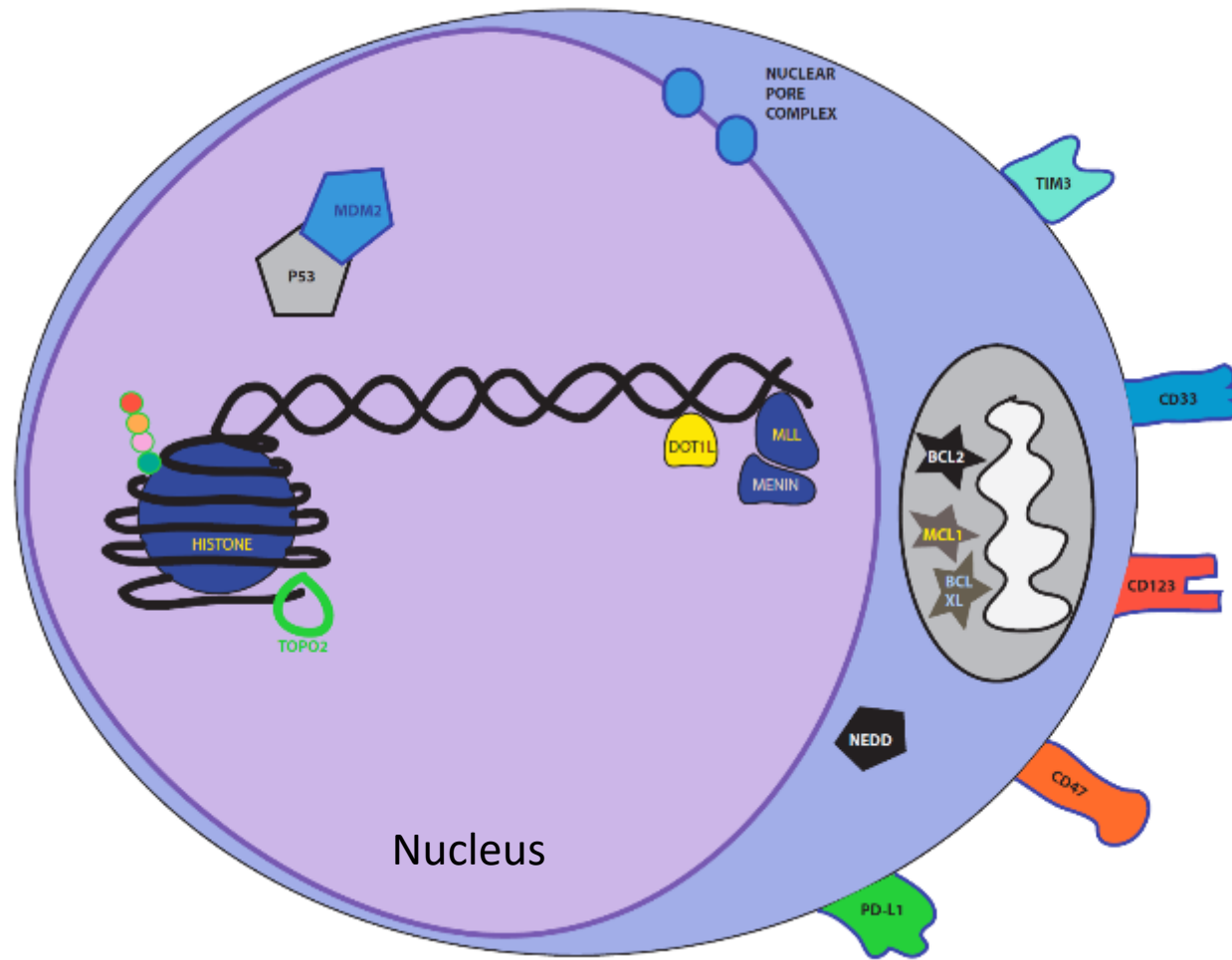
Intracelluláris célok a vizsgálati AML terápiákhoz

MDM2 modulates p53 activity by:

1. Directly inhibiting p53 transcriptional activity
2. Transporting p53 out of the nucleus
3. Ubiquitinating and tagging p53 for proteasomal degradation



Extracelluláris célok a vizsgálati AML terápiákhoz



Agent

MBG453

AMV564

UCAR123

Magrolimab

Nivolumab

Modality

Monoclonal Ab

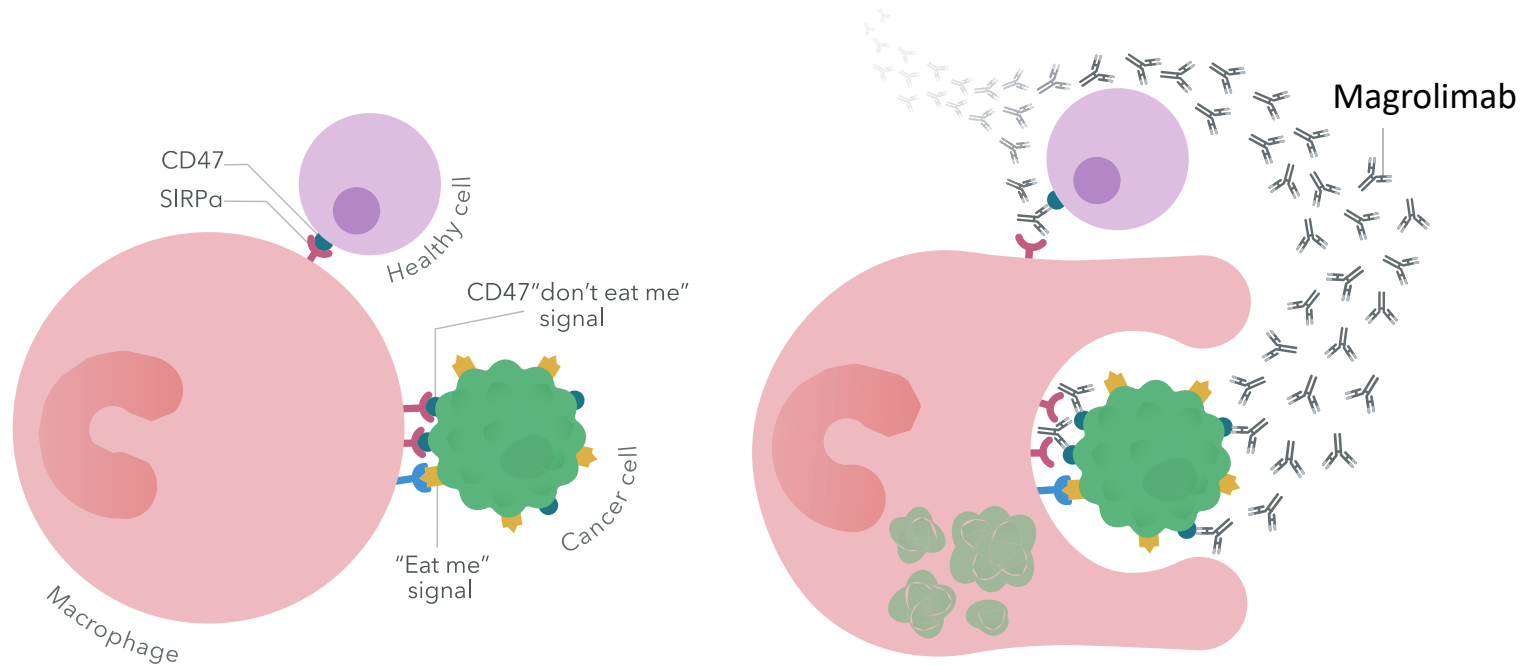
BITE

CAR-T

Monoclonal Ab

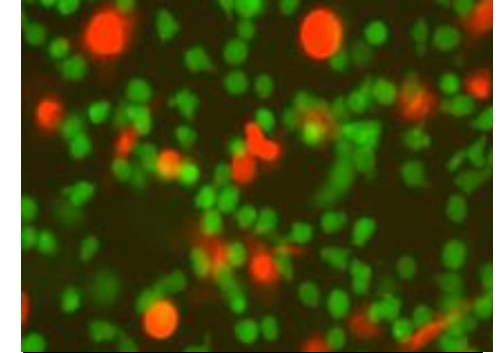
Monoclonal Ab

Magrolimab egy makrofág Checkpoint Gátlószer

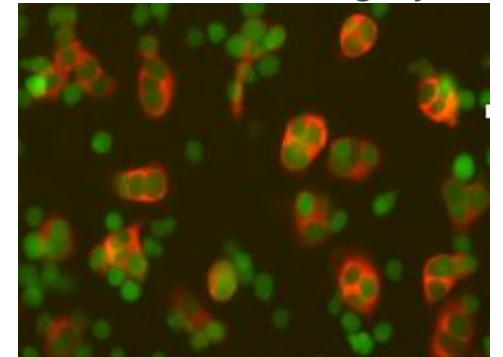


- Magrolimab is an IgG4 anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

Control mAb: No Phagocytosis

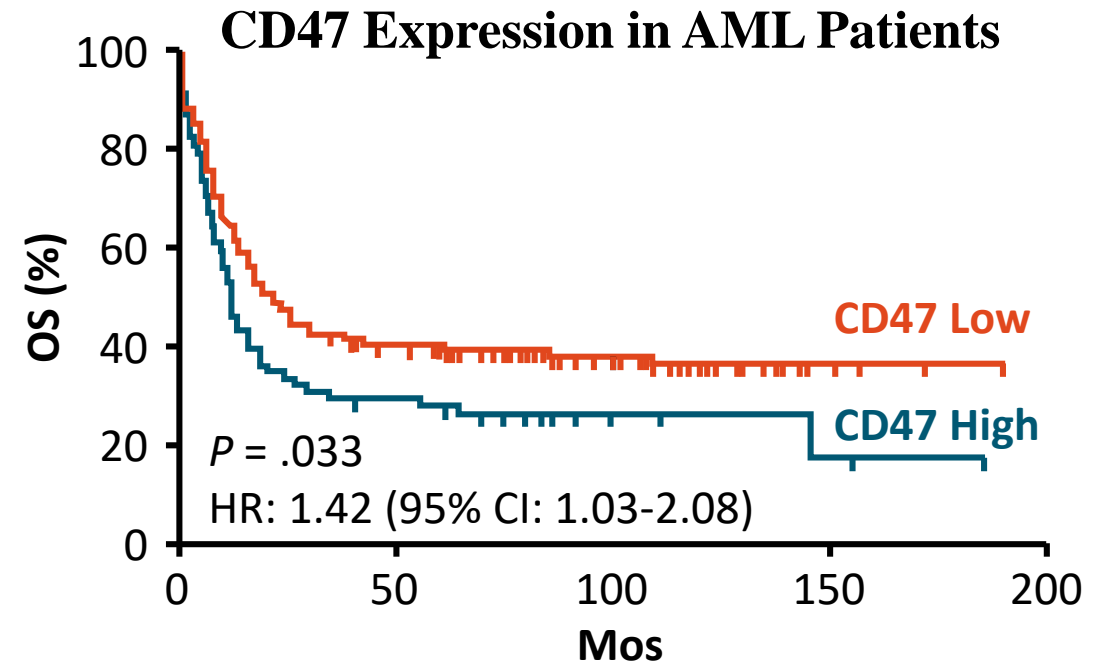
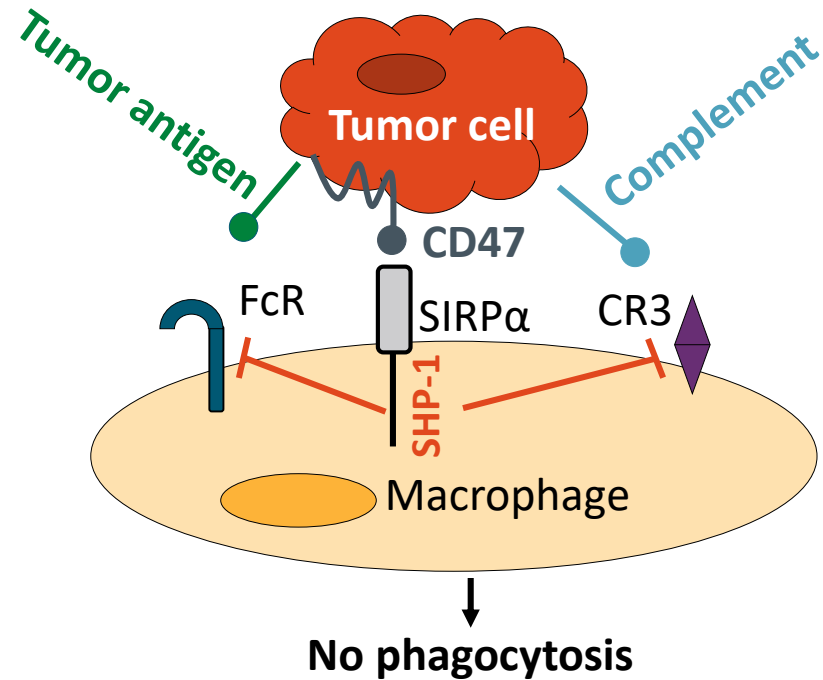


Anti-CD47 mAb: Phagocytosis



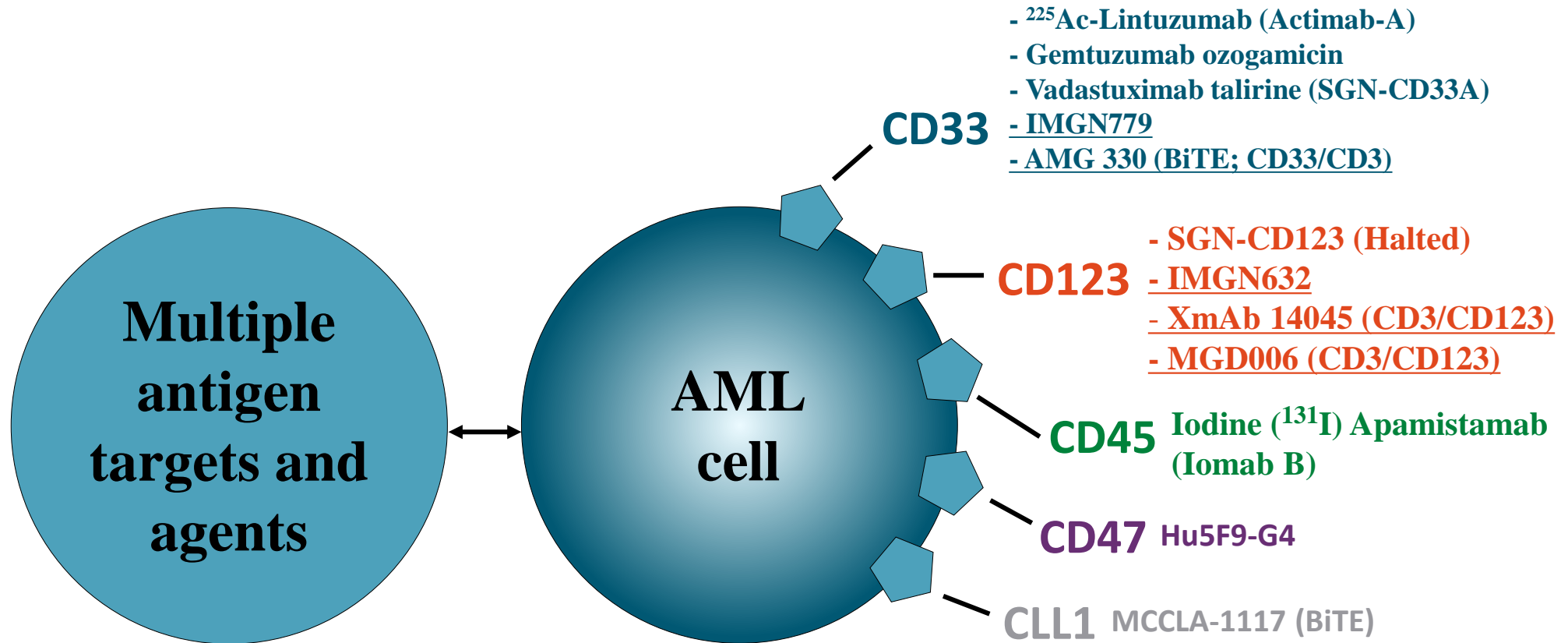
Macrophages Cancer cells

CD47: Impact in Myeloid Malignancies including MDS and AML

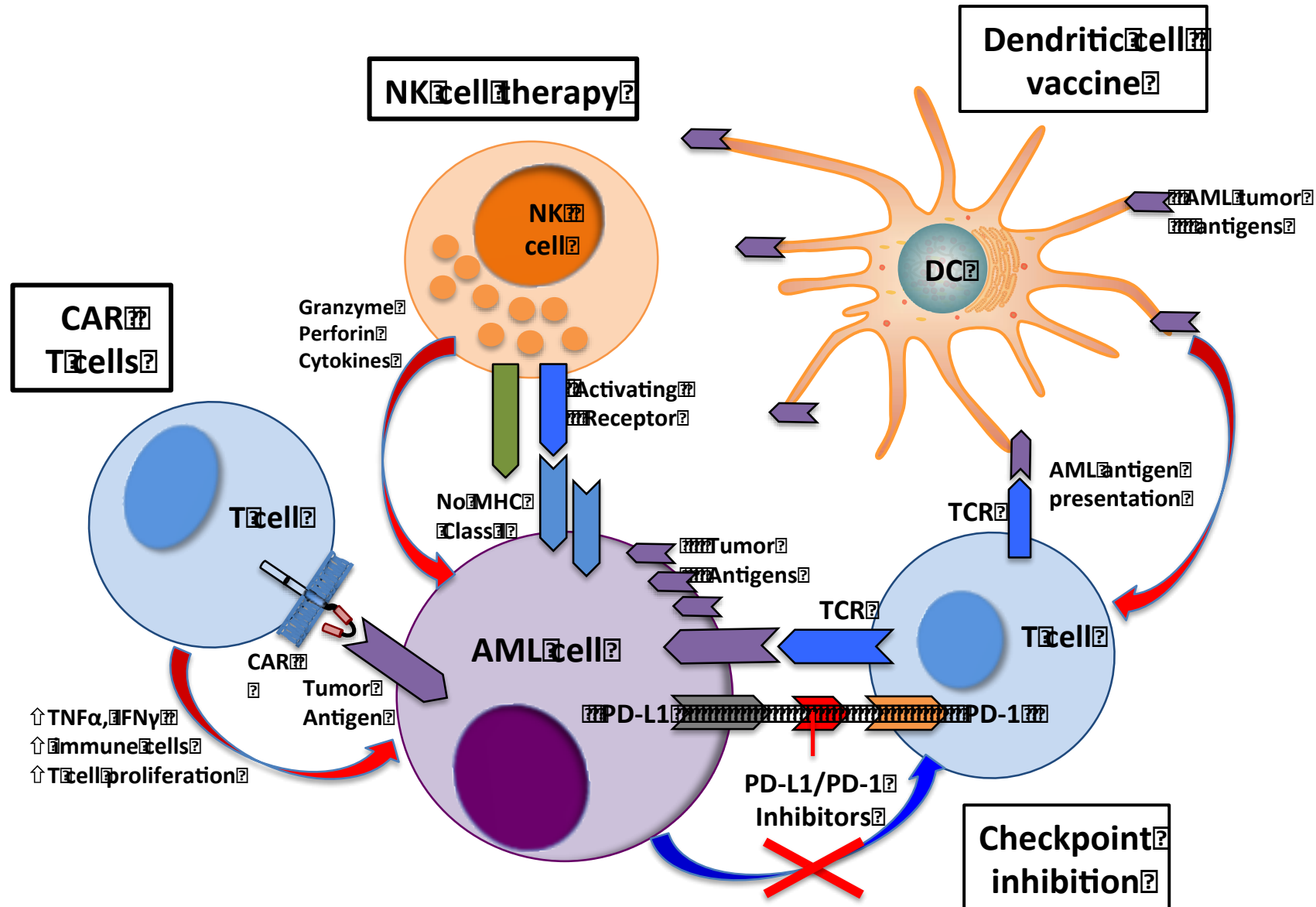


- CD47 is a “do not eat me” signal on cancers that enables macrophage immune evasion.
- Increased CD47 expression predicts worse prognosis in AML patients

Cél antigének és új antitestek az AML kezelésében

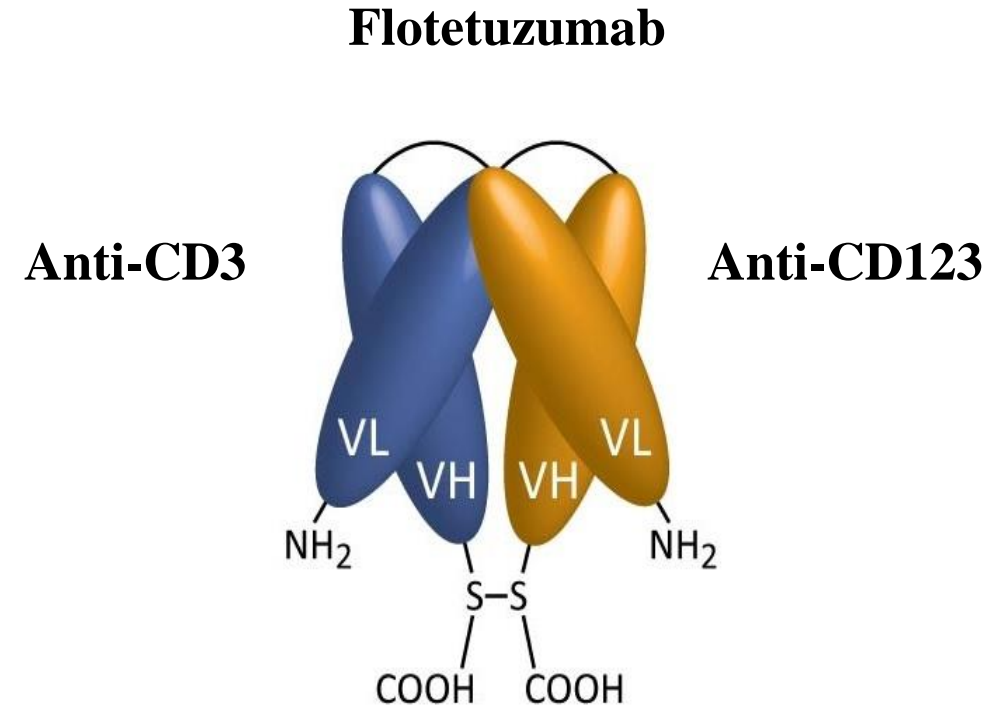


AML immunoterápia



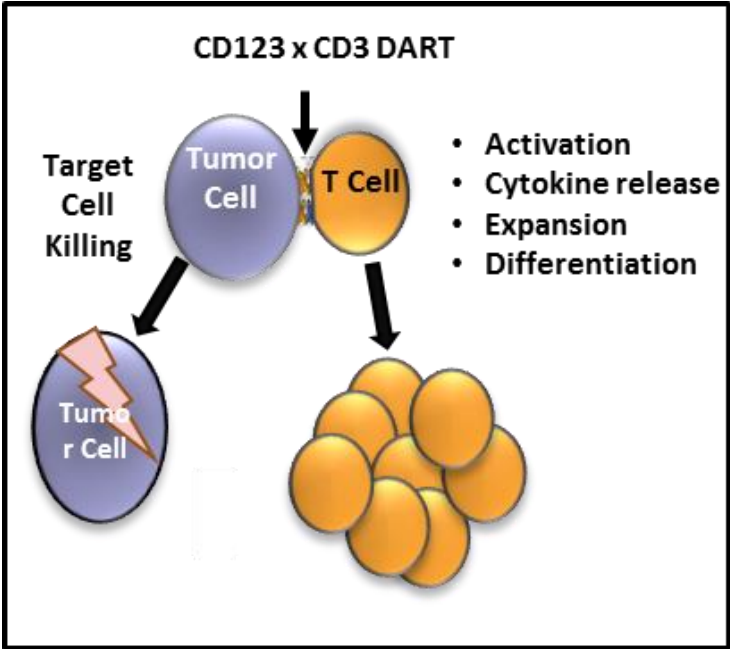
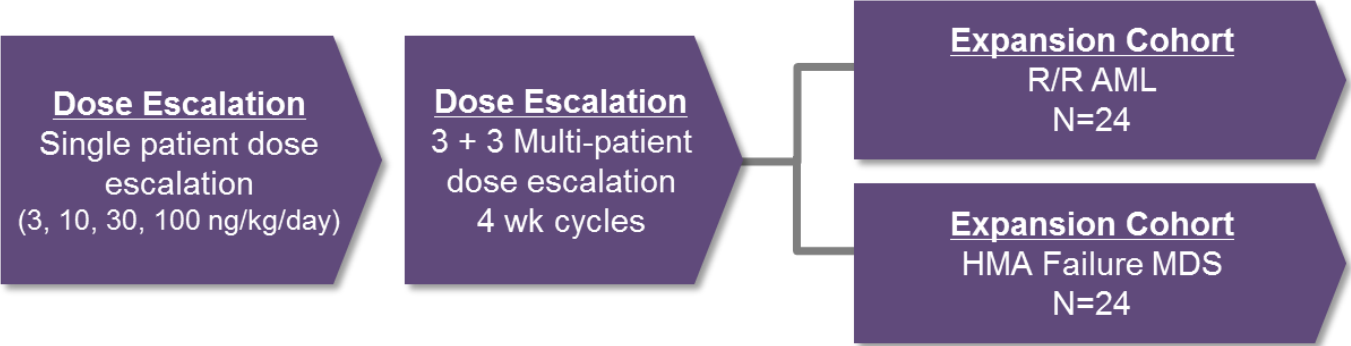
Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART Molecule

