# None-Kinase inhibitors (ib)

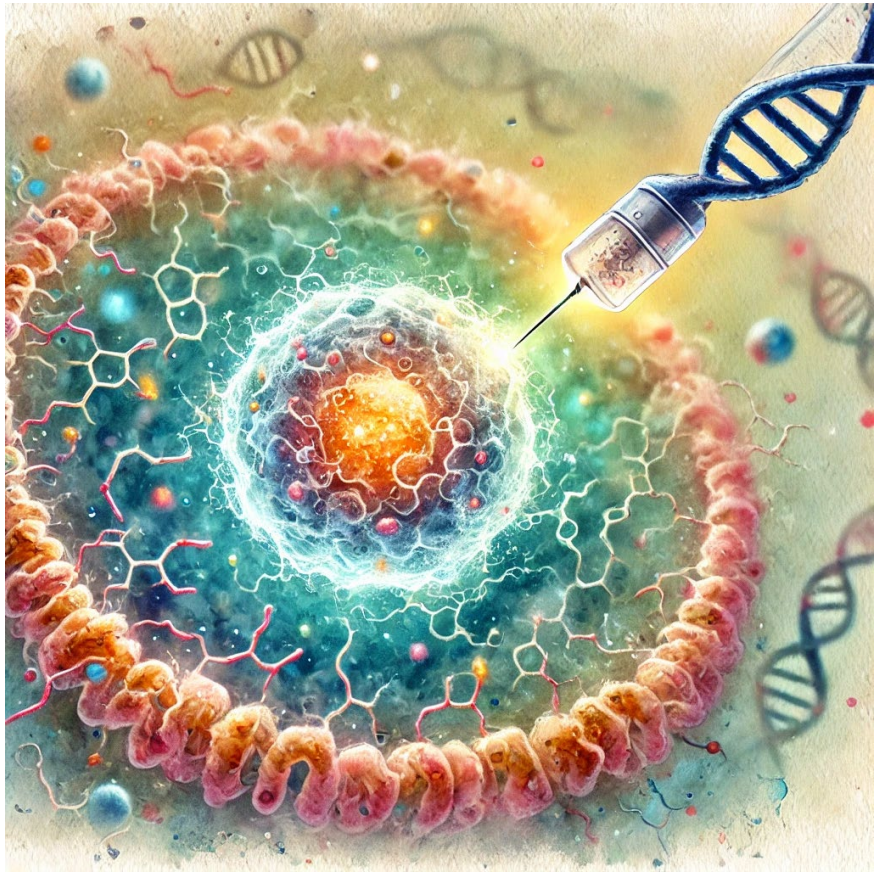
Presenter : Lihua Fang pharmacist

# None-Kinase inhibitors (ib)

- Nucleus : are applied to treat blood cancers, particularly due to their ability to modulate gene expression and tumor suppressor pathways
  - DNMTI (DNA Methyltransferase Inhibitor) : Azacitidine (Vidaza)、Decitabine (Dacogen)
  - HDAC (Histone deacetylases ) Inhibitors
  - EZH2 inhibitor : Tazemetostat
  - Hedgehog pathway inhibitors
  - PARP Inhibitors (Poly ADP-ribose polymerase inhibitor)
  - XPO1 Inhibitor(exportin 1 (XPO1) )
- Mitochondria
  - BCL2 Inhibitors :
  - IDH1, IDH2 Inhibitors
- Cytoplasm
  - KRAS Inhibitors
  - Proteasome inhibitors : (multiple myeloma )
  - IMiDS
  - STAMP Inhibitors

# Nucleus : are applied to treat blood cancers, particularly due to their ability to modulate gene expression and tumor suppressor pathways

- DNMT inhibitor
- EZH2 inhibitor : Tazemetostat
- HDAC Inhibitors
- Hedgehog pathway inhibitors
- PARP Inhibitors (Poly ADP-ribose polymerase inhibitor) :
- XPO1 Inhibitor(exportin 1 (XPO1) )