- Bivalent, bispecific (CD3 x CD123) construct co-engaging T-cells with a tumor-associated antigen
- DART: dual-affinity retargeting agent
- CD123: low-affinity receptor for IL-3
 - Usually present on basophils, monocytes, hematopoietic progenitor cells, plasmacytoid dendritic cells
 - Overexpressed on leukemic stem cells in hematologic malignancies, including AML
- Flotetuzumab engineered to redirect T-cells to kill tumor cells and recognize tumors regardless of TCR, MHC



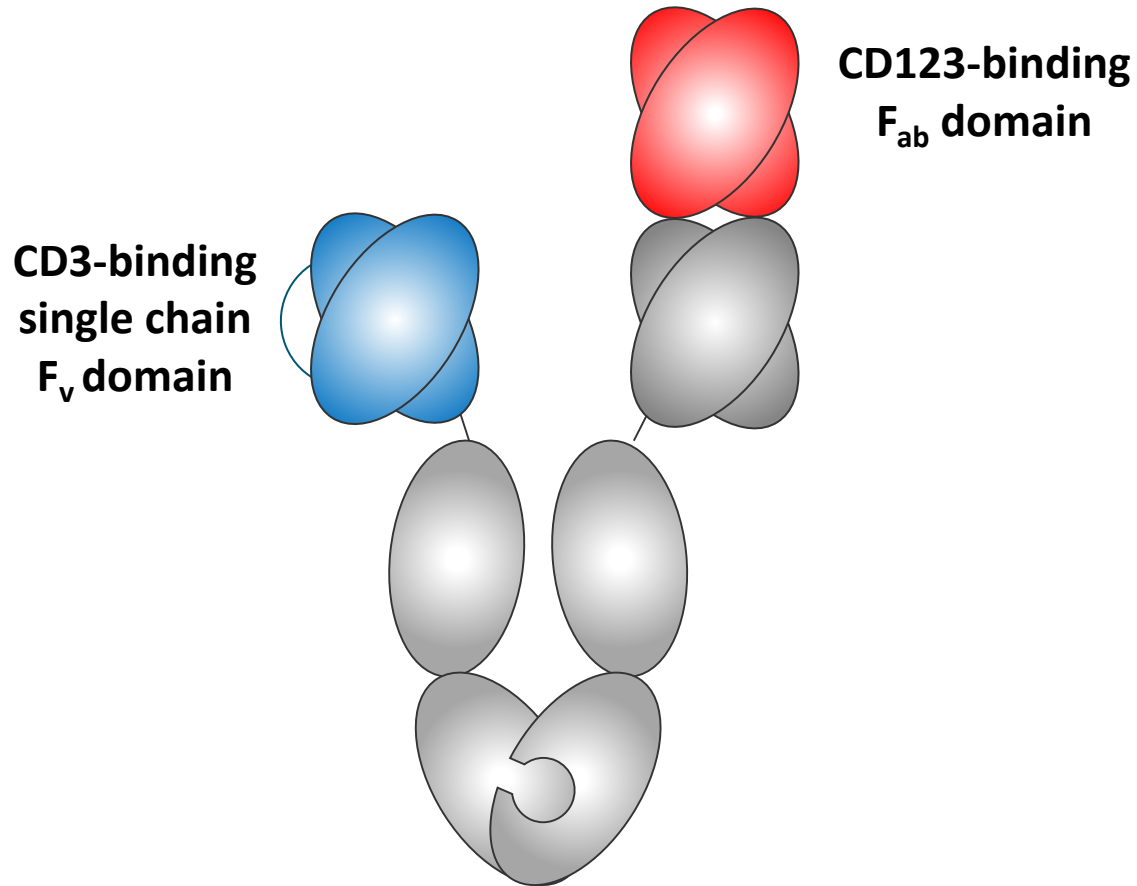
Flotetuzumab (MGD006): CD123 x CD3 Bispecific DART Protein

Phase I clinical trial in relapsed/refractory AML



Schedule	Dosing
Lead-in dose	▪ Wk 1: 30 ng/kg/day x 3 days, 100 ng/kg/day x 4 days
Cycle 1 Wks 2-4	▪ Arm A (cohorts 2-5): 4 days on/3 days off ▪ Arm B (cohorts 6-10): 21-day continuous infusion
Cycle 2 and beyond	▪ 4 days on/3 days off

Vibecotamab (XmAb14045): CD123 x CD3 Bispecific Antibody

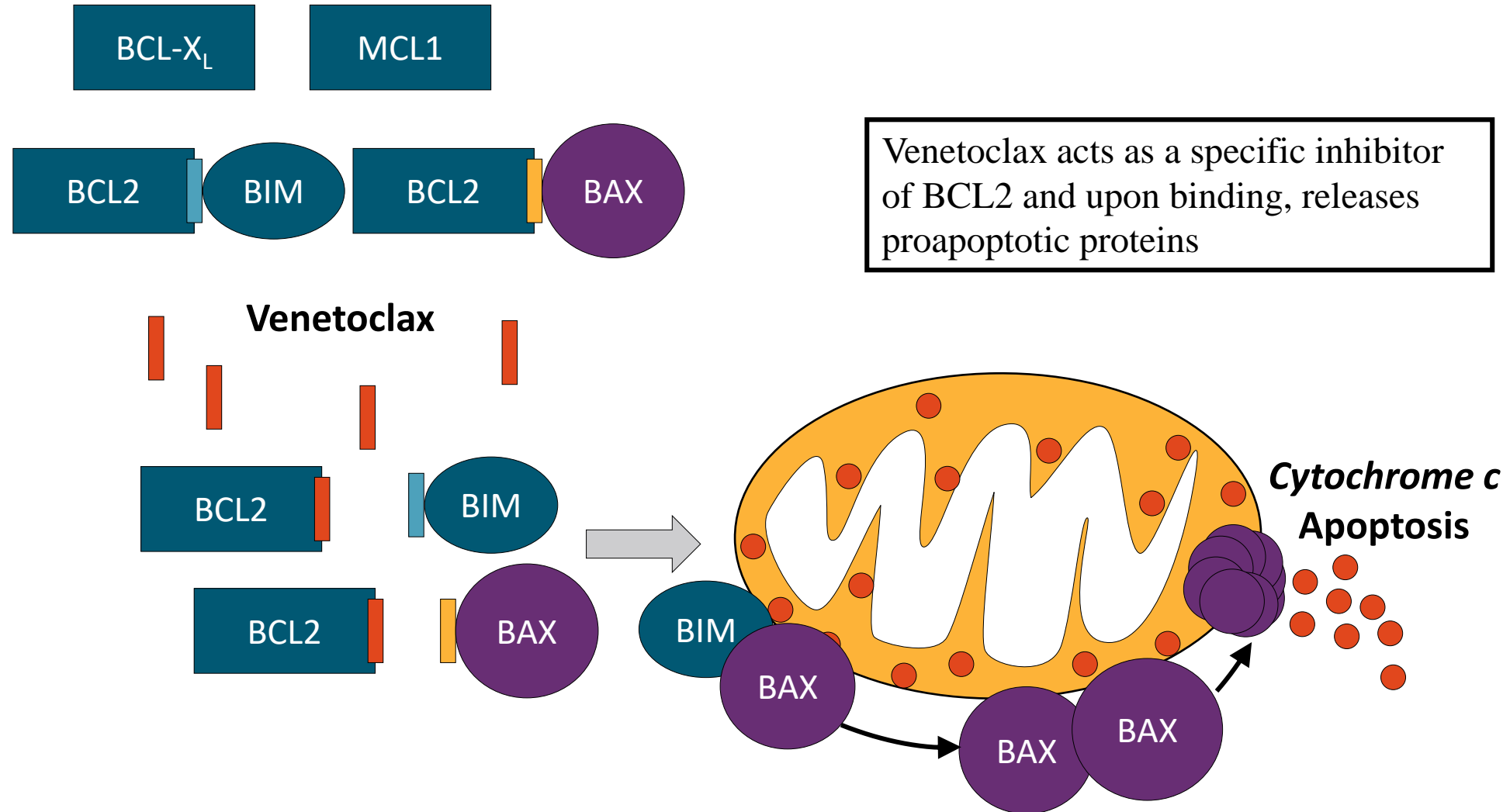


- Full-length IgG developed for intermittent dosing
 - Smaller constructs (eg, DART or BiTE bispecific Abs) need to be continuously infused
- Stimulates T-cell–mediated killing of CD123-positive cells independent of T-cell antigen specificity
- Ablation of Fcγ receptor binding eliminates possible receptor-mediated crosslinking, activation of T-cells

Venetoclax: BCL-2 szelektív inhibitora

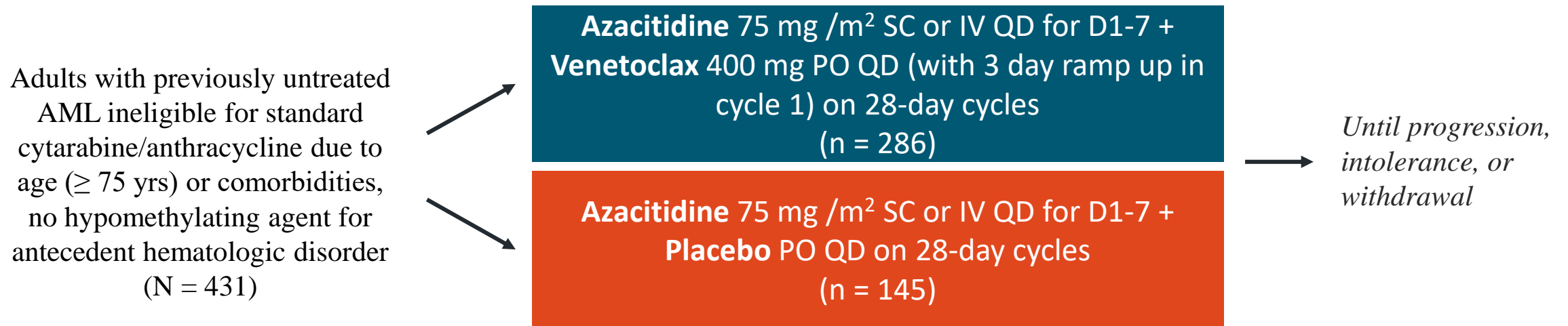
- Venetoclax elősegíti az apoptózist azáltal, hogy szelektíven gátolja a BCL-2-t.
- BCL-2 overexpressziója lehetővé teszi a daganatos sejtek számára, hogy proapoptotikus fehérjék szekveszterásával elkerüljék az apoptózist.
- Venetoclax szelektíven kötődik a BCL-2-hez, ezáltal felszabadítva a proapoptotikus fehérjéket az apoptózis elindításához.

AML: BCL-2 célzott inhibitora Venetoclax-al



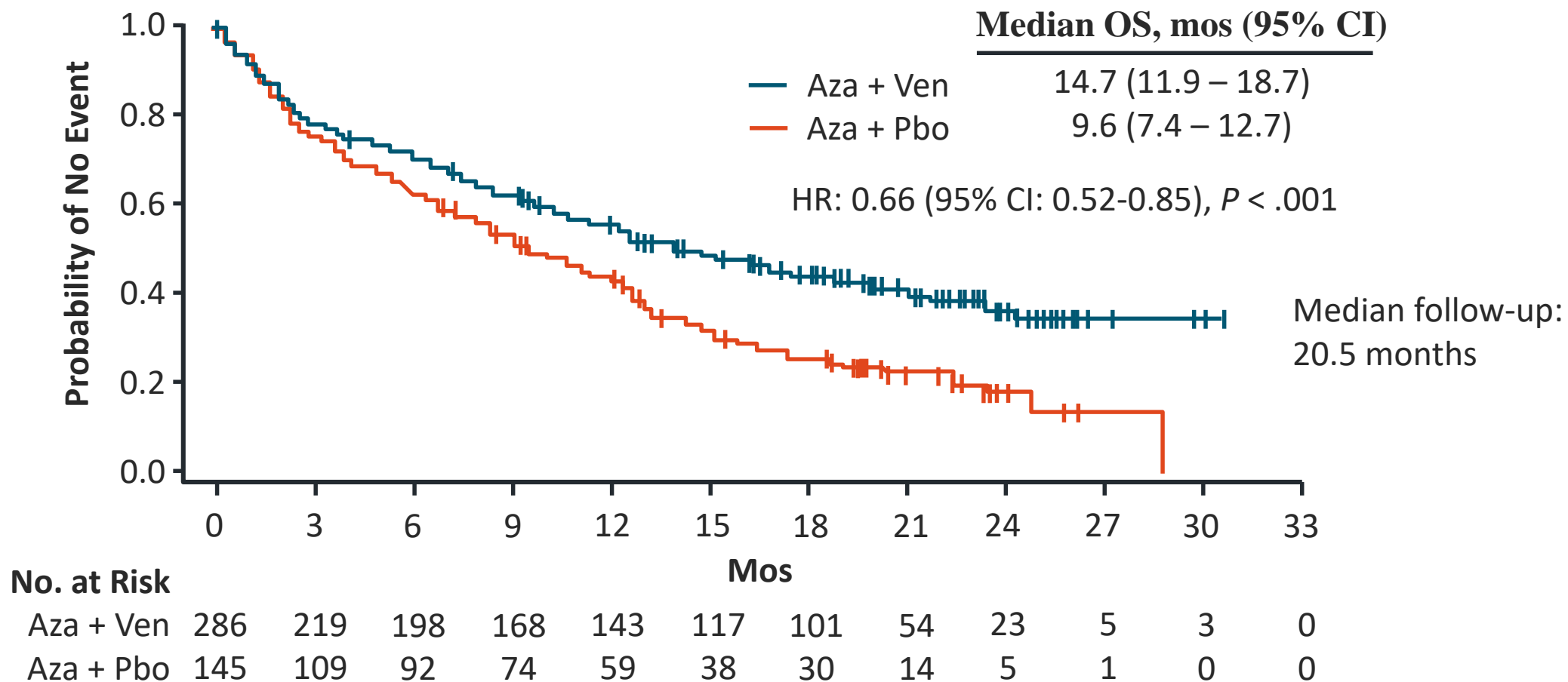
VIALE-A: Azacitidine ± Venetoclax in Treatment-Naive AML Ineligible For Standard Induction Therapy

- Multicenter, double-blind, placebo-controlled, randomized phase III trial

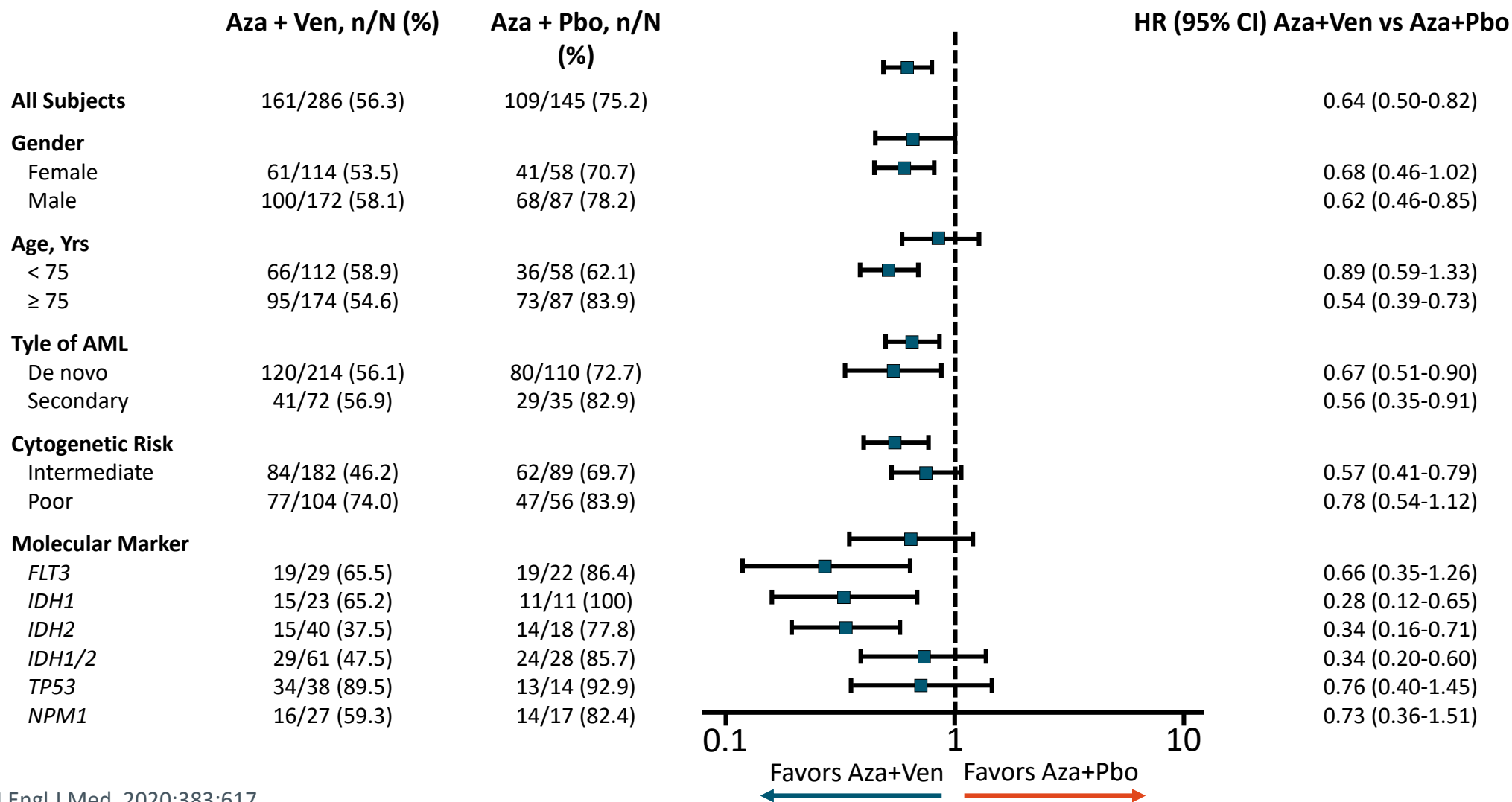


- Primary endpoint: OS, rate of CR + CRi (outside the US)
- Other endpoints: composite CR or CRi, EFS, OS by molecular subtype, QoL, CR, transfusion independence

VIALE-A: OS



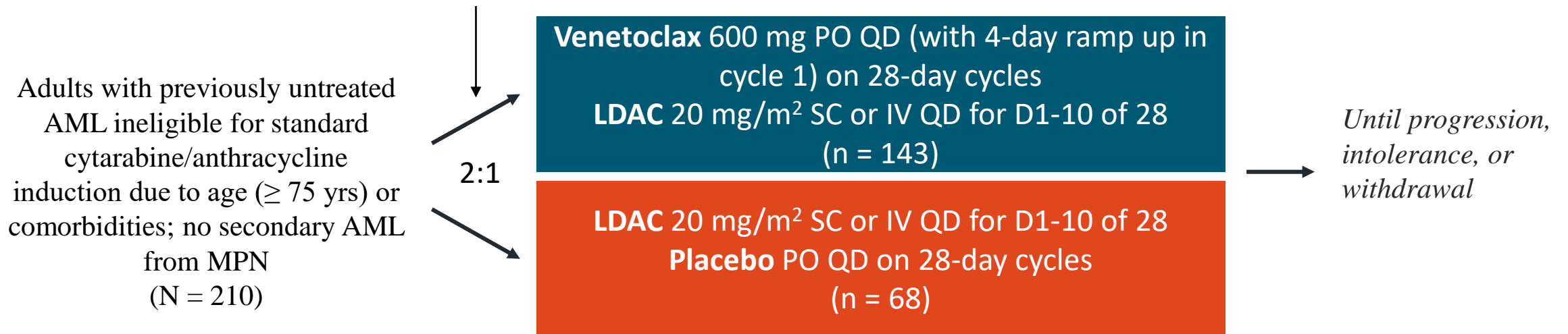
VIALE-A: OS by Subgroup



VIALE-C: LDAC ± Venetoclax in Treatment-Naive AML Ineligible For Standard Induction Therapy

- Multicenter, global, double-blind, placebo-controlled, randomized phase III trial

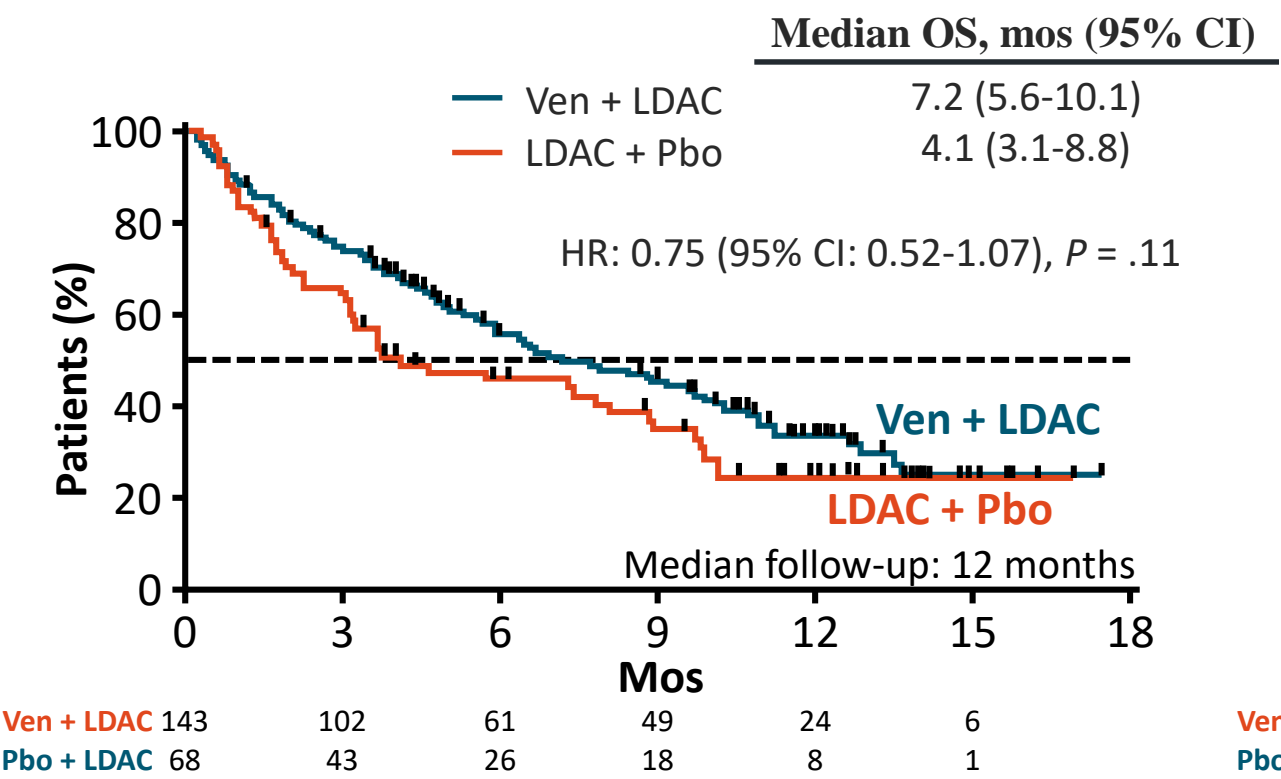
Stratified by AML status (secondary vs de novo), age (18-74 vs > 74), region (US vs Europe vs China vs Japan vs rest of world)



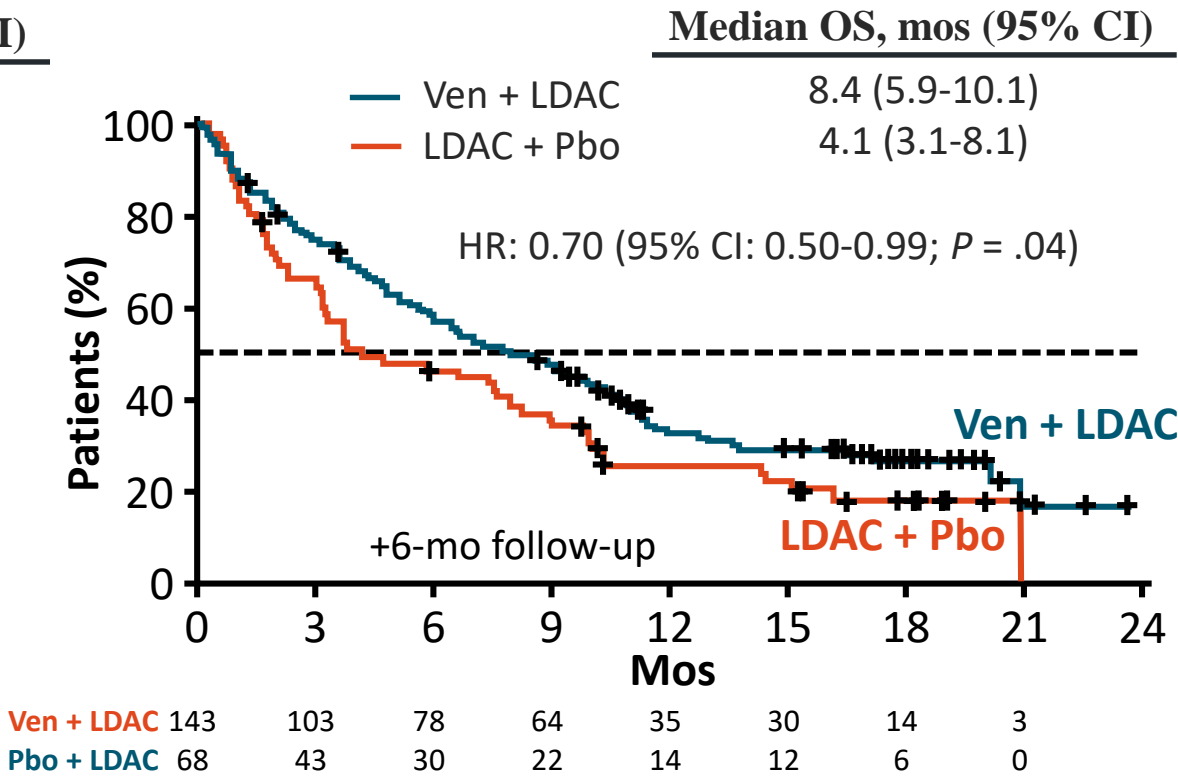
- Primary endpoint: OS
- Other endpoints: CR, CR+CRh, CR+CRi, CR/CRi and CR/CRh by cycle 2, EFS, MRD, response rates and OS by molecular subtype, QoL, transfusion independence

VIALE-C: OS

Preplanned OS analysis (median F/U: 12.0 months)



OS analysis with 6 additional months of F/U



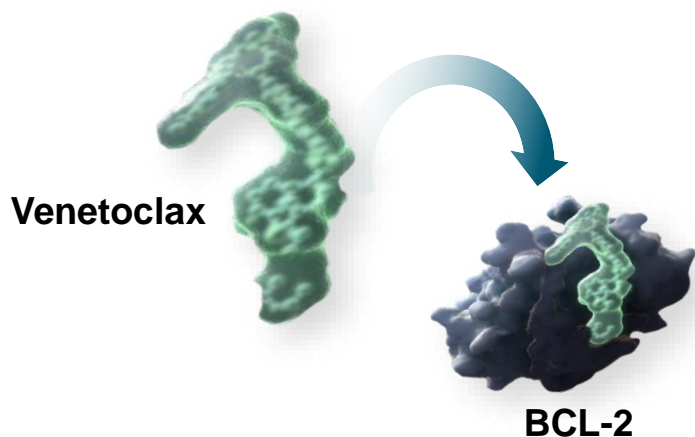
Comparison of randomized prospective studies on venetoclax-based combinations in AML: AZA + venetoclax vs LDAC + venetoclax

Regimen	AZA + venetoclax	LDAC + venetoclax
Phase	III VIALE-A trial	III VIALE-C trial
Population	Age > 75 years or unfit for chemotherapy	
Control arm	AZA	LDAC
h/o HMA	No	Yes, allowed (20%)
Patient number	431 (286 in AZA + venetoclax)	211 (143 in LDAC + venetoclax)
Median age (range), years	76 (49–91)	76 (36–93)
30-day mortality, %	7%	13%
cCR (CR) rate, %	66.4% (36.7%)	48% (27%)
MRD negativity, %	N/A	6%
Time to CR (response)	1.3 months (0.6–9.9)	N/A most response at the end of cycle 2
Median DOR, months	17.5 (13.6 to NR)	NA
Median OS, months	14.7 (11.9–18.7)	8.4 (5.9–10.1)

Summary of venetoclax-based combinations in AML

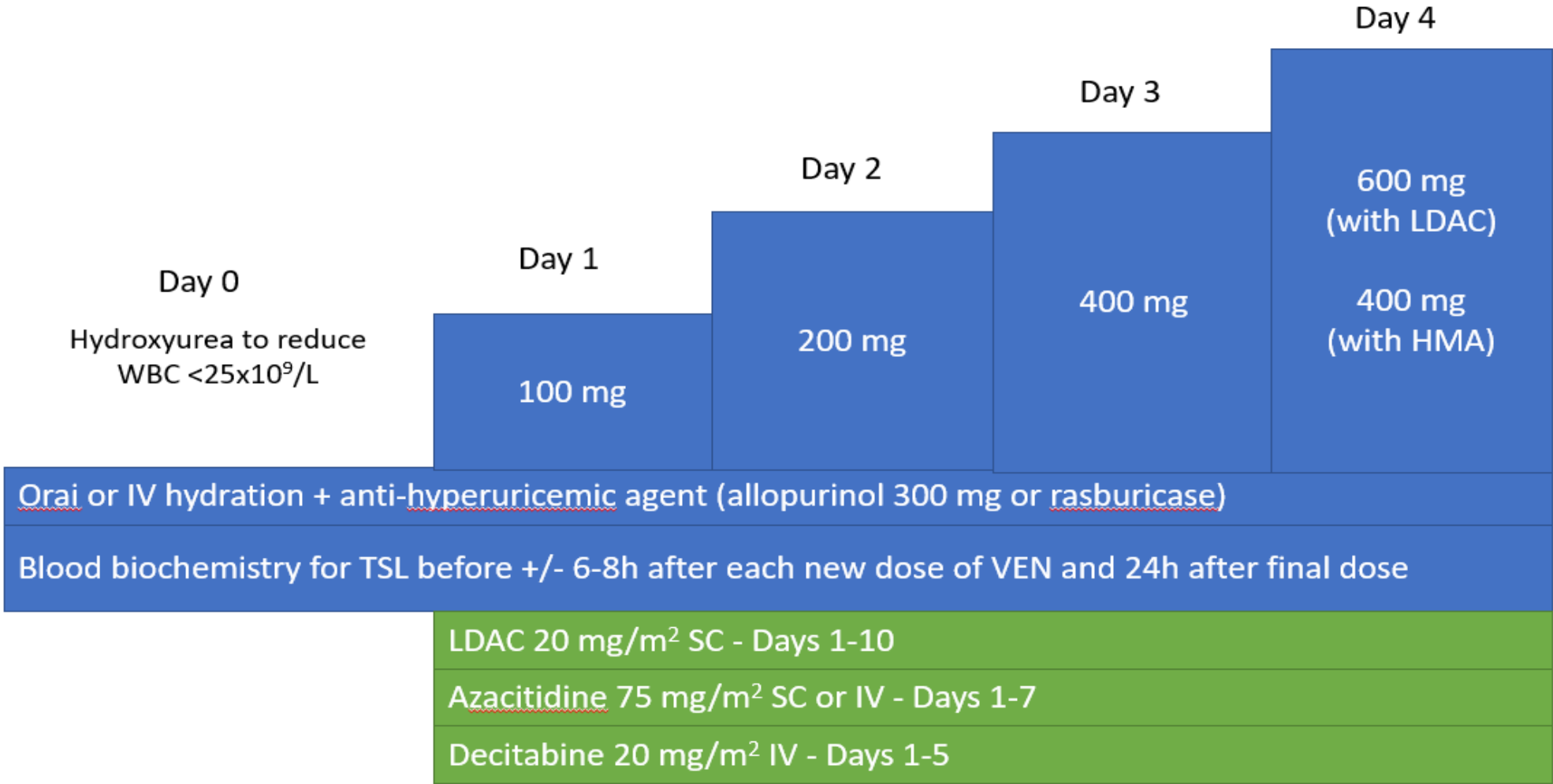
Combination	Phase	Disease status	Patient number	CR/CRi rate, %
FLA-Ida	Retrospective	R/R AML	13	69%
FLAG-ida	Ib/II	ND AML R/R AML	27 35	89% in ND AML 66% in R/R AML
CAVEAT (5 + 2)	Ib	ND AML	51	72% in all 97% in de novo AML 43% secondary AML
DEC10	II	ND AML R/R AML	70 55	86% in ND AML 42% in R/R AML
CLIA	II	ND AML	18	88%
CLAD/LDAC, alternating with AZA	II	ND AML	48	94%
CPX-351	II	R/R AML ND AML	17 1	37%
CPX-351 LIT	Ib	ND AML	44 planned	NA
GO	Ib	R/R AML	24 planned	NA

Venetoclax az AML terápiában: mit kell tudni?



- Prophylaxis TLS
- Drug interactions & venetoclax dose adjustments
- Management of cytopenia with venetoclax-based combination regimens

Venetoclax dózis emelése (dose ramp-up) és a TLS megelőzési intézkedések



HMA, hypomethylating agents; IV, intravenously; LDAC, low-dose cytarabine; SC, subcutaneously; TLS, tumor lysis syndrome; VEN, venetoclax; WBC, white blood cell count.

Gyógyszerkölsönhatások és a venetoclax dózisának módosítása

CYP3A4 inhibitors*

Moderate CYP3A4 inhibitors:

Azole antifungals: fluconazole, isavuconazole
Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir
Calcium-channel blockers: diltiazem, verapamil
Others: aprepitant, ciprofloxacin, erythromycin

Reduce dose of venetoclax by 50%

Strong CYP3A4 inhibitors:

Azole antifungals: posaconazole, voriconazole
Protease inhibitors: indinavir, lopinavir/ritonavir, telaprevir
Others: clarithromycin, conivaptan, telithromycin

Reduce dose of venetoclax by 75%

CYP3A4 inducers*

Moderate CYP3A4 inducers:

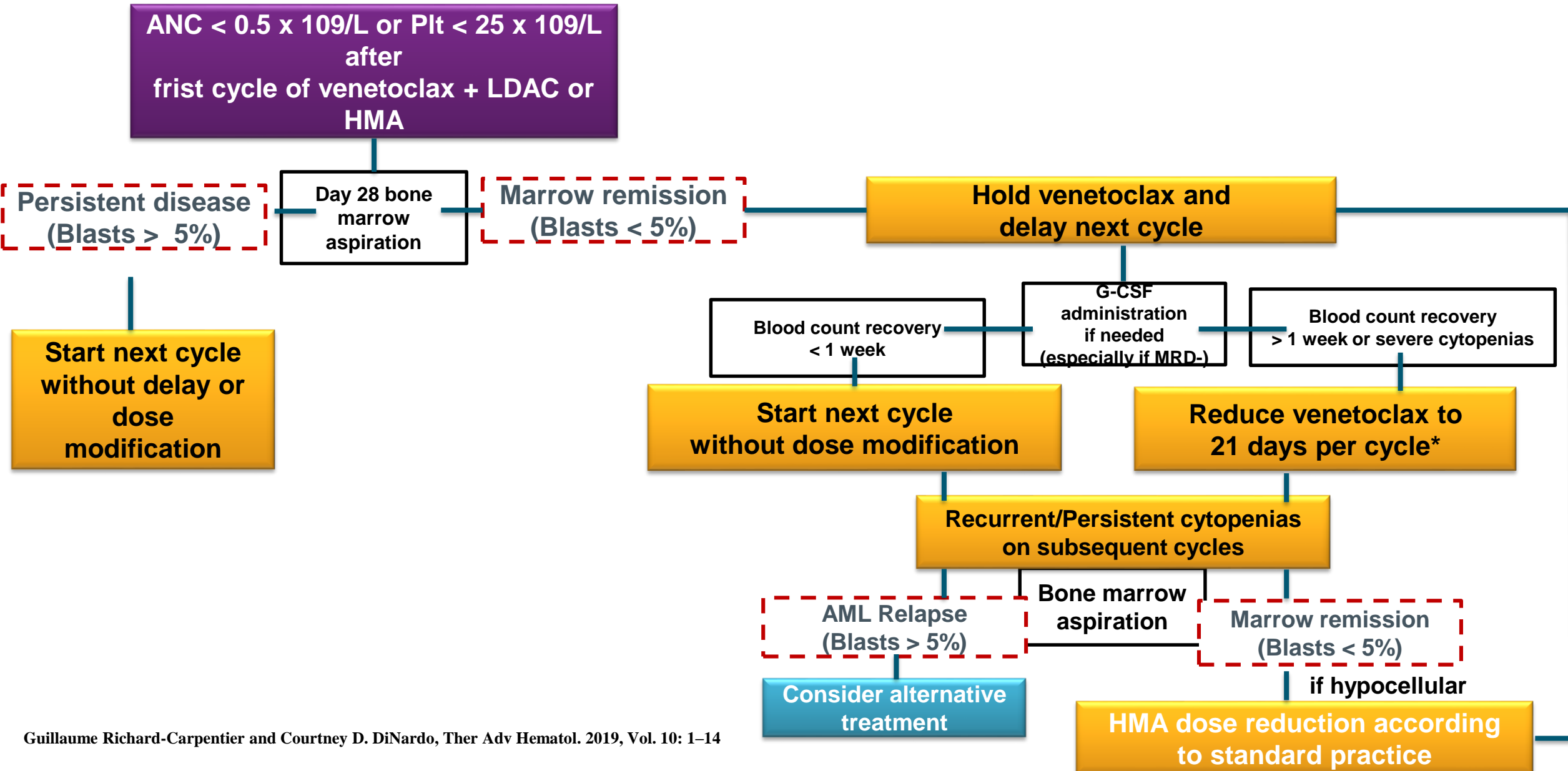
Bosentan, efavirenz, etravirine, modafinil, nafcillin

Avoid concomitant administration
Consider changing to alternative drugs

Strong CYP3A4 inducers:

Avasimibe, carbamazepine, phenytoin, phenobarbital, rifampin,
St. John's wort

Algoritmus a citopenia kezelésére venetoclax-alapú kombinációs sémákkal



Venetoclax plus hypomethylating agent treatment schema

Cycle 1

All Subsequent Cycles

Hypomethylating Agent

Venetoclax

Day 1

Day 28

- Start both therapies concomitantly on day 1
- Escalate venetoclax with inpatient monitoring and prophylaxis for TLS
- Initiate antimicrobial prophylaxis, if clinically indicated

- Transfusion support as clinically indicated
- Do not hold or change dosing strategy based on cytopenias

- Bone marrow biopsy for response assessment on day 28
- If morphologic remission, delay next cycle up to 14 days with growth factor support, if warranted
- Concern for treatment failure if no morphologic response after two cycles

Hypomethylating Agent

Venetoclax

Day 1

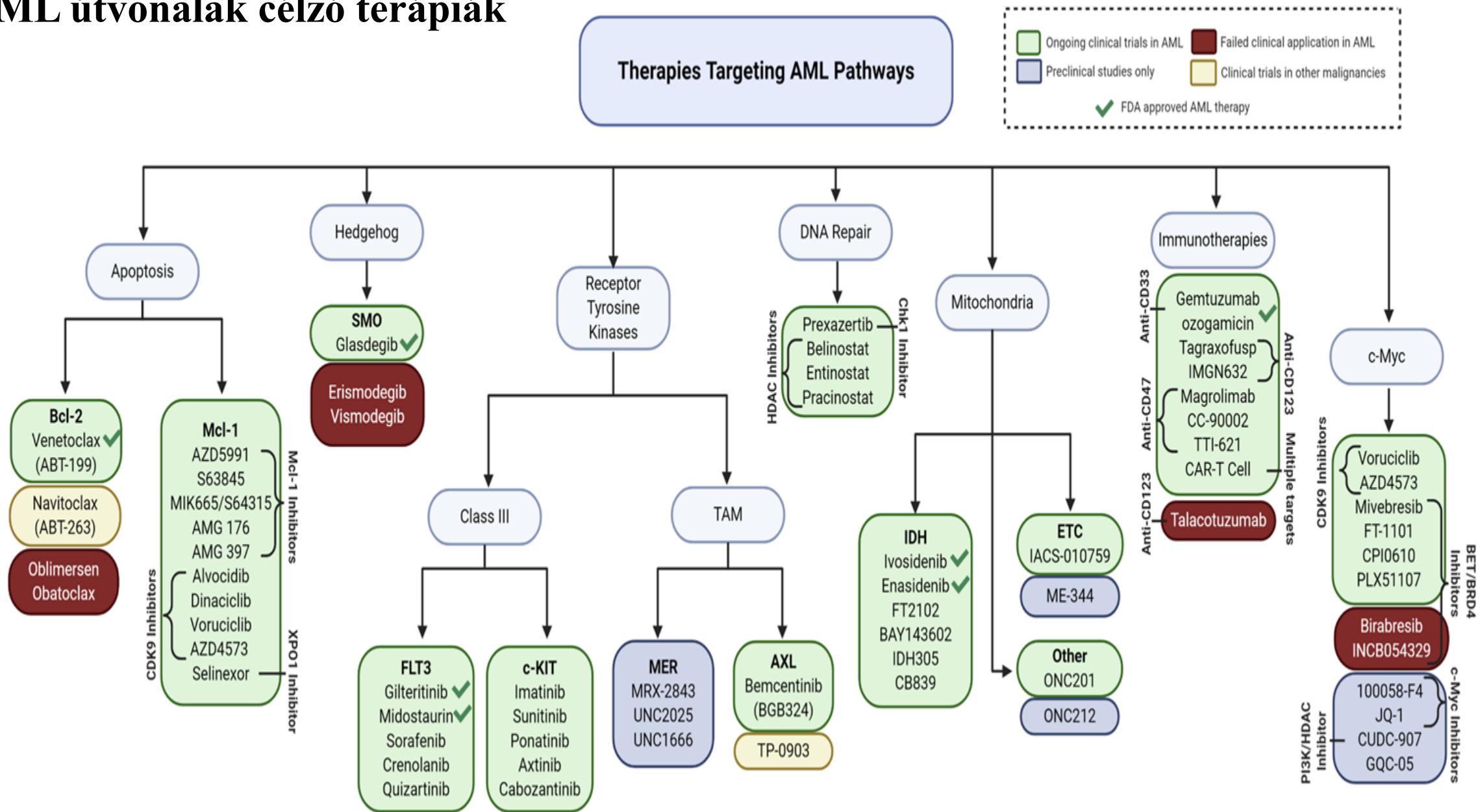
Day 28

- Start both therapies concomitantly on day 1
- Outpatient setting without TLS monitoring or prophylaxis
- Consider dose reductions to HMA or decreasing duration of venetoclax, depending on cytopenias from previous cycles
- Wean antimicrobial prophylaxis, if started, as clinically indicated

- Transfusion support as clinically indicated

- Bone marrow biopsy for response assessment on cycle 2 day 28 if no morphological response after cycle 1
- If in morphologic remission, consider routine bone marrow biopsies after cycle 4 and every 6 months or any time disease progression suspected
- Delay subsequent cycles up to 14 days with growth factor support, if warranted

Az AML útvonalak célzó terápiái



Comparison of randomized prospective studies on venetoclax-based combinations in AML: AZA + venetoclax vs LDAC + venetoclax

Regimen	AZA + venetoclax	LDAC + venetoclax
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MRD negativity, %	N/A	6%
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CPX-351 LIT	Ib	ND AML	44 planned	NA
GO	Ib	R/R AML	24 planned	NA

Summary of combination of targeted-therapy trials in IDH1/2-mutant newly diagnosed AML

Regimens	Phase	Patient Number	CR/CRi rate, %	Time to CR or response (median), months	OS (median), months
HMA + venetoclax	Ib	35	71	2.1	24.4
AZA + venetoclax	III	46	75.4	N/A	N/A
AZA + venetoclax	Pooled data from two trials	79	72	1.0	24.5
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AZA + ivosidenib	Ib	23	69.6	3.7	N/A
AZA + enasidenib	II	68	68	5	22.0
Venetoclax + ivosidenib	Ib/II	12	83	NA	NA
AZA + venetoclax + ivosidenib	Ib/II	6	67	NA	NA

Immunotherapies in AML

Modality	Targets	Agents	Clinical setting	Efficacy
Checkpoint inhibitors	CTLA-4	Ipilimumab	Relapse after SCT	CR in 4/12 with extramedullary relapse
	PD-1/PD-L1	Nivolumab	R/R AML	ORR of 33%
		Durvalumab	ND AML	No difference between Durvalumab + AZA vs AZA alone
		Nivolumab	maintenance	Promising from single arm Phase II Randomized Phase II in CR1 is pending
Macrophage “Do not eat me”	CD47	Magrolimab	ND AML	ORR: 65% ORR: 71% for TP53 mutated AML
Leukemia stem cell	Tim-3	MBG453 + HMA	ND AML R/R AML	With AZA: ORR: 29% for ND and R/R With Decitabine: ORR: 41% for ND ORR: 24% R/R
ADC	CD123	IMGN632	R/R AML	ORR: 18%
BiTE/DART	CD123	Flotetuzumab	R/R AML	ORR: 42%
		Vibecotamab	R/R AML	ORR: 15%; 26% with low burden disease
CAR T	Various targets: CD33, CD123,	All in the early phase	R/R AML	Too early to tell

Roadmap of AML treatments

ND AML	IC candidate	FLT3 mutation	7 + 3 + midostaurin Clinical trial: 7 + 3 + midostaurin vs 7 + 3 + gilteritinib
		Low, Intermediate risk (CD33 +)	7 + 3 + GO
		Secondary AML	CPX351
		IDH1/2 mutation	7 + 3 or clinical trial
		No targetable Mutation	Clinical trial or 7 + 3 like regimens
		TP53 mutation	Clinical trial or HMA-based regimens
	Not IC candidate	IDH1/IDH2 mutation	Clinical trial HMA + venetoclax LDAC + venetoclax AZA + IDH inhibitor
		FLT3 mutation	Clinical trial HMA + venetoclax LDAC + venetoclax HMA + gilteritinib
		No mutation	Clinical trial HMA + venetoclax LDAC + venetoclax
		TP53 mutation	Clinical trails AZA + magrolimab AZA + APR-246 Off trial: HMA + venetoclax LDAC + venetoclax 5 day or 10 day Decitabine
R/R AML		IC candidate	Re-induction best on the clinical trial
		CD33 +	Clinical trials or GO based regimens,
		IDH1/2 mutation	Ivosidenib/enasidenib alone or HMA combination Venetoclax-based combinations (2 drugs or 3 drugs)
		FLT3 mutation	Gilteritinib alone or combinations with HMA Venetoclax-based combination, (2 drugs or 3 drugs)
		NPM1 mutation or MLL rearrangement	Clinical trials with NPM1/MLL inhibitors Venetoclax-based combination, (2 drugs or 3 drugs)
		TP53 mutation	Clinical trials
		No mutation	Clinical trials Novel first in class agents HMA-base combinations Immunotherapy: MoAbs ADC BiTE/DART Cellular therapies, CAR T, NK cells...

Kulcsfontosságú előrelépések 1.

- Az újonnan diagnosztizált AML-s betegek „7+3” kemoterápiájához hozzáadott fms-related tirozin kináz 3 (FLT3) inhibítorok az FLT3-mutációt hordozó AML-s betegek esetében javította az OS-t a standard kemoterápiához képest.
- Az R/R AML betegek kezelésére orálisan alkalmazott célzott mutáns IDH inhibitorok jelentős aktivitást mutattak és tartós választ eredményeztek a klinikai vizsgálatokban.
- Az újonnan diagnosztizált szekunder és terapia-asszociált AML-s felnőtt betegekben a liposzomás citarabin és a daunorubicin 5:1 molarányban szignifikánsan javította a RR, EFS és a medián OS-t a standard „7+3” terápiához képest randomizált fázis III klinikai vizsgálatban.

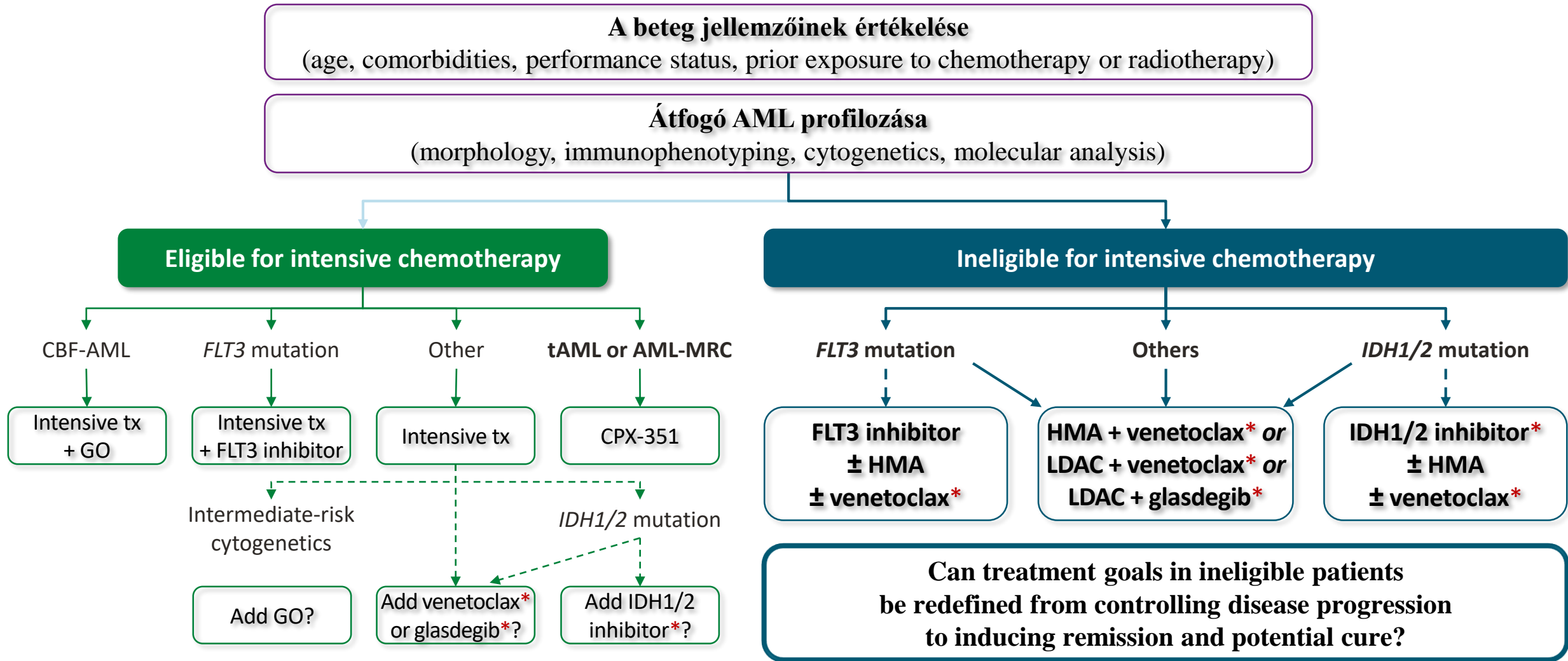
Kulcsfontosságú előrelépések 2.

- Idősebb, intenzív kemoterápiára nem alkalmas betegeknél a BCL-2 inhibitor venetoclax hozzáadása az alacsonyabb intenzitású AML terápiákhoz, pl. a HMA-ekhez vagy az alacsony dózisú Ara-C-hez, jelentősen javította az OS-t.
- Az AML-s betegek klinikai és genetikai adatai, ideértve a teljes exom és RNS szekvenálást, valamint a >100 ágens ex vivo érzékenységeinek elemzését, már szabadon elérhetőek, és valószínűleg felgyorsítják és lehetővé teszik a jövőbeli felfedezéseket.

Összefoglalás

- Új terápiás lehetőségek jelentek meg az időskori AML-es betegek kezelésére, melyek biztató eredményeket mutattak mind a jó állapotú fitt, mind a kevésbé jó általános állapotú betegek esetében.
- „One-size fits all” megváltozott a „személyre szabott-egyenre szabott” molekulárisan célzott kezelésre.
- Jövőben különösen fontos szempont lesz az intenzív és a kevésbé intenzív kezelésekhez történő megfelelő betegválasztás.
- Az MCL-1 egy fontos terápiás célmolekulává vált AML-ben, ami a BCL-2 inhibitorokkal szembeni rezisztenciában is fontos szerepet játszik.
- A mutált TP53 fehérjét és a makrofág immun checkpoint-ot célzó új célzott terápiák is biztató jövőbeli terápiás lehetőséget kínálnak.
- A kombinált terápia tovább növelheti a hatékonyságot.
- Az AML-kezelés jövője ígéretesnek tűnik.
-

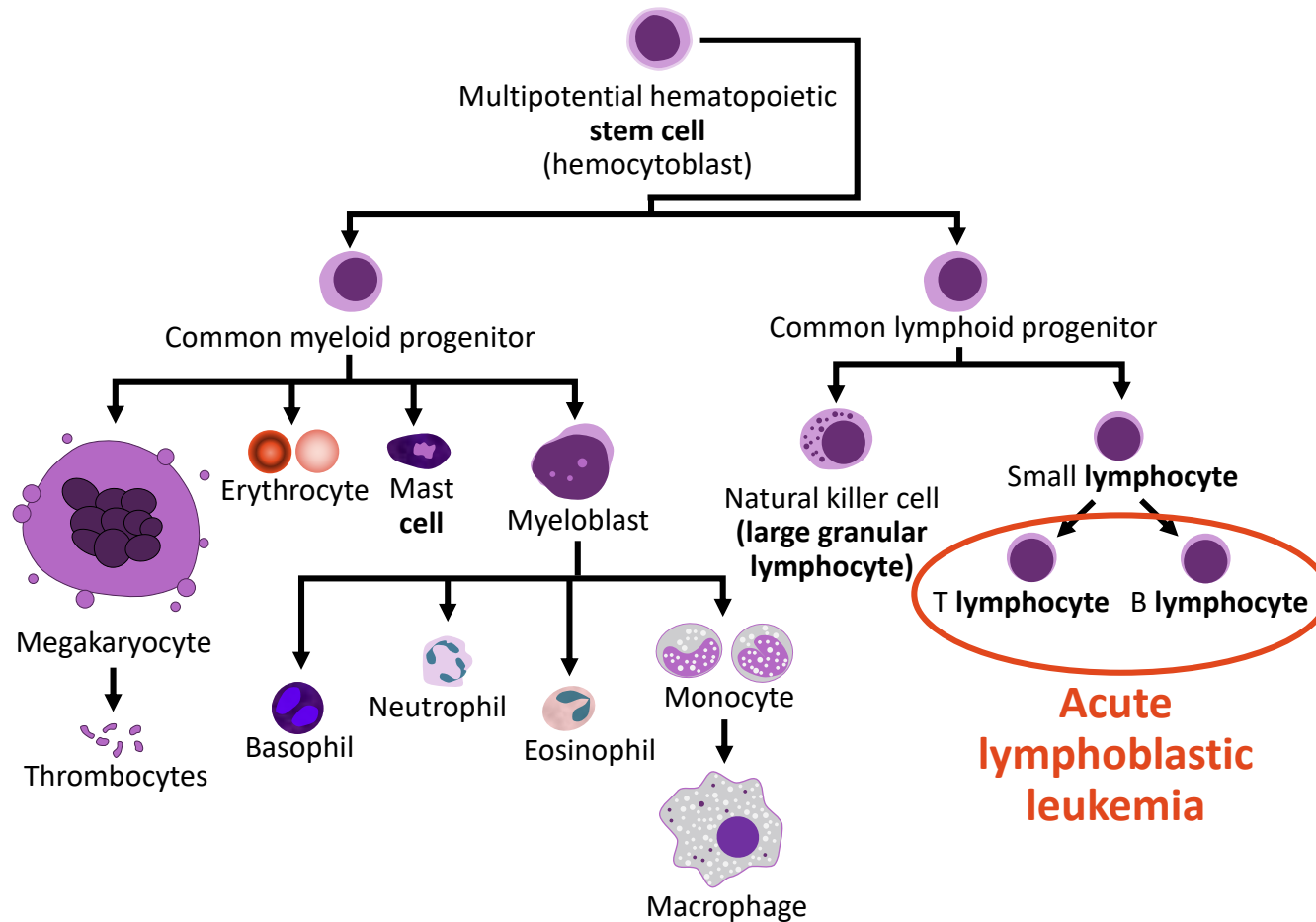
Az AML változó arca: Mit hozhat a jövő?



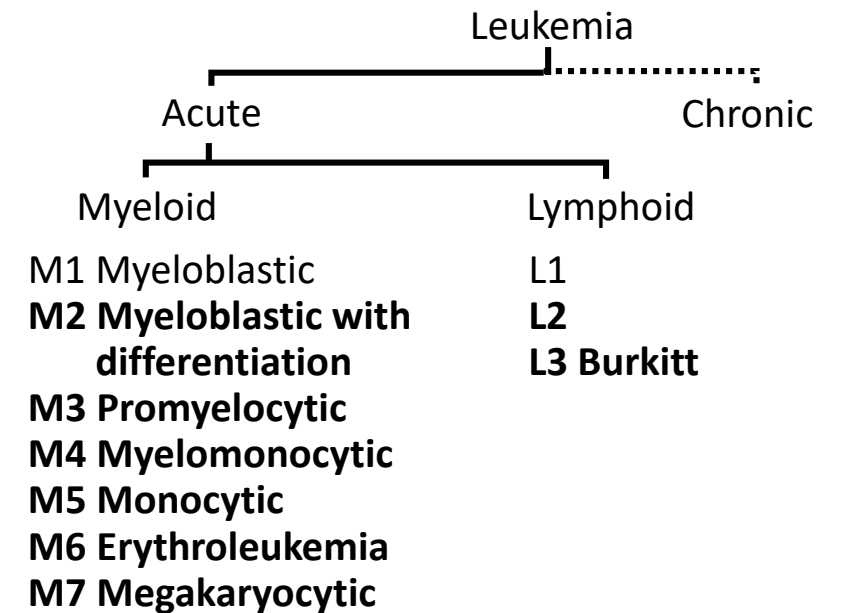
* Note: At the time of this presentation, these agents do NOT have EMA approval for the treatment of AML.

CBF, core binding factor; HMA, hypomethylating agent; LDAC, low-dose cytarabine; MRC, with myelodysplasia-related changes; tAML, therapy-related AML; tx, chemotherapy.

Hematopoiesis and Acute Leukemias



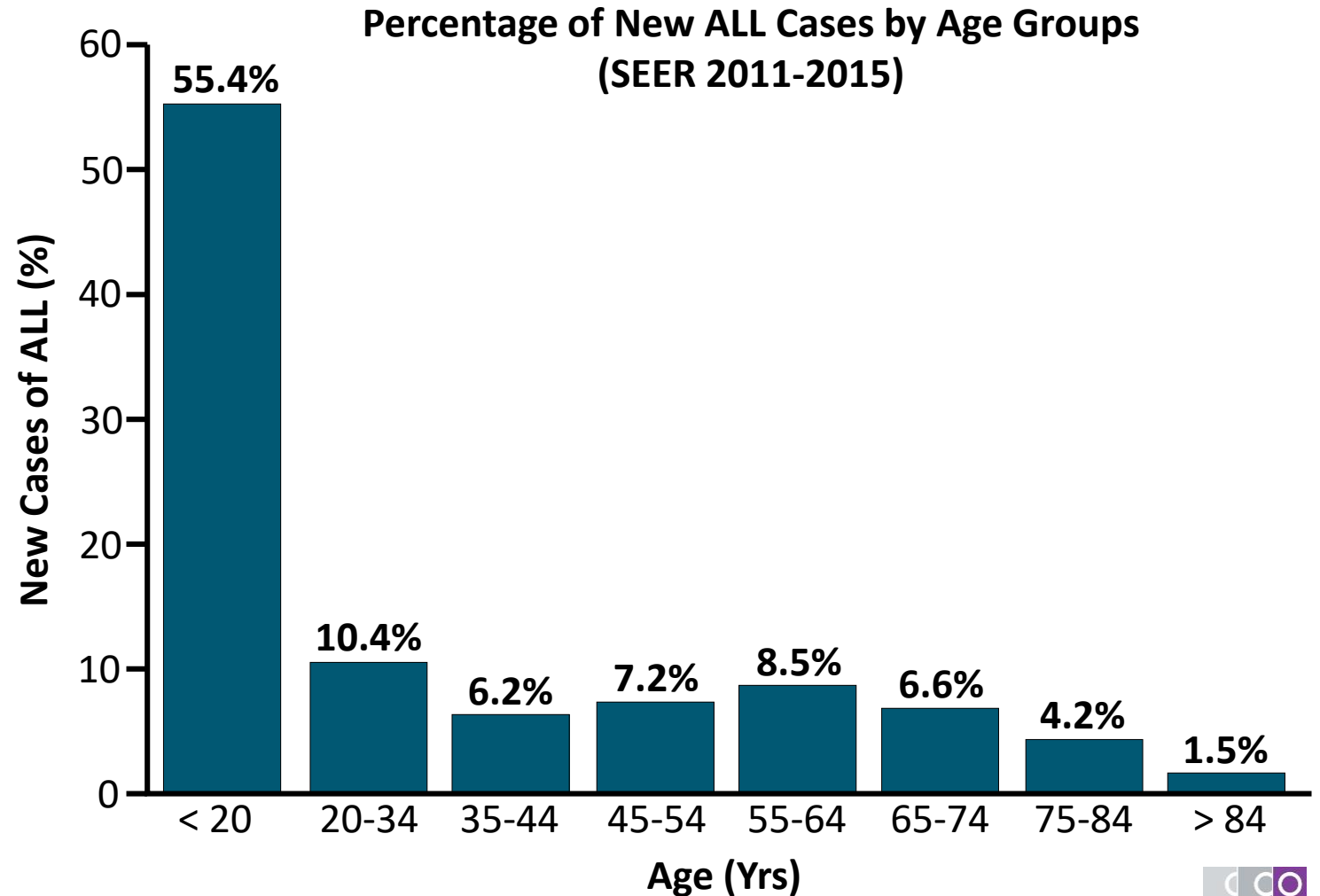
FAB Classification of Leukemias



Left image from Mikael Häggström, derived from original by A. Rad. Permission is granted to copy, distribute and/or modify this image under the terms of the GNU Free Documentation License, Version 1.2, or any later version published by the Free Software Foundation.

Epidemiology of ALL in the United States

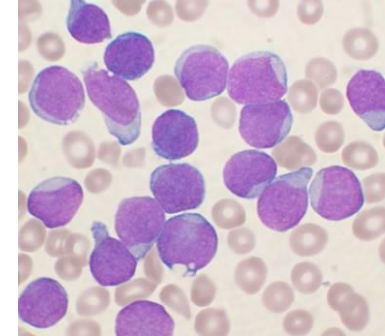
- Estimated new ALL cases in United States: 5960 (1.7 per 100,000 individuals)
 - Estimated deaths: 1470
 - Median age at death: 56 yrs



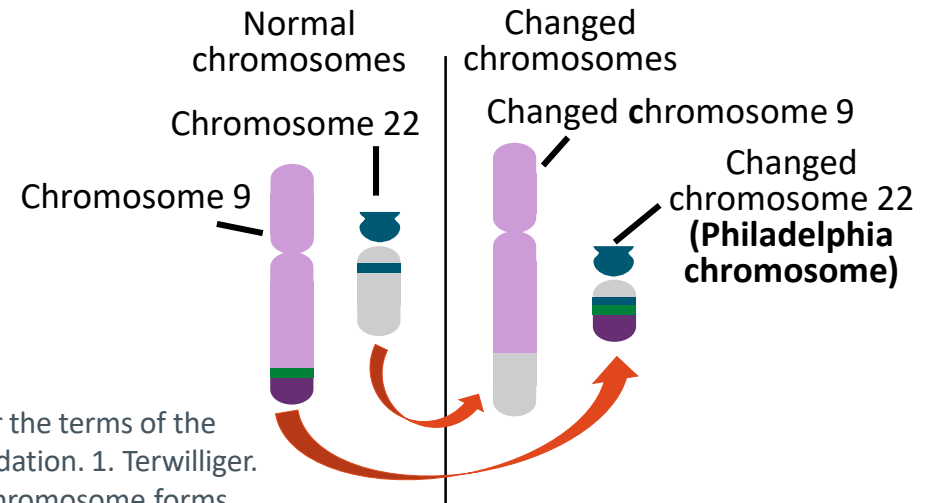
B-Cell ALL: Therapeutic Context

- Approximately 75% of adult cases are precursor B-cell ALL^[1]
- Prognosis poorer in adults, worsens with age at diagnosis^[1]
 - Presence of high-risk Philadelphia chromosome increases with age
- Relapse common: 3-yr DFS of 30% to 50%^[2]
- CR rates with conventional CT for R/R ALL range from 31% to 44% (first salvage) and 18% to 25% (second salvage)^[2]
 - Low CR rates impact attempts of bridging to SCT as a curative paradigm

BM Aspirate of Precursor B-Cell ALL



Philadelphia Chromosome Translocation^[3]

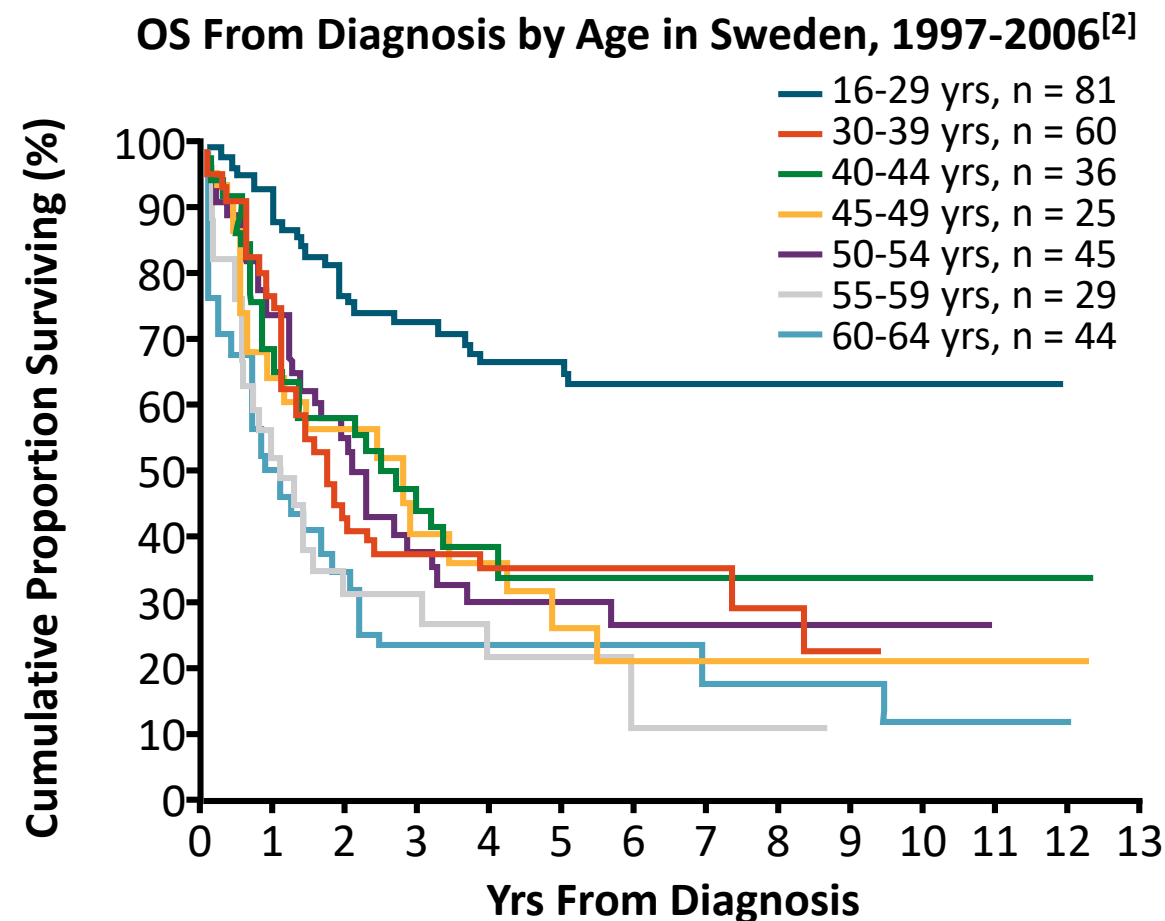
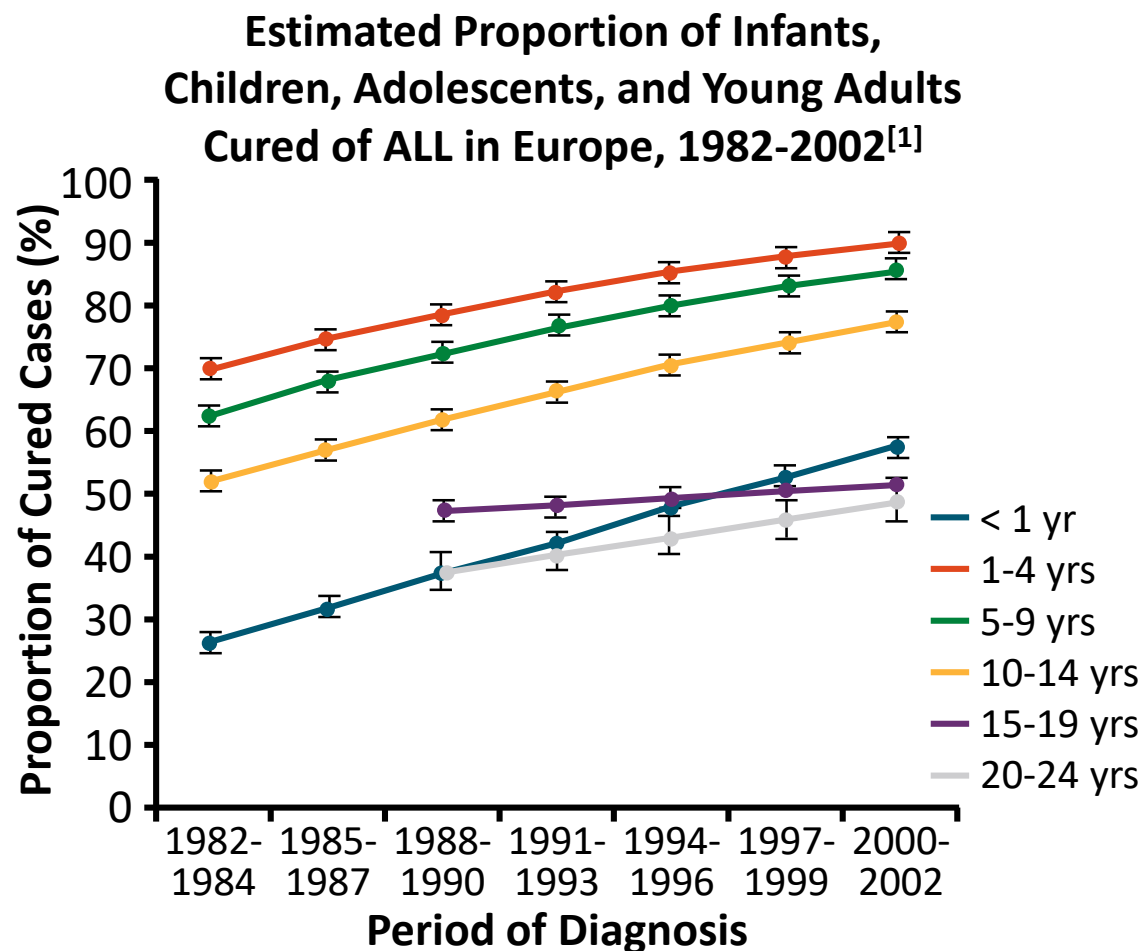


Upper image from Vashi Donsk. Permission is granted to copy, distribute and/or modify this image under the terms of the GNU Free Documentation License, Version 1.2, or any later version published by the Free Software Foundation. 1. Terwilliger. Blood Cancer J. 2017;7:e577. 2. Kantarjian. NEJM. 2016;375:740. 3. Mayo Clinic. How the Philadelphia chromosome forms.

Risk Factors in Adult ALL

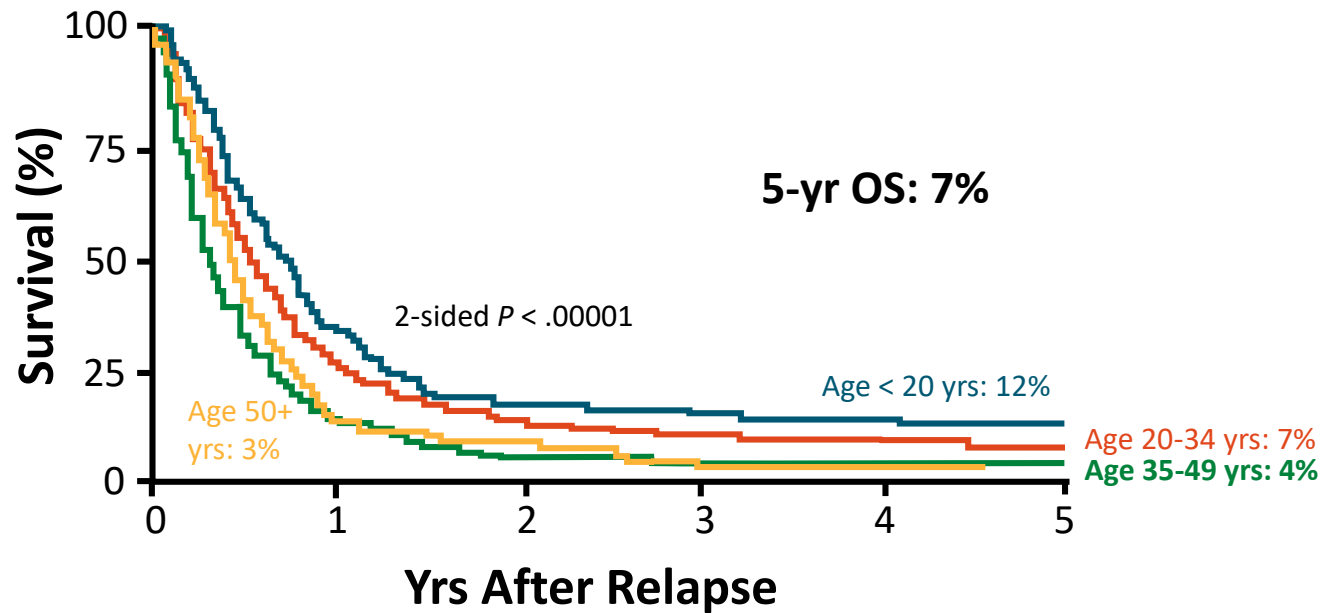
- > 30 yrs of age
- WBC count > 30K in B-cell ALL, > 100K in T-cell ALL
- Ph positive: t(9;22), *BCR-ABL* translocation
- Ph-like lesions
- Other chromosomal aberrations
 - t(4;11), 11q23+, *MLL* rearrangement
 - Hypodiploidy (≤ 44 chromosomes)
- CNS involvement
- MRD positive ($> 10^{-4}$ or 0.01%) after induction

ALL Cure Rates Decrease With Age

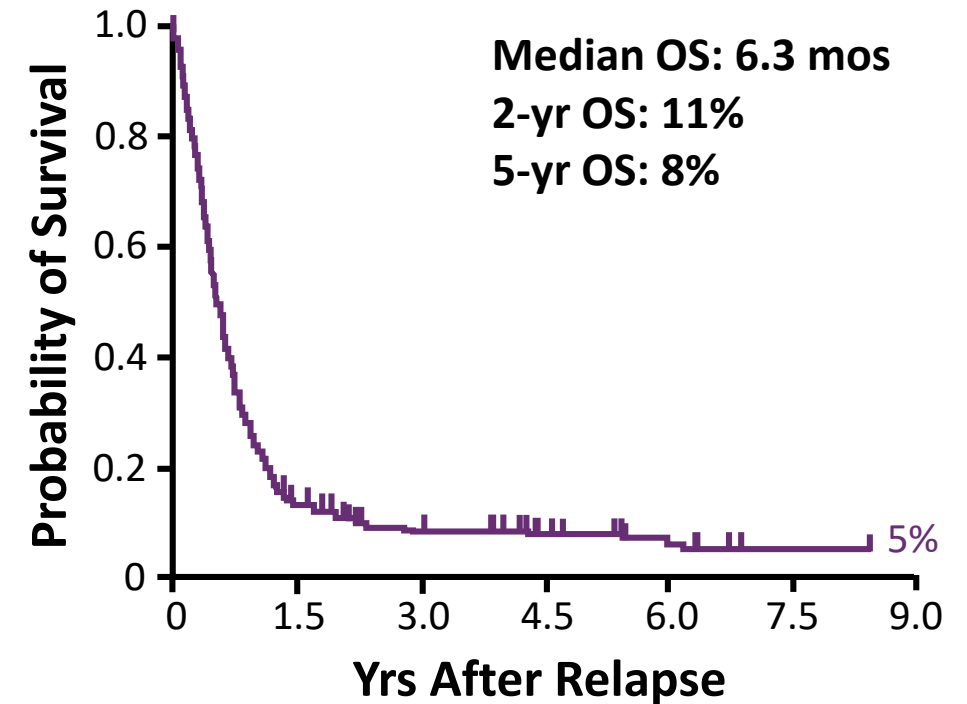


Poor Prognosis of Relapsed ALL in Adults

**MRC UKALL2/ECOG2993: OS After First Relapse
by Age at Diagnosis (N = 609)**

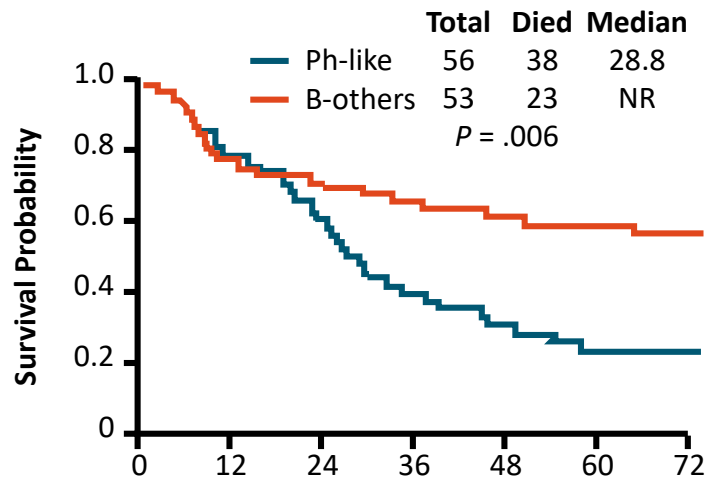
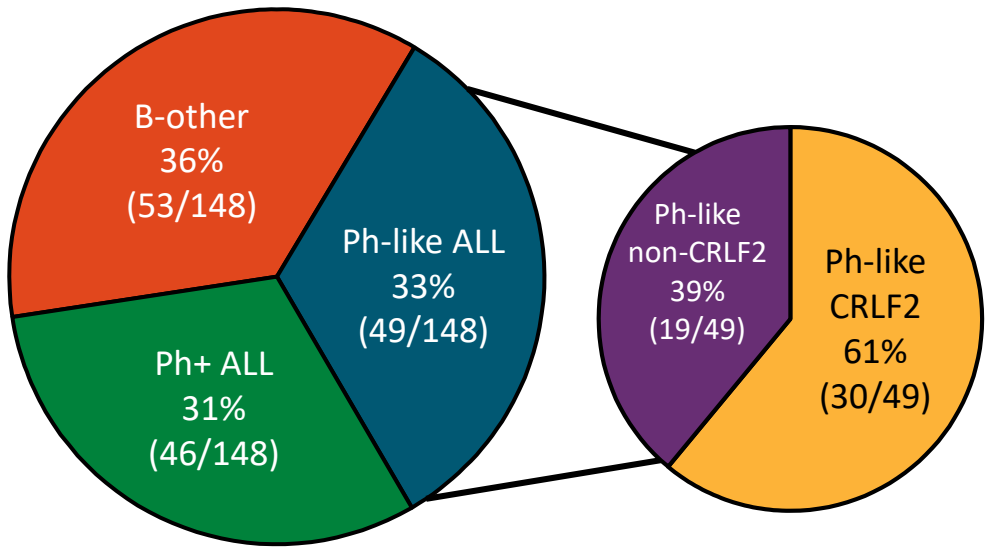


LALA-94: OS After First Relapse (N = 421)



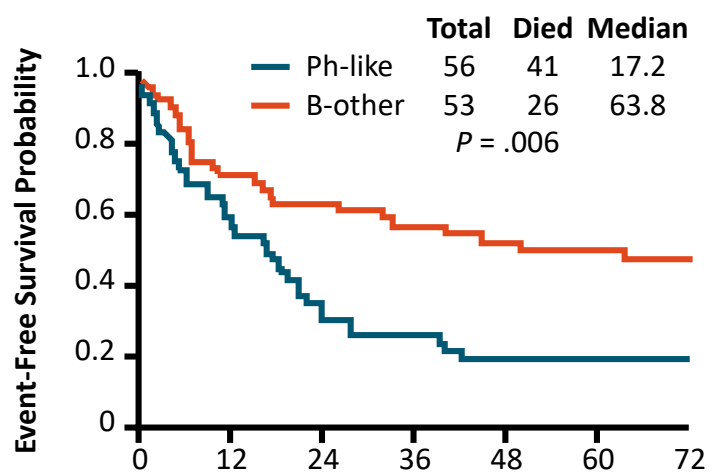
**Patients received either autoSCT, alloSCT, or
chemotherapy before and after relapse**

Ph-Like Lesions in ALL



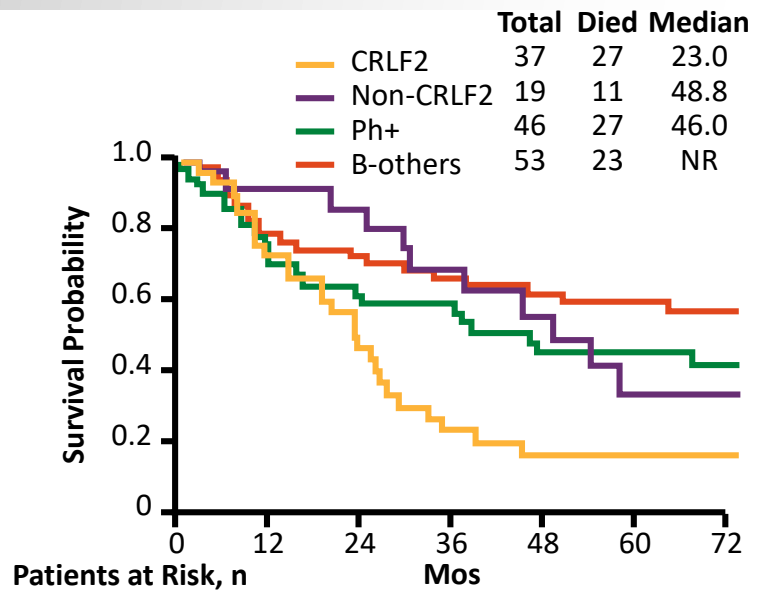
Patients at Risk, n

	0	12	24	36	48	60	72
Ph-like	56	42	30	18	13	9	8
B-other	53	40	36	32	27	23	15



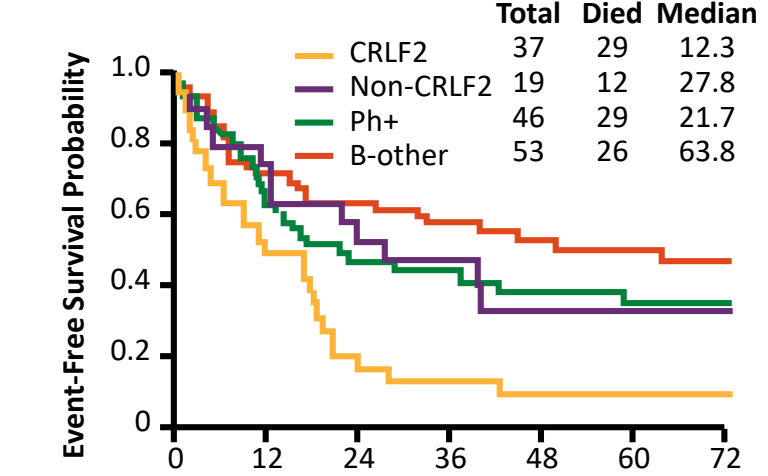
Patients at Risk, n

	0	12	24	36	48	60	72
Ph-like	56	32	16	11	8	7	6
B-other	53	37	32	28	23	20	13



Patients at Risk, n

	0	12	24	36	48	60	72
CRLF2	37	25	14	7	5	5	5
Non-CRLF2	19	17	16	11	8	4	3
Ph+	46	33	26	22	16	13	11
B-other	53	40	36	32	27	23	15



Patients at Risk, n

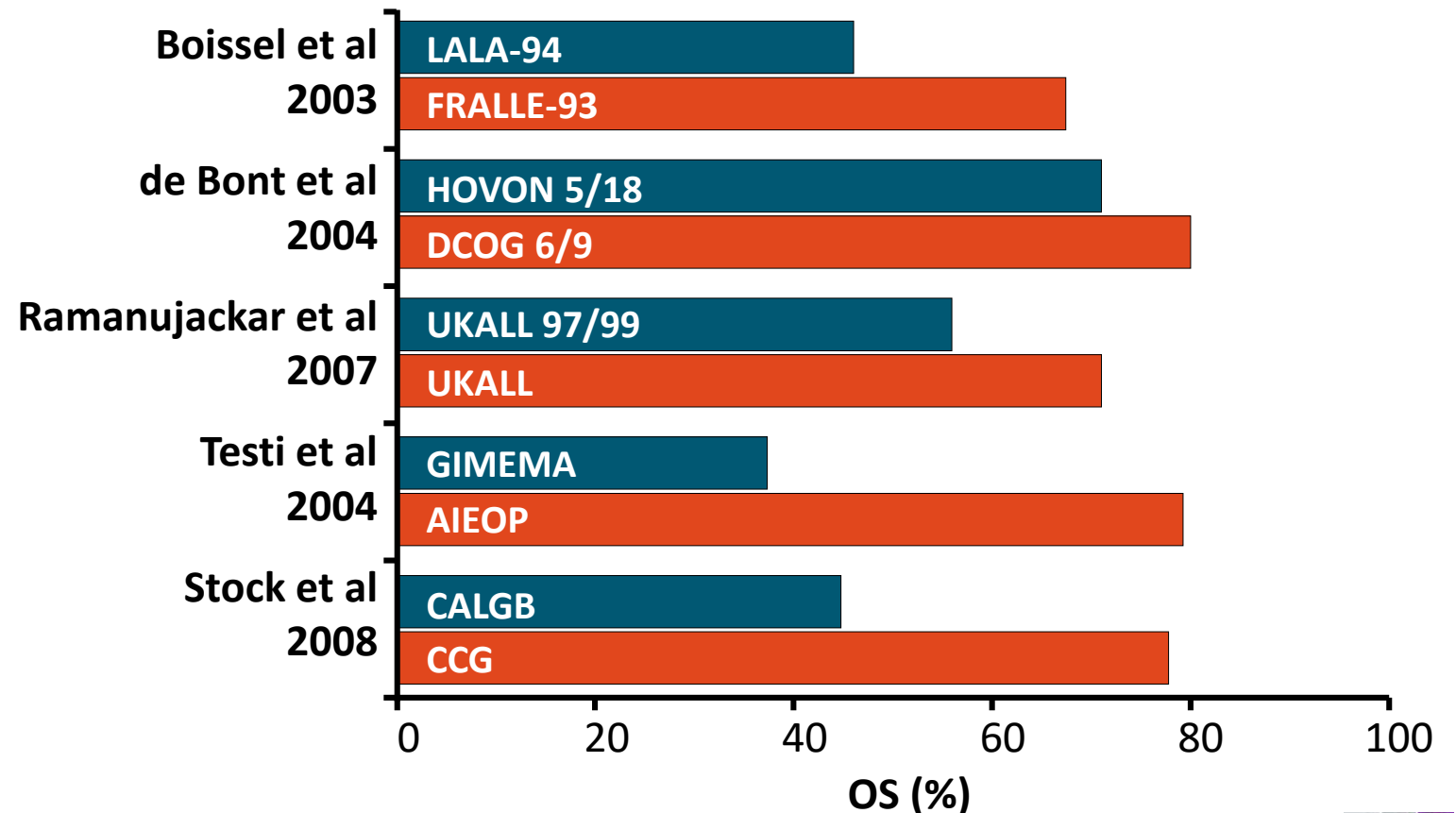
	0	12	24	36	48	60	72
CRLF2	37	18	6	4	3	3	3
Non-CRLF2	19	14	10	7	5	4	3
Ph+	46	29	21	16	13	9	8
B-other	53	37	32	28	23	20	13

Pediatric vs Adult Regimens for ALL

■ Pediatric regimens

- Involve more intensive use of
 - Corticosteroids
 - Vincristine
 - Asparaginase
- Emphasize timely administration of therapy
- Typically include MRD quantification to assess response to treatment

Outcomes in Adolescents and Young Adult Patients Treated With Pediatric or Adult ALL Regimens



CHROMOSOMAL ABNORMALITIES IN ALL

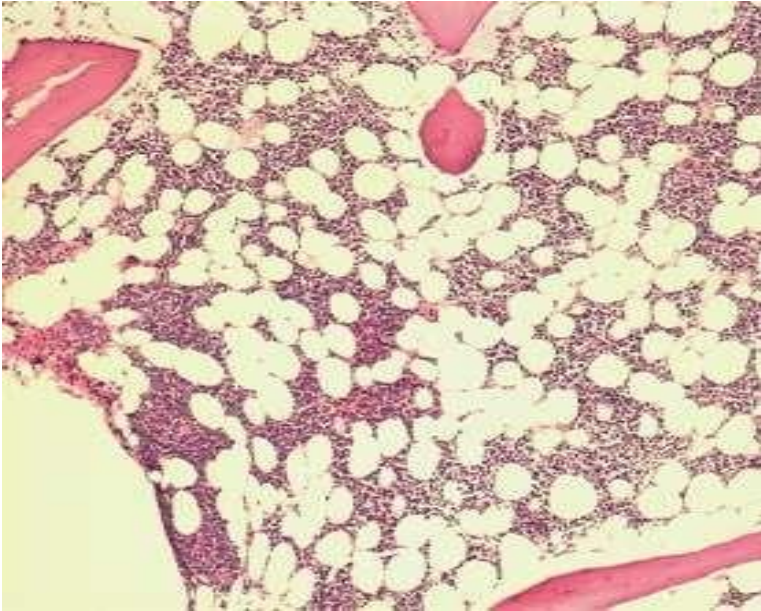
ABNORMALITIES	ADULTS(%)	CHILDREN(%)
Normal karyotype	16-34	9
Hypodiploidy	4-9	1
Hyperdiploidy	2-9	25
t (9;22)	11-30	4
t (4;11)	3-7	6
t (10;14)	4-6	4
t (8;14)	4	2
t (1;19)	3	5
9p abnormality	5-16	7-13
6q abnormality	2-6	4-6
12p abnormality	4-5	22

FACTORS PREDISPOSING ALL

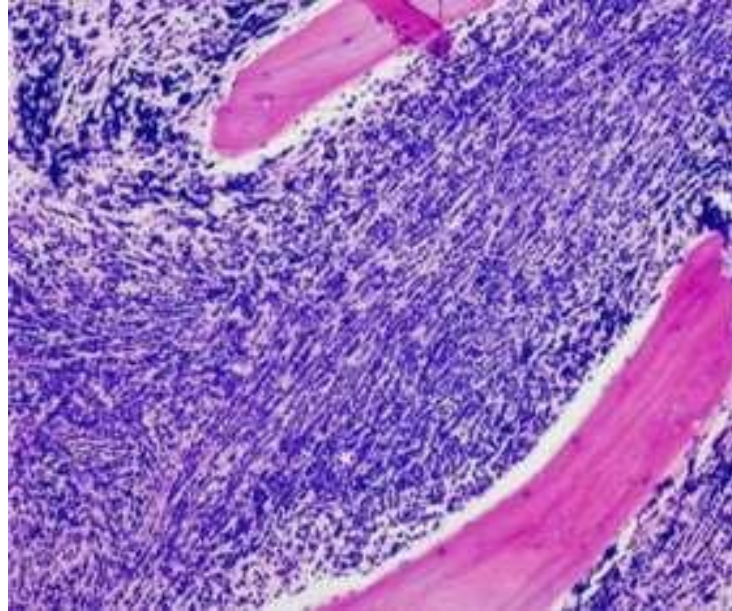
GENETIC	ENVIRONMENTAL
Downs,turner, klinefelter	Ionising Radiation
Fanconi,diamond blackfan	Drugs
NF Type1	Alkylating Agents
Ataxia telangiectasia	Nitrosourea
SCID	Epipodophyllotoxin
PNH	Benzene Exposure
Li-fraumeni syndrome	Advanced Maternal Age
Blooms syndrome	Paternal Smoking

ENTIRE MARROW REPLACED BY BLAST

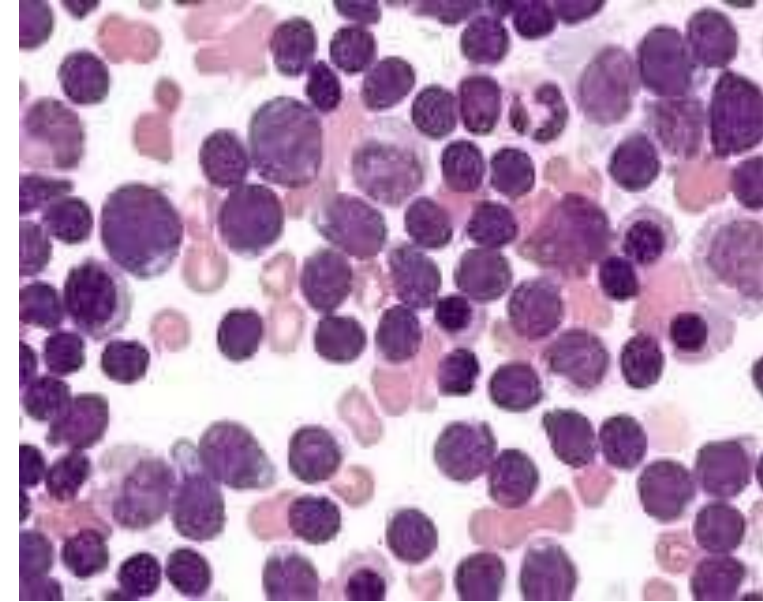
NORMAL MARROW



**ENTIRE MARROW
REPLACED BY BLAST**



**MARROW SHOWING
BLASTS**



CLASSIFICATION OF ALL(WHO)

Immunologic Subtype	% Of Cases	FAB Subtype	Cytogenetic Abnormalities
Pre B ALL	75	L1,L2	t(9;22),t(4;11) t(1;19)
T cell ALL	20	L1,L2	14q11 Or 7q34
Mature Bcell All(burkitt Leukemia)	5	L3	t(8;14)

TREATMENT

Pre Chemotherapy supportive care Chemotherapy

Pre-induction

Remission induction-phase 1 & 2

Re-induction

CNS preventive therapy

Consolidation

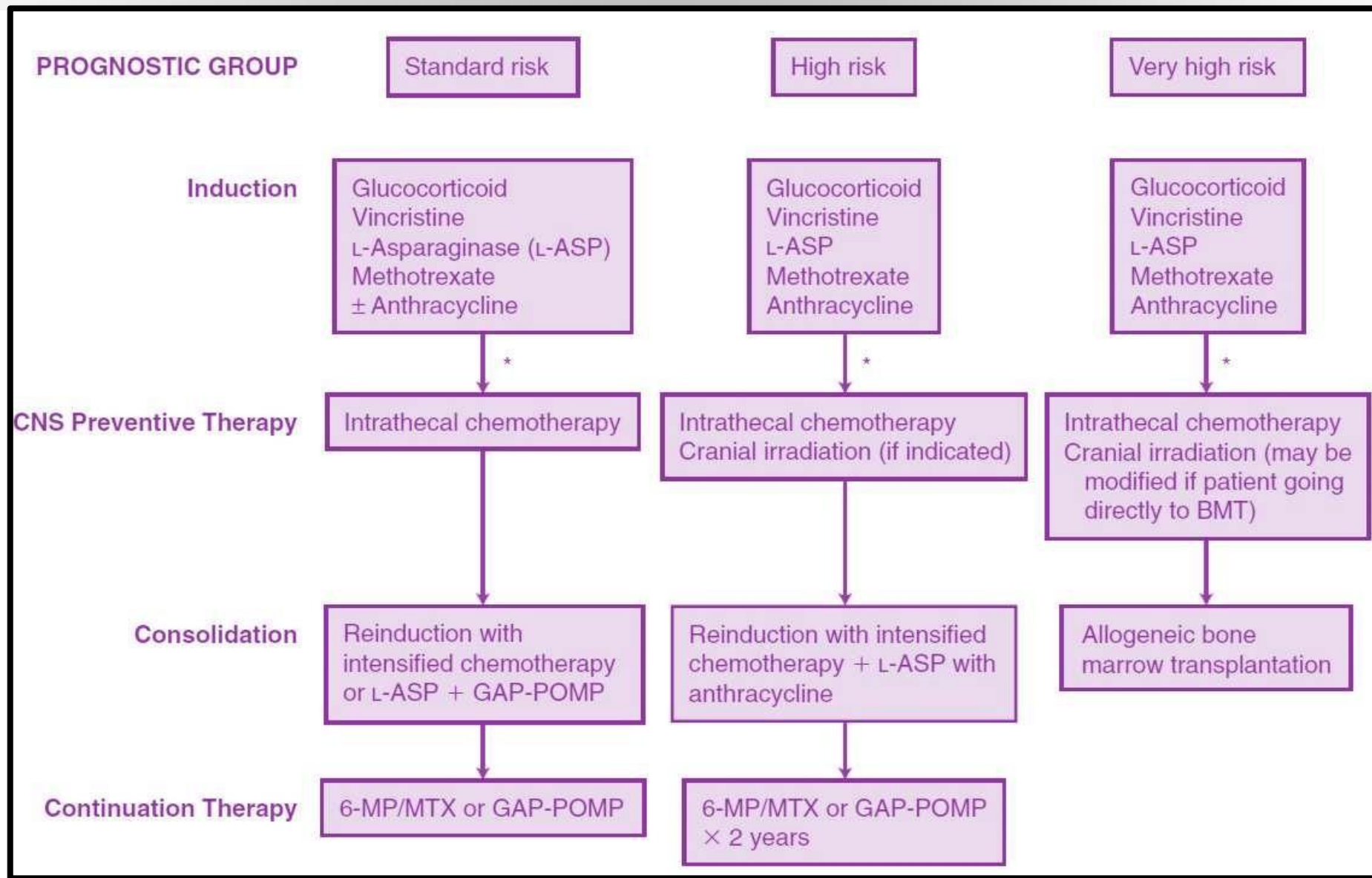
Maintenance therapy

Allogenic stem cell transplantation Newer drugs

Supportive care Treatment of relapse Effects of treatment

REASSESS

- After 4 weeks of phase 1 induction assess marrow for remission.
 - If there is remission taper prednisolone and after 1 week of restart phase2 induction,
 - If there is no remission give 2 more weekly doses of vincristine and doxo and then assess, if still no remission go for alternate regimen.
-



6-MP, 6-mercaptopurine; BMT, bone marrow transplant; CNS, central nervous system; MTX, methotrexate. GAP- POMP (GAP refers to the schedule of mercaptopurine administration given on 14 days of each 21-day cycle, thus a 7- day GAP) repeats a 3-week cycle until 2 years of continuous complete remission: vincristine, prednisone, mercaptopurine, methotrexate; high-dose cycle; vincristine, mercaptopurine, high-dose intravenous and intrathecal methotrexate.

CNS PROPHYLAXIS

- In most regimens, CNS prophylaxis for patients at lower risk is achieved with systemic and intrathecal chemotherapy without cranial irradiation.
- Children with high-risk features are at an increased risk of CNS relapse and, historically, have received prophylactic cranial irradiation.
- These features include a presenting WBC count of 50,000/ μ L or greater; those with WBC counts over 100,000/ μ L are at particularly high risk of CNS relapse.
- Additional high-risk features that are indications on some treatment protocols for cranial irradiation are T-cell phenotype, Ph chromosome–positive ALL, and the presence of t(4;11).
- Infants younger than age 12 months with 11q23 abnormalities are at high risk of CNS relapse but because of their young age are usually treated without cranial irradiation, using intensified systemic and intrathecal chemotherapy to treat the CNS.

NEWER DRUGS

Monoclonal antibodies: CD20 (Rituximab), CD22 (Epratuzumab), CD52 (Alemtuzumab), CD33 (Gemtuzumab)

Antimetabolites: Clofarabine, Nelarabine

TKI: Imatinib, Nilotinib, Dasatinib, etc.

Others: Vornistat, Sirolimus, Everolimus, Oblimersen,

Inotuzumab Ozogamicin in ALL: Background

- CD22 expression in > 90% of ALL
- InO produces high response rate in refractory lymphomas:

	CR, %	OR, %	Median PFS, Mos
Indolent	32	68	11
Aggressive	8	15	2

- Phase II dose 1.8 mg/m² IV every 3-4 wks
- DLT: thrombocytopenia

Inotuzumab Ozogamicin in R/R ALL: Schedule

Monthly:

Cycle 1
1.8 mg/m²



D1

D8

D15

D22

Cycle 2

1.8 mg/m²



D29

D8

D15

D22

Up to 8 cycles

Weekly:

Cycle 1

0.8 mg/m²



D1

0.5 mg/m²



D8

0.5 mg/m²



D15

D22

Cycle 2

0.8 mg/m²



D29

0.5 mg/m²



D8

0.5 mg/m²



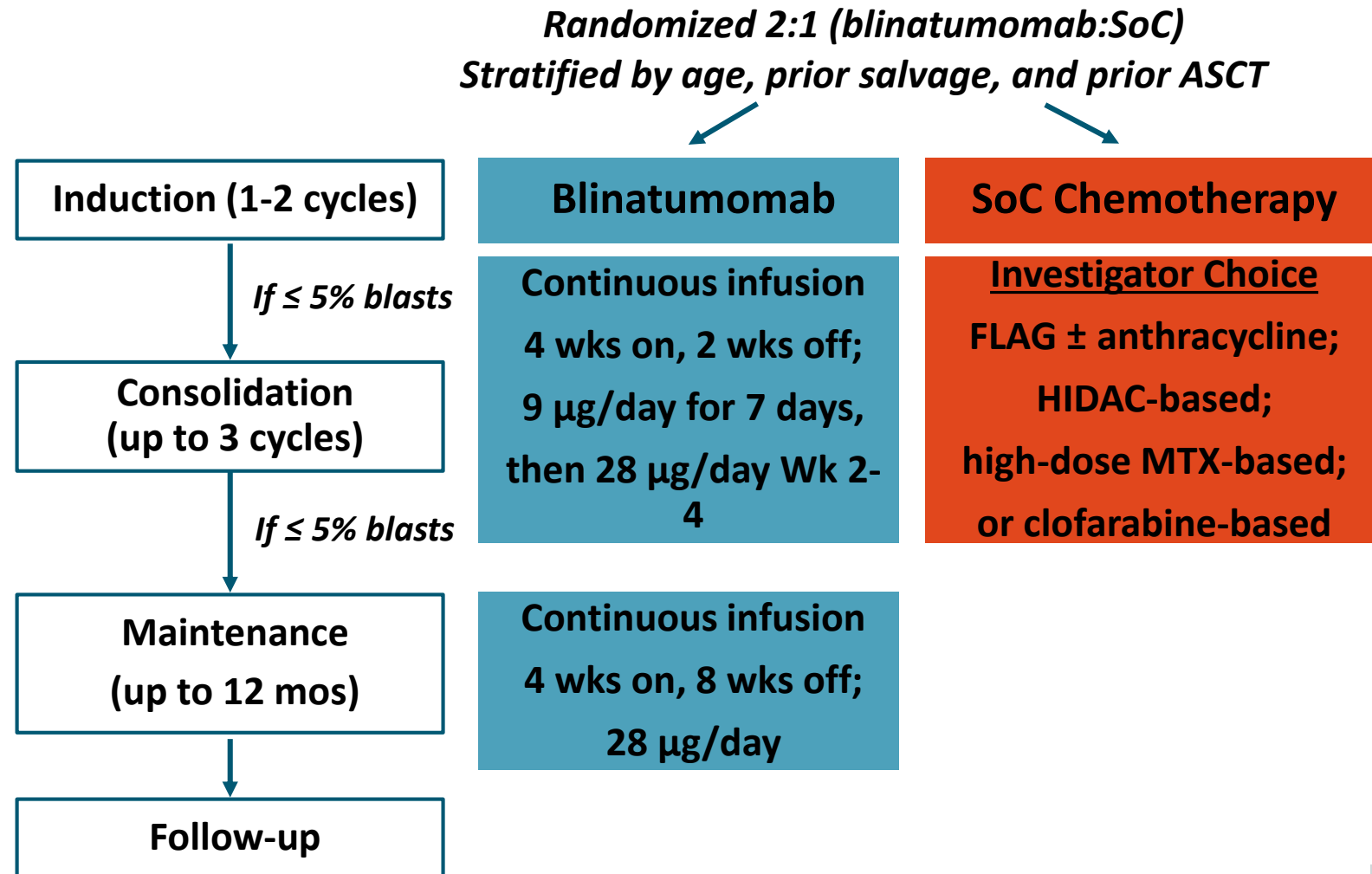
D15

D22

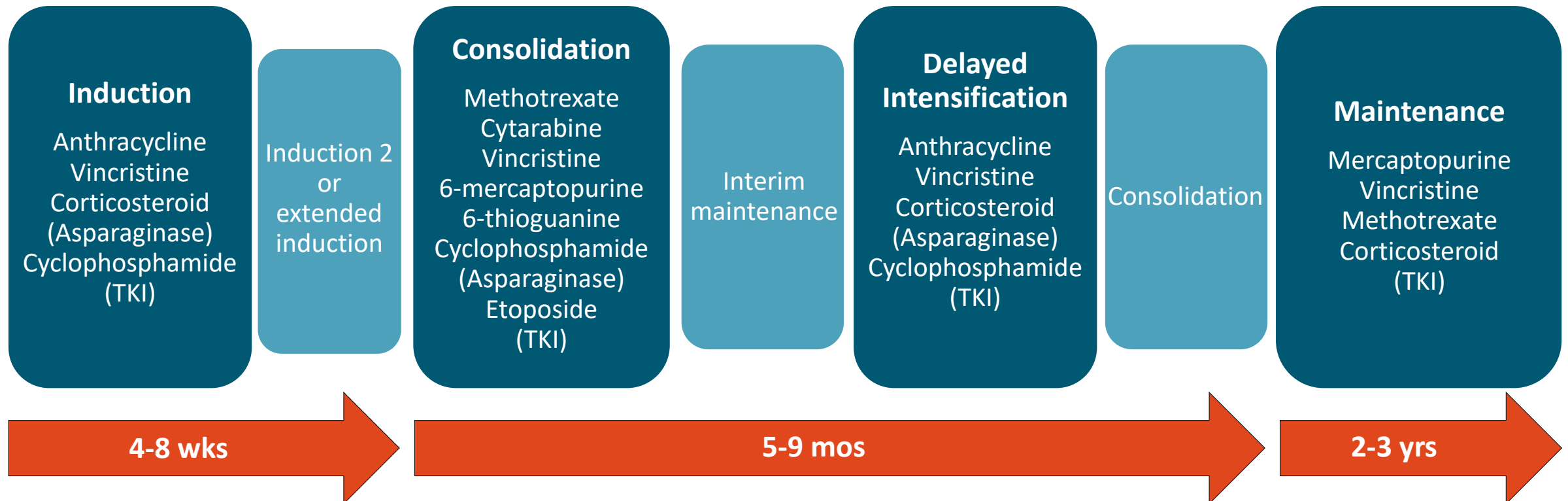
Up to 8 cycles

Phase III TOWER Trial of Blinatumomab vs Chemotherapy in R/R B-Cell ALL: Study Design

- N = 405 patients with heavily pretreated B-cell ALL
- Primary endpoint: OS



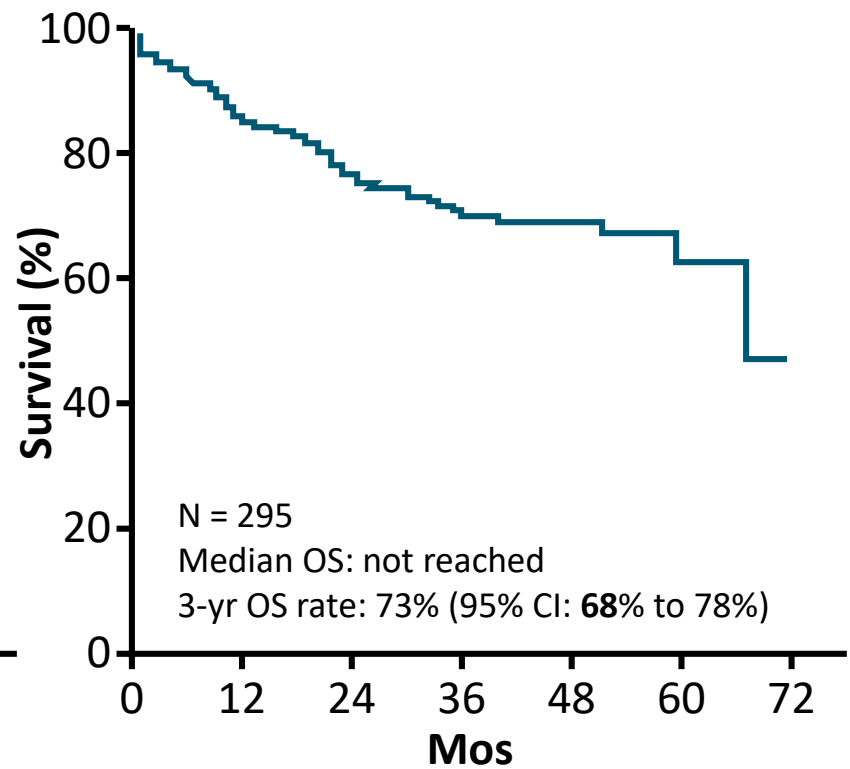
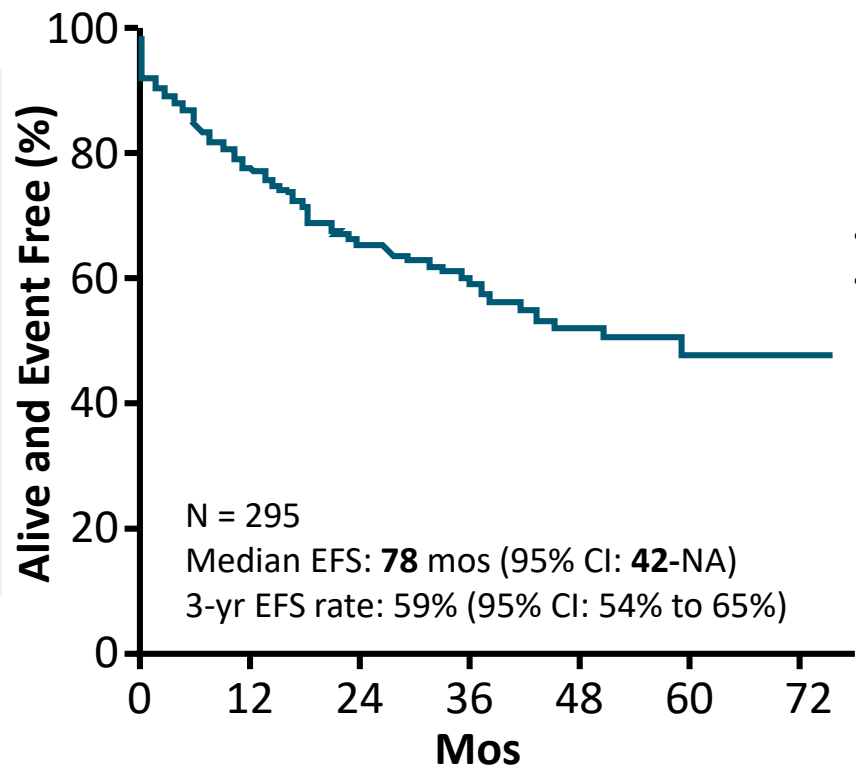
Pediatric vs Adult Regimens for ALL



Intergroup C10403: Pediatric-Like Regimen for Adolescents and Young Adults With ALL

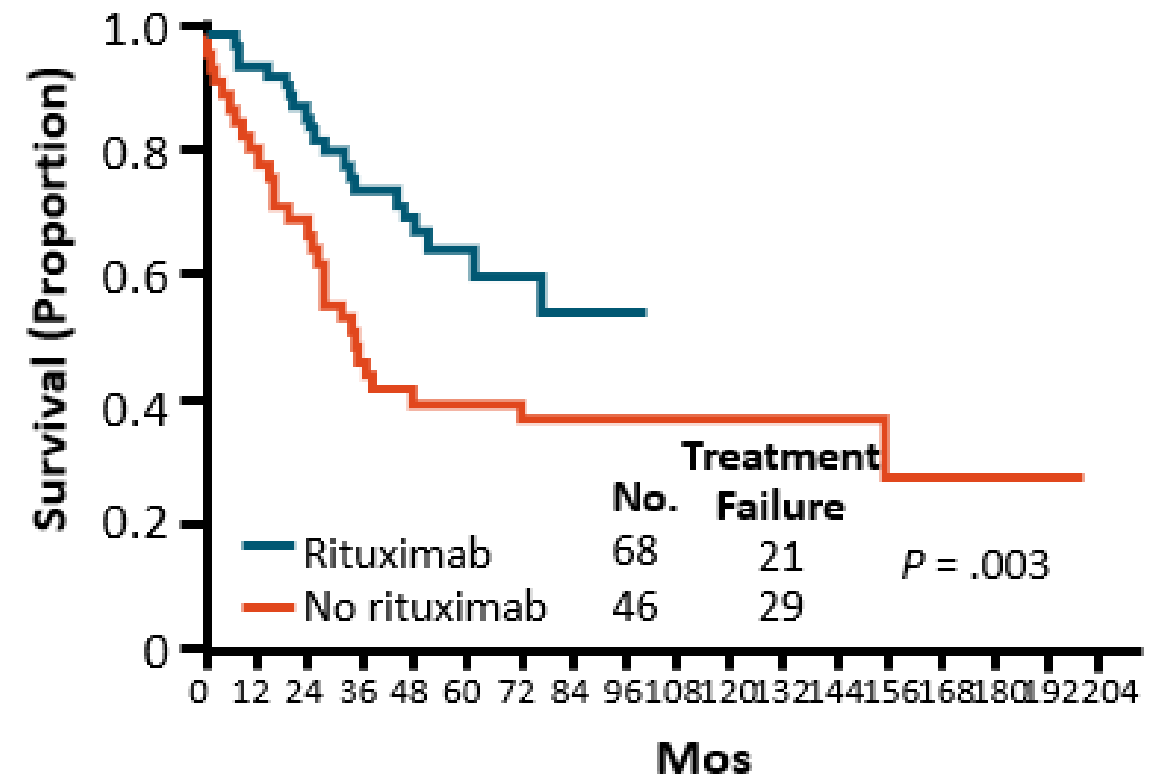
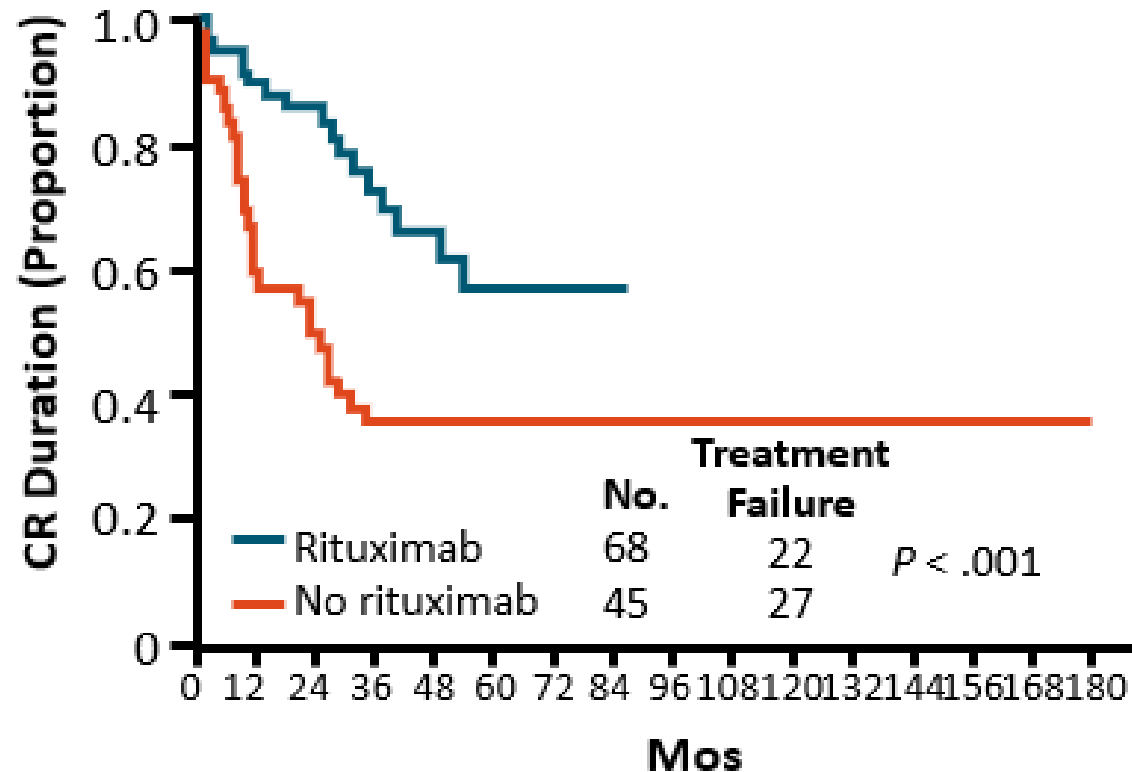
- CALBG historical control median event-free survival: 30 mos

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT MTX	Peg-Asp	MTX
IT MTX	Ara-C		Ara-C	IT MTX
IT Ara-C	6MP		6-TG	
	IT MTX		IT MTX	

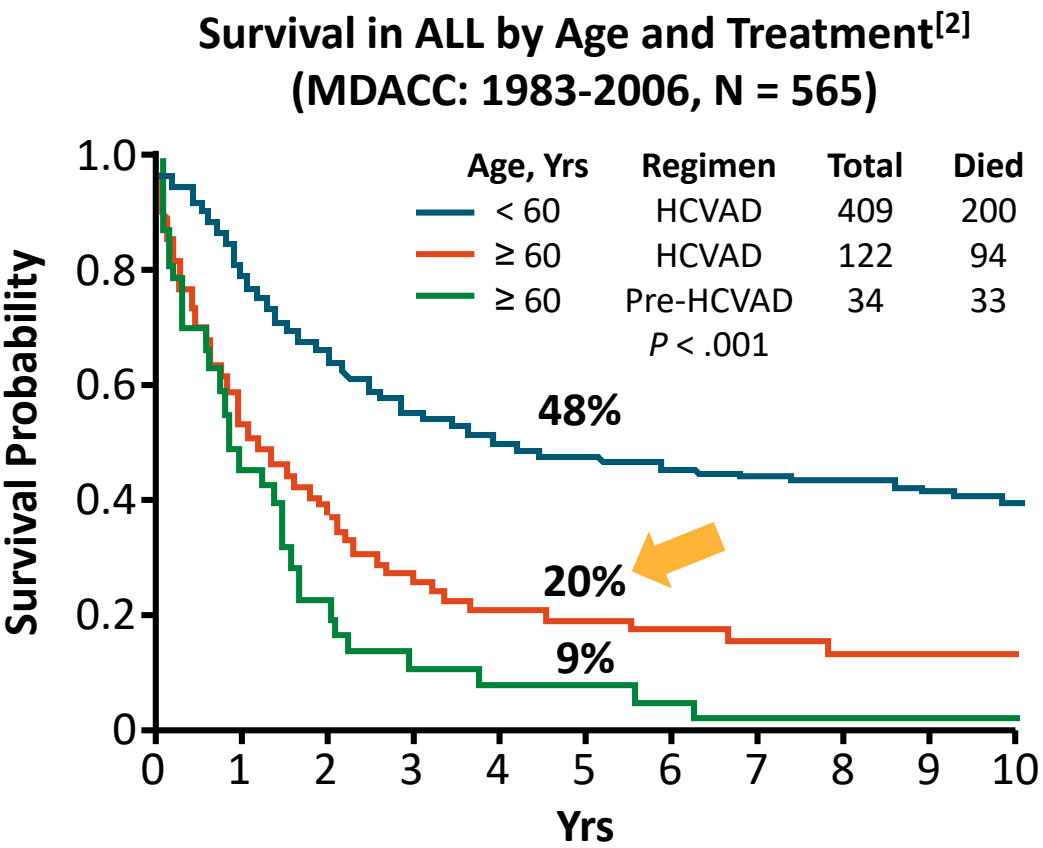
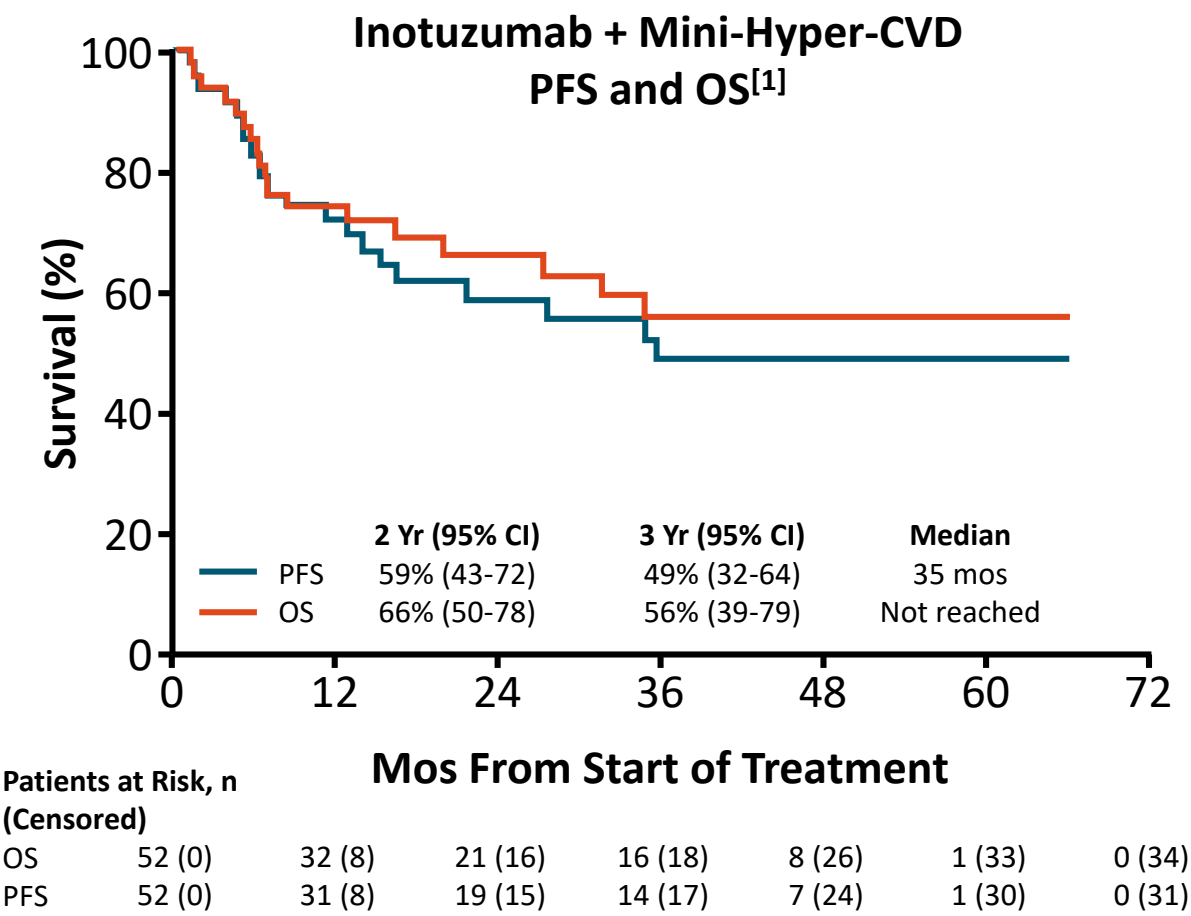


Rituximab Improves Outcome for CD20+ ALL

Rituximab + Hyper-CVAD



Inotuzumab Ozogamicin + Mini-Hyper-CVD as Frontline Therapy in Patients > 60 Yrs of Age

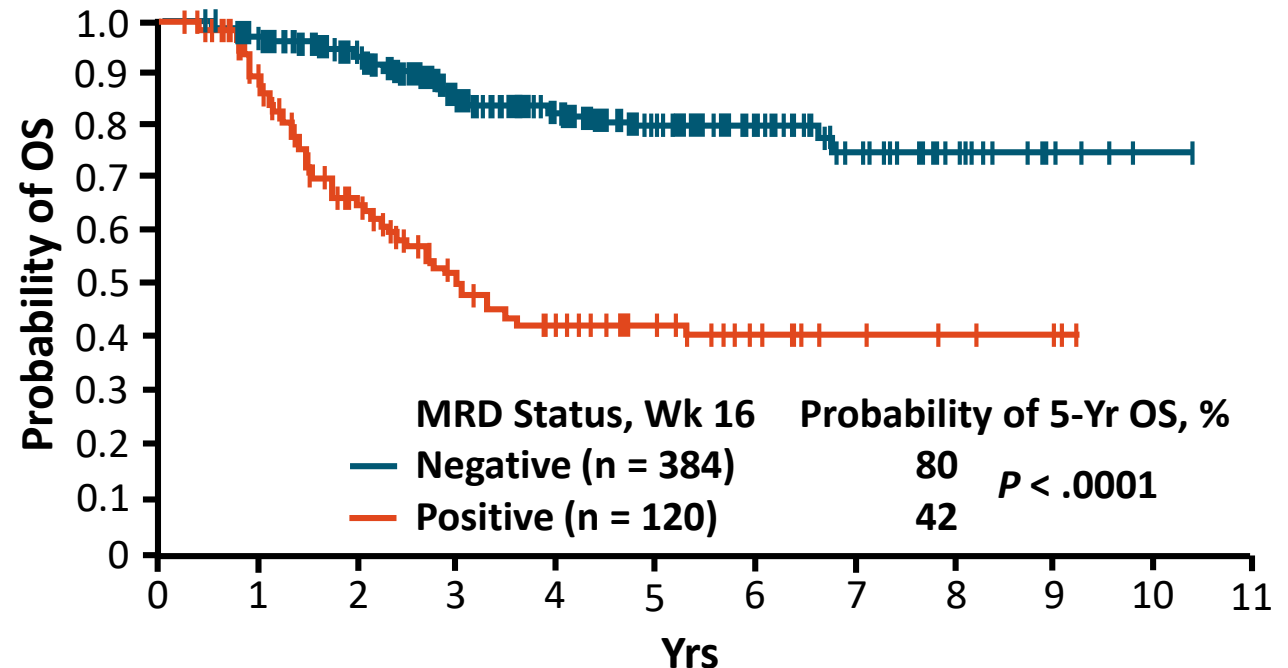


1. Kantarjian. Lancet Oncol. 2018;19:240. 2. O’Brien. Cancer. 2008;113:2097.

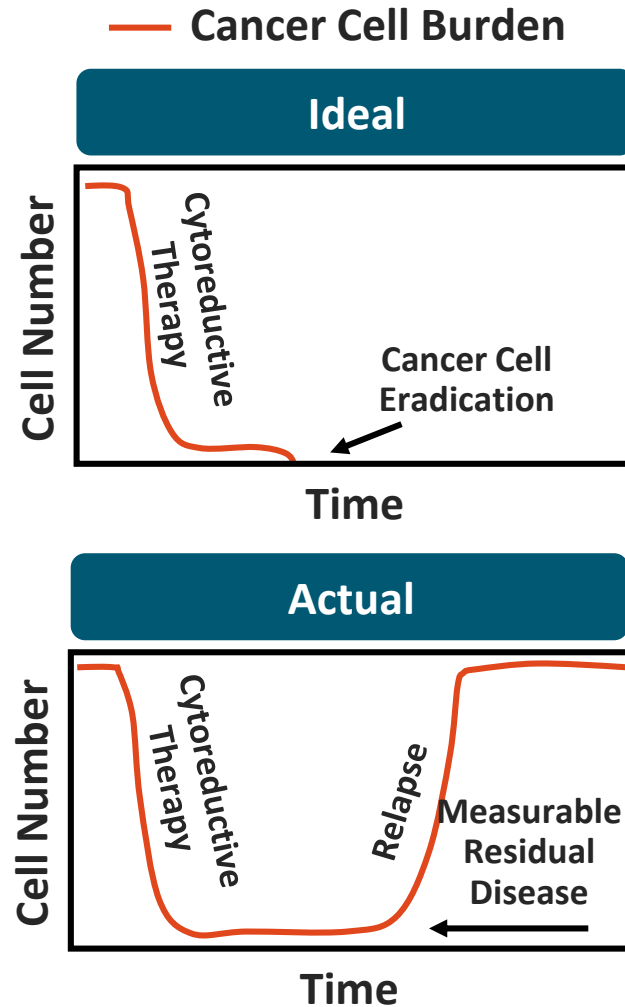
MRD and Its Status as Prognostic Factor for OS in ALL

- Measurable residual disease (formerly *minimal* residual disease; MRD): low-level molecular disease in patients achieving CR according to conventional analyses^[1]
- MRD detected by more sensitive methods^[2]
 - Flow cytometry for leukemia-associated immunophenotype
 - FISH or PCR for leukemia-specific fusion transcripts or gene rearrangements
- MRD-positive status prognostic for poor survival outcomes in ALL^[1-3]

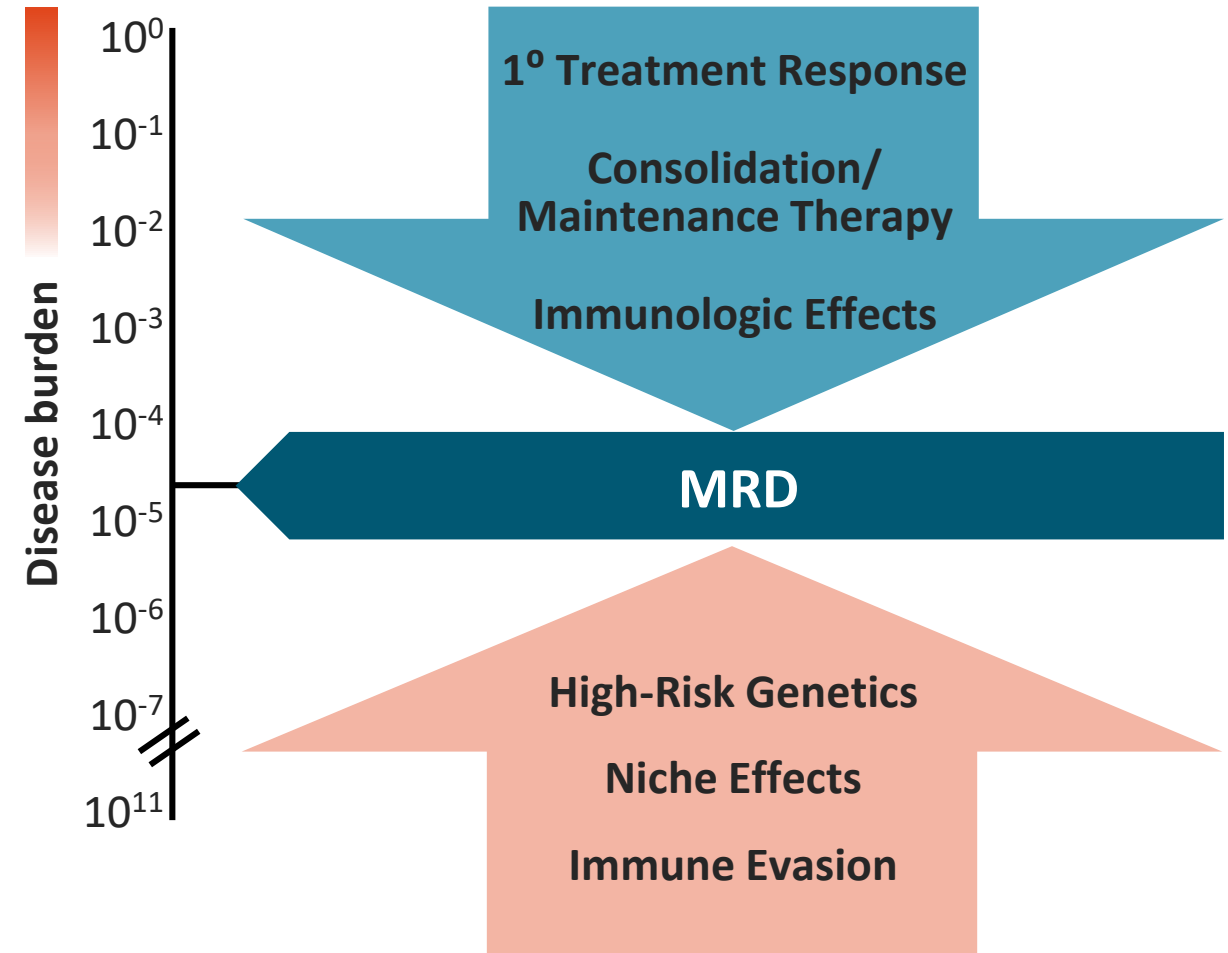
GMALL 06/99 and 07/03: OS by MRD Status After Intensive Chemotherapy Induction and Consolidation^[3]



MRD Overview



Clinical relapse



Methods for MRD Quantification in ALL

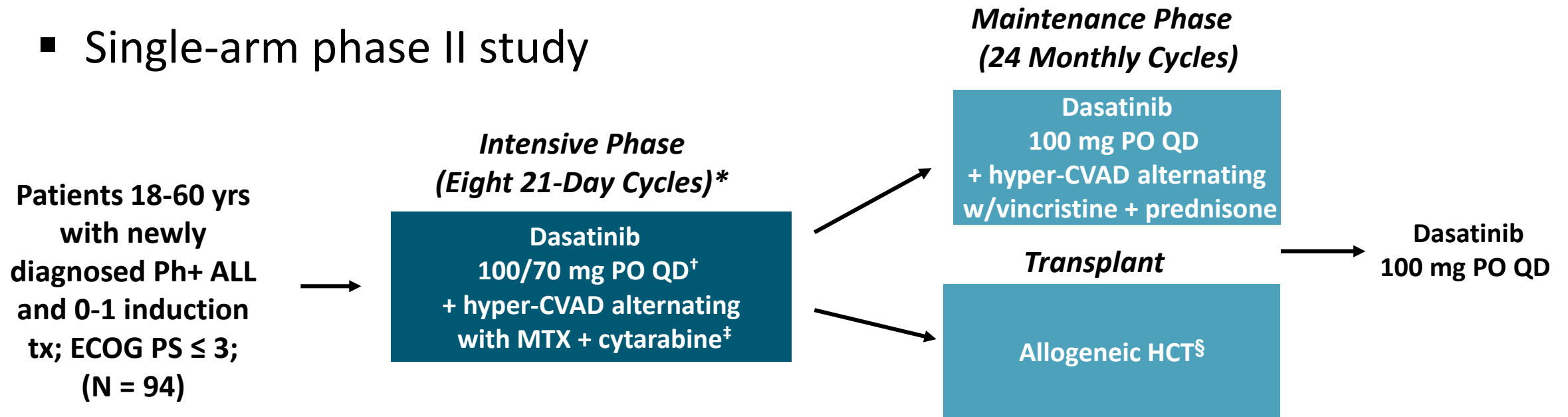
	Flow Cytometry	ASO-PCR	NGS
Sensitivity	10^{-4} (to 10^{-5})	10^{-4} to 10^{-5}	10^{-6}
Samples	Fresh	Fresh or Frozen	Fresh or Frozen
Availability	Widely available*	Not widely available	Universally via centralized reference lab
Customization	Not required [†]	Patient-specific probes and primers	Not required
Cost	Expensive	Expensive	Expensive

*Conventional analysis may not be adequate for MRD quantification.

[†]Phenotype of cancer cells must be different from normal cells.

Hyper-CVAD + Dasatinib in Ph+ ALL: Study Design

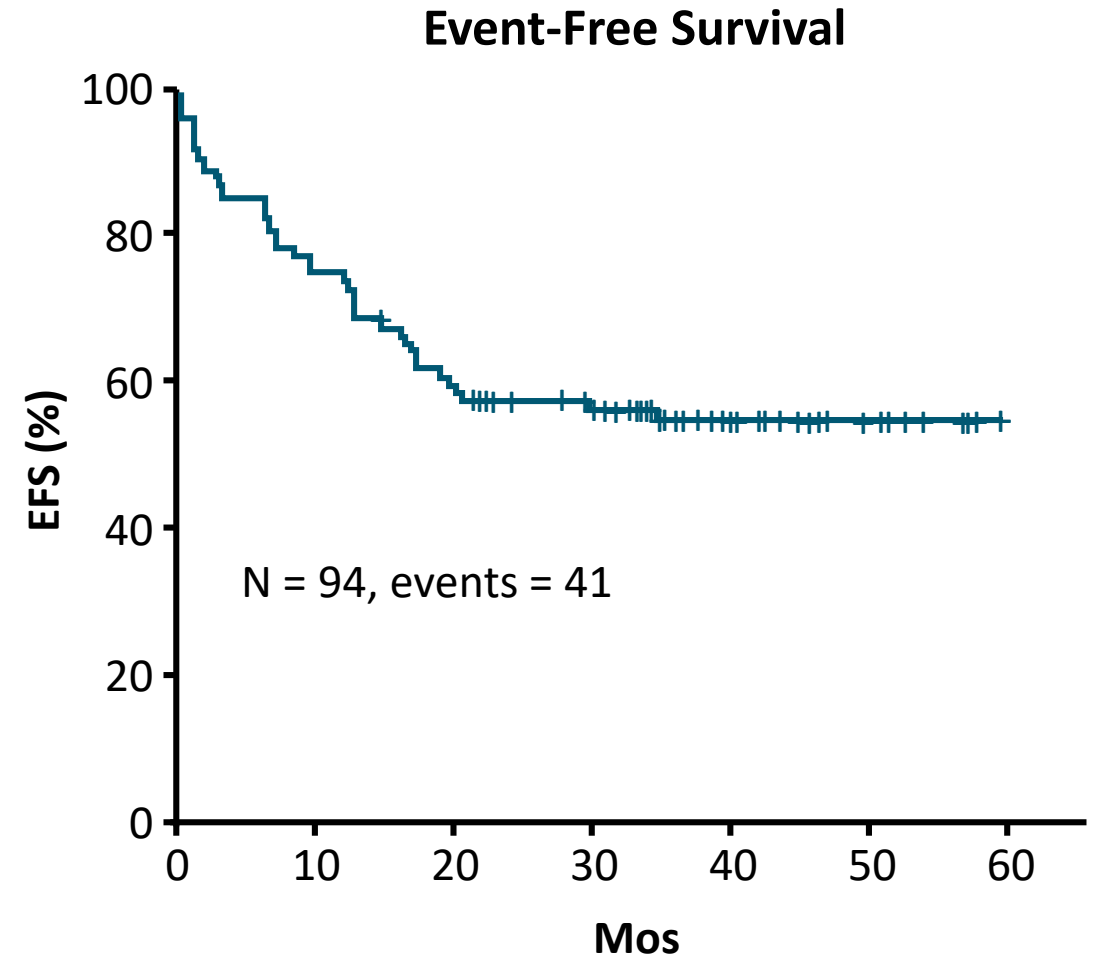
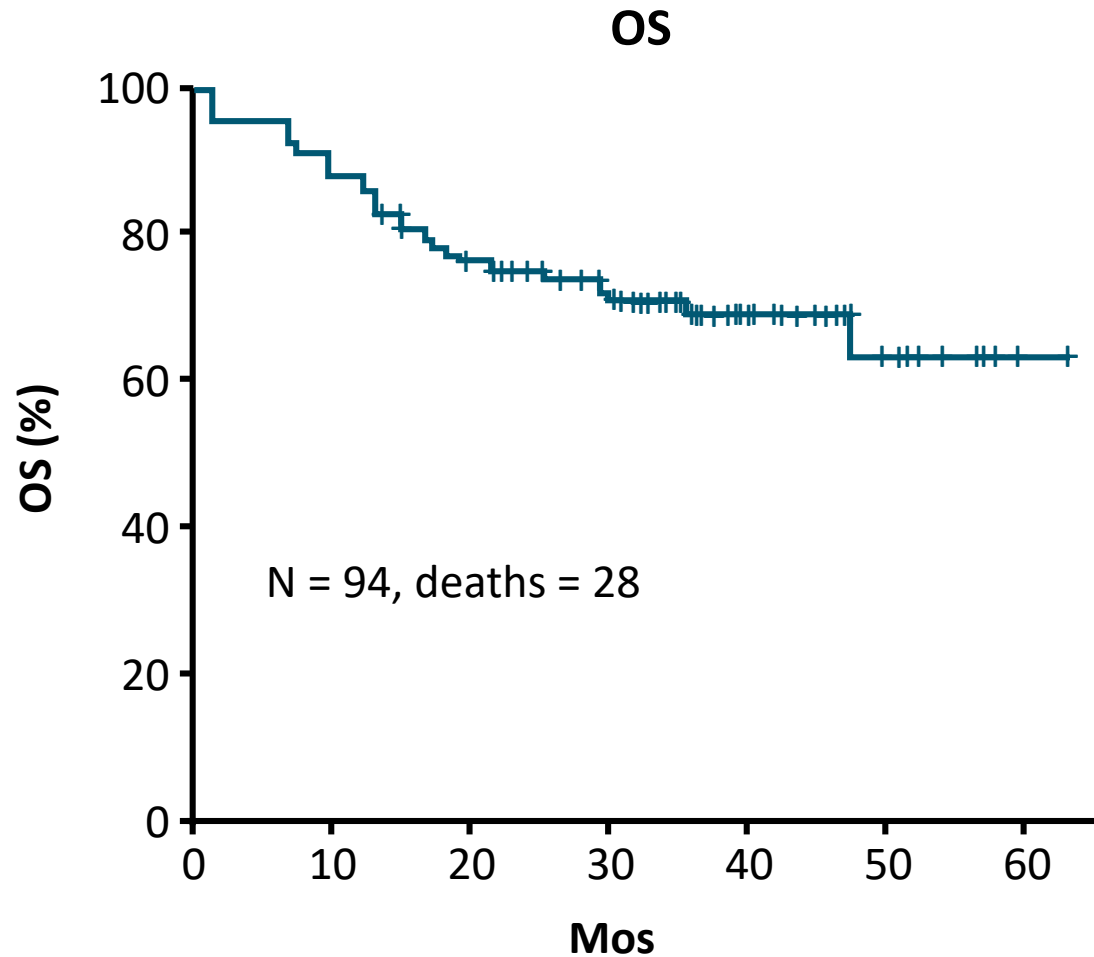
- Single-arm phase II study



*Patients received intrathecal CNS prophylaxis 2 x during cycles 1-4. †Postamendment patients received **100 mg** on Days 1-14 of first cycle and then 70 mg continuously cycles 2-8. **Prior patients initially received 50 mg BID, and then 100 mg QD following initial amendment, on Days 1-14 of each cycle.** ‡Alternating between each cycle. §Patients with available donor.

- Primary endpoint: 12-mo RFS
- Additional endpoints: CCR, OS, MRD

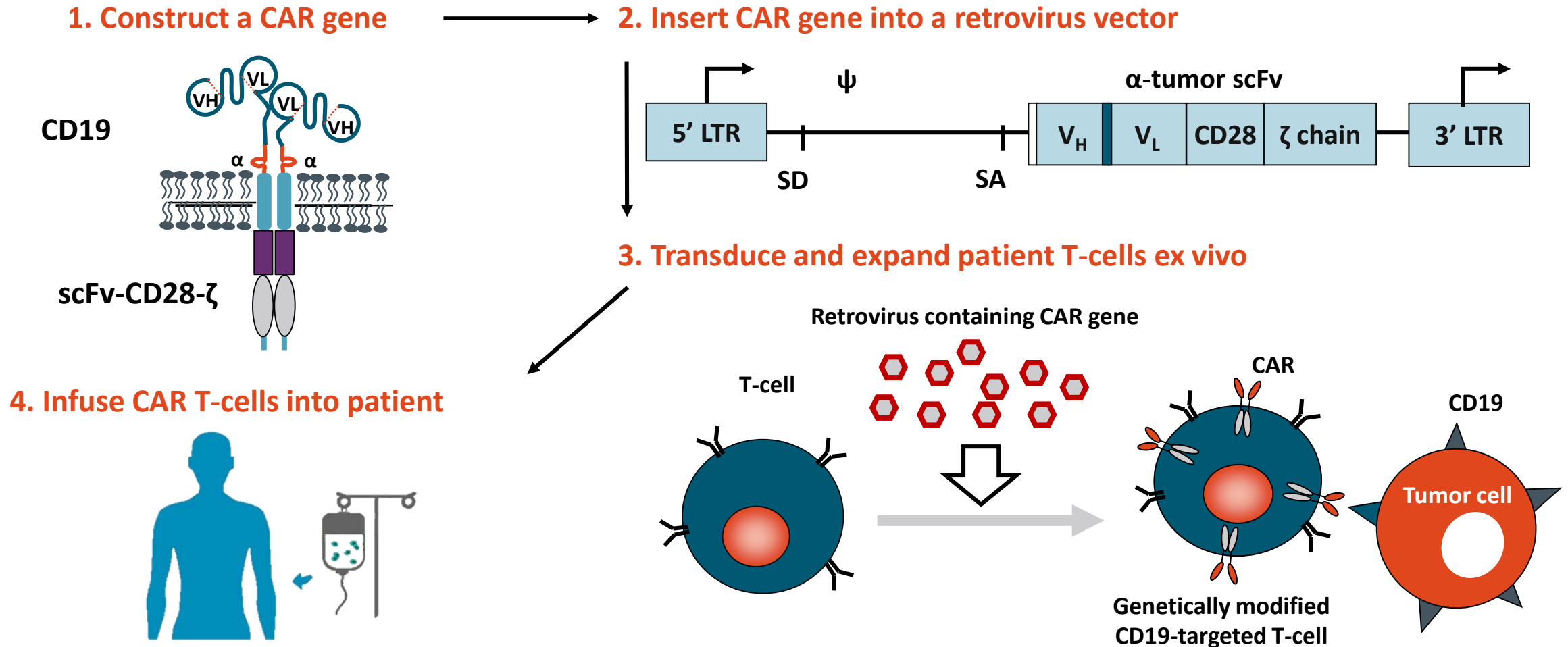
Hyper-CVAD + Dasatinib in Ph+ ALL: Results



Ravandi. Blood Adv. 2016;1:250.

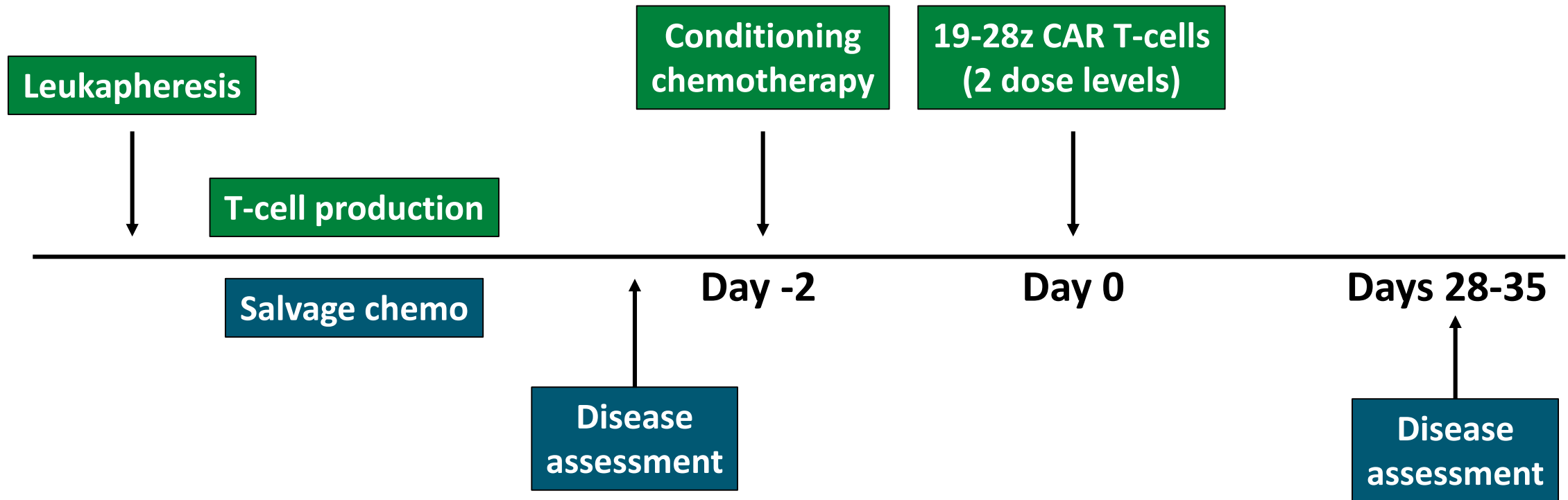
— Total patients (N = 94)

Generation of TAA-Targeted CAR T-Cells for Treatment of Cancer



Sadelain. Nat Rev Cancer. 2003;3:35. Brentjens. Nat Med. 2003;9:279. Park. NEJM. 2018;378:449.

CAR T-Cell Manufacturing, Treatment, Assessment



Park. NEJM. 2018;378:449.

Phase II ELIANA Trial of Tisagenlecleucel in Pediatric and Young Patients With B-Cell ALL: Study Design

- Multicenter, open-label, single-arm phase II study of CD19-targeted CAR T-cell therapy

Patients aged 3-21 yrs* with
B-cell ALL; $\geq 5\%$ BM
lymphoblasts; no isolated
extramedullary disease
relapse, prior CD19-directed
therapy, or prior gene therapy
(N = 92)

*From 3 yrs at screening to 21 yrs at initial diagnosis.



Fludarabine
30 mg/m² IV QD for 4 doses
Cyclophosphamide
500 mg/m² IV QD for 2 doses

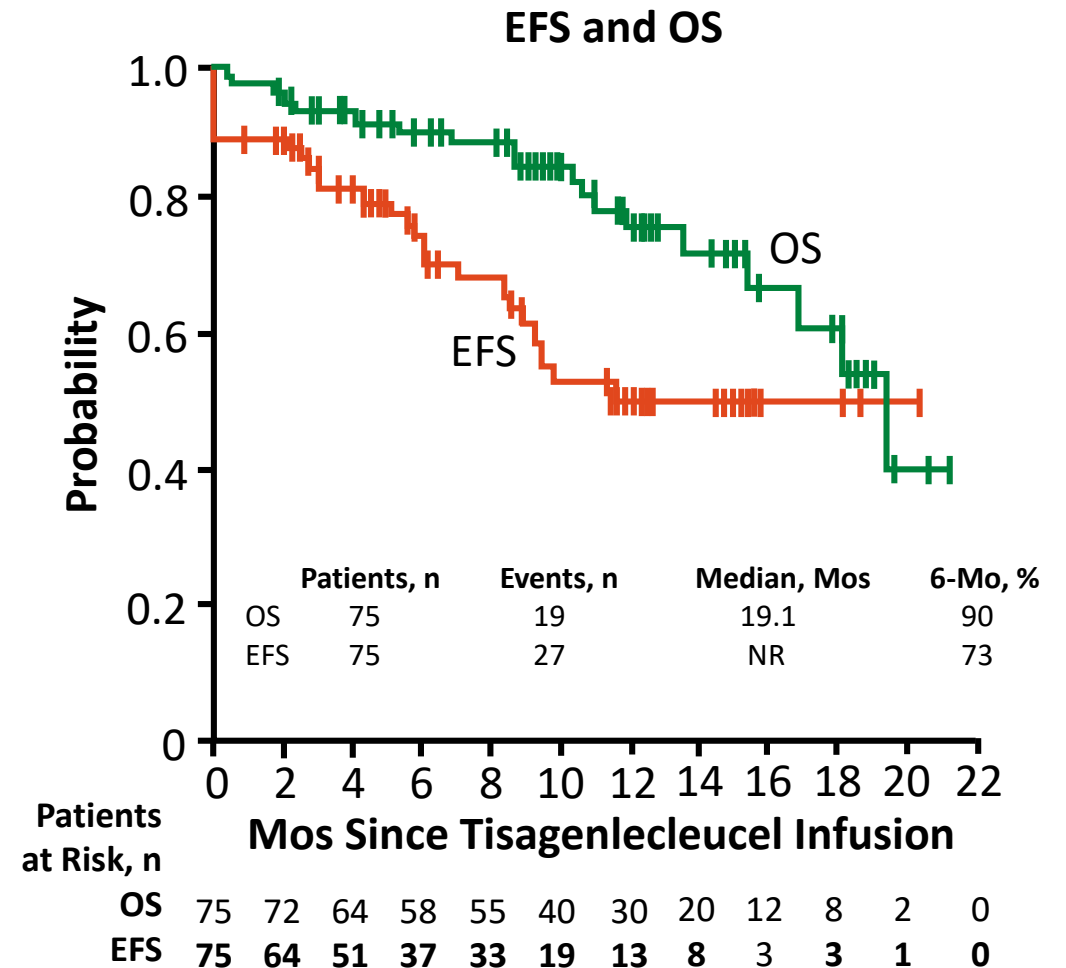
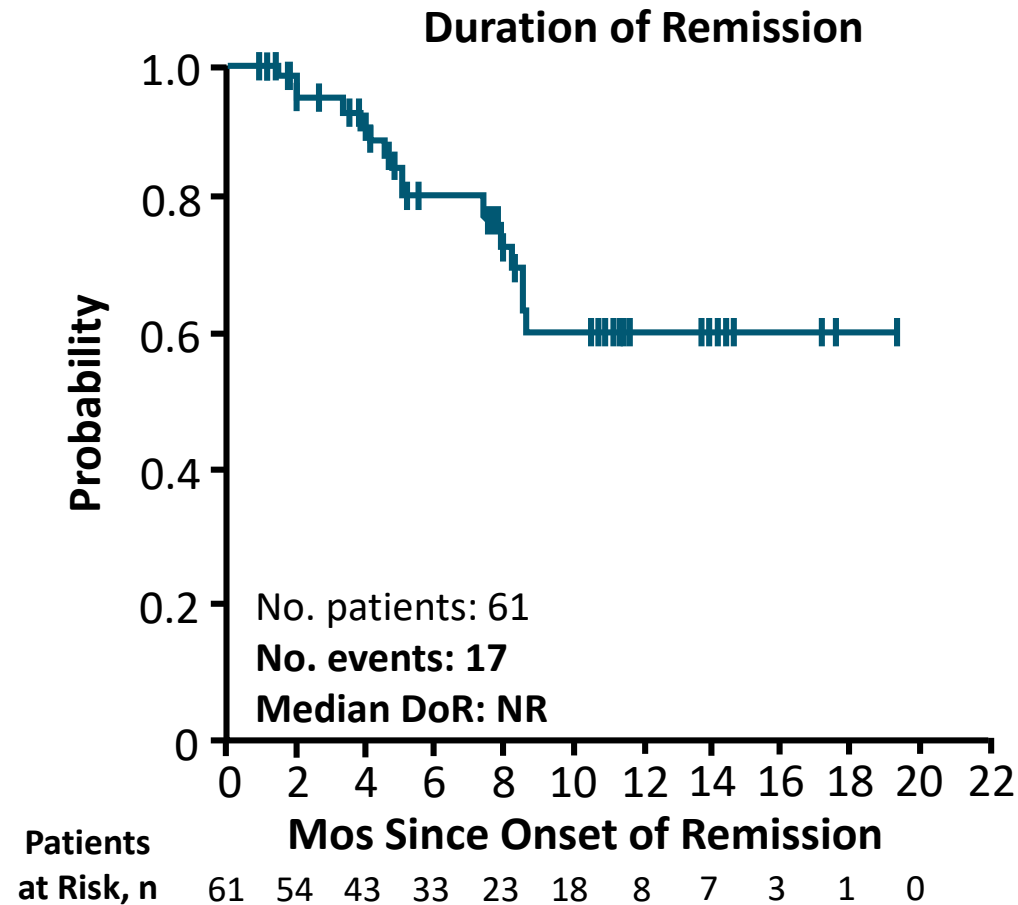


Single-dose tisagenlecleucel
0.2-5.0 x 10⁶/kg IV if ≤ 50 kg
0.1-2.5 x 10⁸ IV if > 50 kg
(n = 75[†])

[†]17 patients discontinued before
infusion: deaths, n = 7; manufacturing
failures, n = 7; AEs, n = 3.

- **Primary endpoint: ORR (CR + CRi) within 3 mos, assessed by IRC**
 - 4-wk maintenance of remission required
- **Secondary endpoints: MRD status, DoR, OS, cellular kinetics, safety**

ELIANA: Remission and Survival



CAR T-Cell Therapy for ALL: Advantages and Limitations

■ Advantages

- HLA-independent antigen recognition, therefore universal application
- Rapid generation of tumor-specific T-cells
- Minimal risk of GVHD
- A living drug: potential for lasting immunity even after a single infusion
- Selective modification of specific T-cell subtypes
- Additional modification capability of CAR construct

■ Limitations

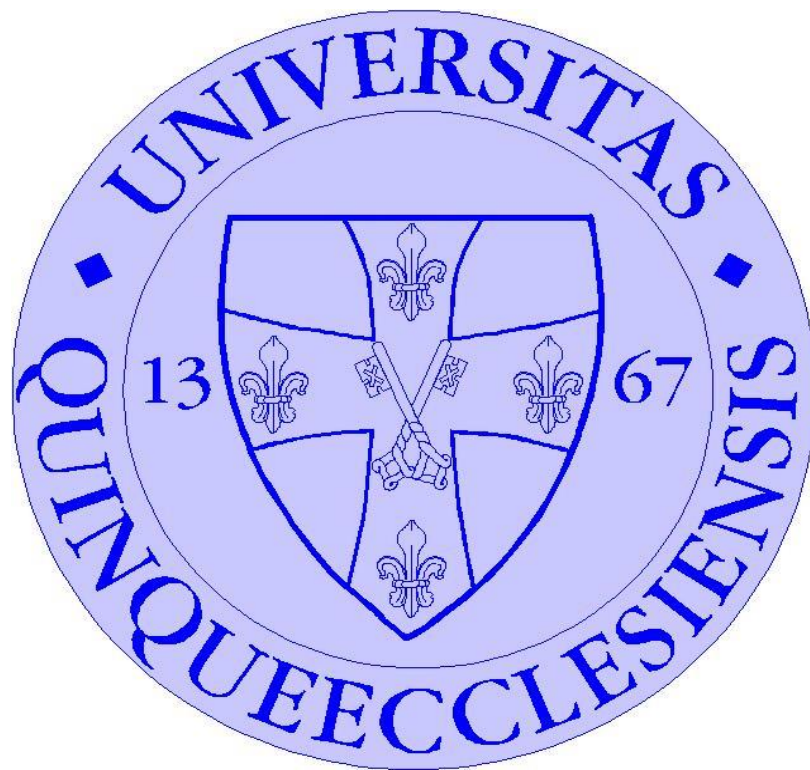
- Cytokine-release syndrome
- Tumor lysis syndrome
- Neurologic toxicity
- On-target, off-tumor toxicity (eg, B-cell aplasia)
- Off-target, off-tumor toxicity (eg, agammaglobulinemia)

Conclusions

- First-line strategies for younger patients appear enhanced with AYA regimens as opposed to conventional regimens, such as hyper-CVAD or CALGB regimen
- Efficacy of conventional first-line approaches for Ph+ ALL markedly improved with incorporation of TKIs
- For older patients, newer, less intensive regimens that incorporate InO or TKIs are showing promise
- Blinatumomab and InO prolonged OS vs SoC chemotherapy regimens in ALL
 - A subset of patients develop unique toxicities that will require vigilant monitoring
- CD19-targeted CAR T-cells can induce CRs in 70% to 90% of patients with R/R ALL

LATE EFFECTS OF TREATMENT

- Cranial irradiation-cognitive and intellectual impairment, CNS neoplasms
 - Chemotherapeutic drugs: secondary AML
 - Endocrine dysfunctions: short stature, obesity, growth retardation, amenorrhea
 - Anthracycline: cardiotoxicity
 - Steroid: avascular necrosis of bone
 - Etc.
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Köszönöm a megtisztelő figyelmet!