# Epigenetic modifiers family 表觀遺傳修飾

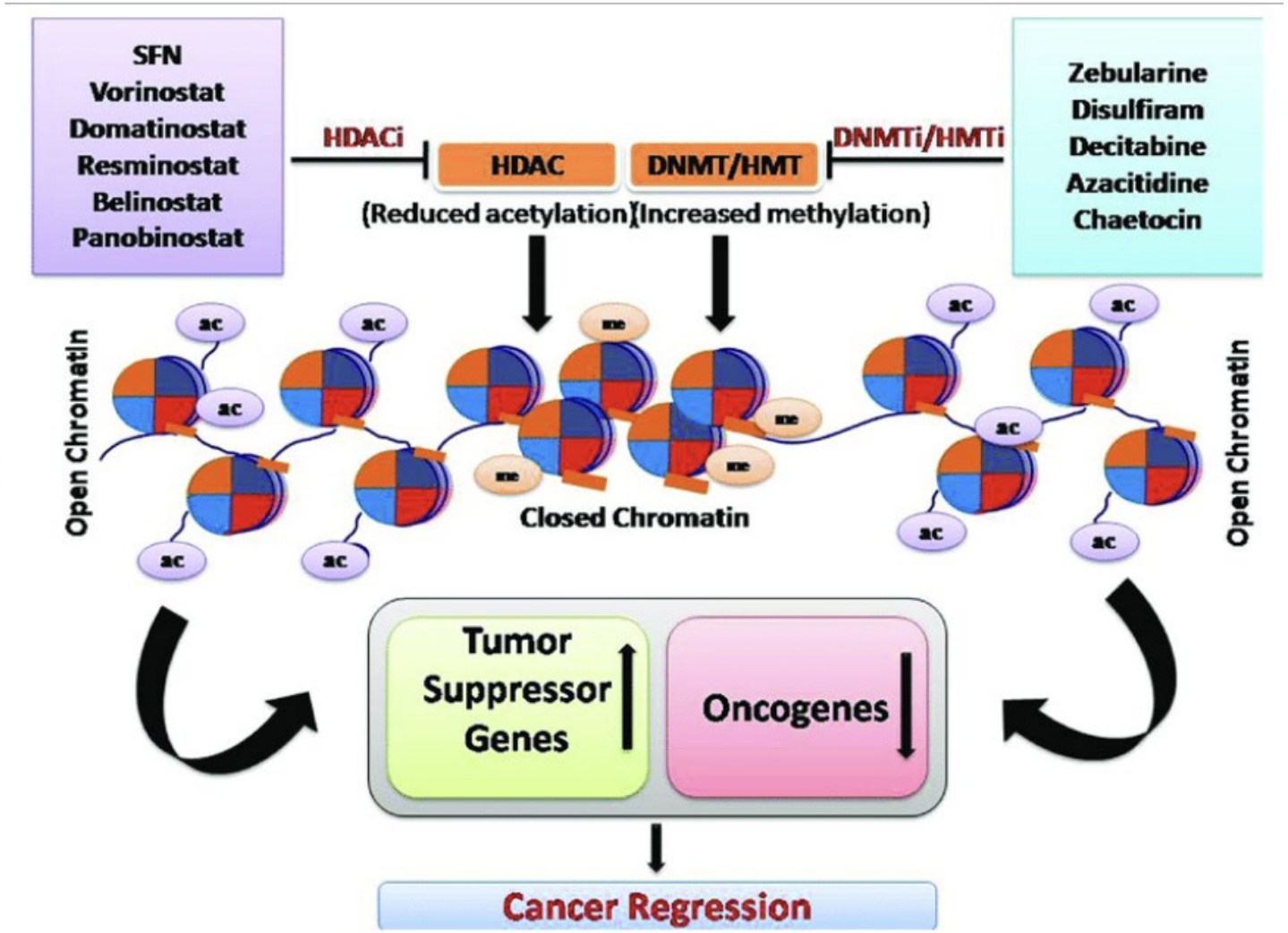
These drugs modify DNA methylation, histone modifications, or chromatin remodeling to reactivate tumor suppressor genes or inhibit oncogene expression.

| Epigenetic Modifier | Function | Effect on Gene Expression | FDA-Approved Drugs |
|---|---|---|---|
| **DNMT Inhibitors (hypomethylation agents)** | Block **DNA methyltransferases (DNMTs)**, which add methyl groups to cytosines in CpG islands | **Reactivates tumor suppressor genes** silenced by hypermethylation | **Azacitidine (Vidaza), Decitabine (Dacogen), Inqovi** |
| **HDAC Inhibitors** | Block **histone deacetylases (HDACs)**, which remove acetyl groups from histones | **Loosens chromatin structure**, increasing gene transcription | **Vorinostat (Zolinza), Romidepsin (Istodax), Panobinostat (Farydak), Belinostat (Beleodaq)** |
| **EZH2 Inhibitors** | Block **EZH2**, a component of the PRC2 complex that methylates histones to repress genes | **Reactivates tumor suppressor genes** silenced by histone methylation | **Tazemetostat (Tazverik)** |

CpG islands : are genomic regions that contain a high frequency of cytosine and guanine nucleotides, connected with a phosphodiester bond. They are typically found in or near promoter regions of the genome, where transcription is initiated, and are present in as high as 40%–50% of the human genes.

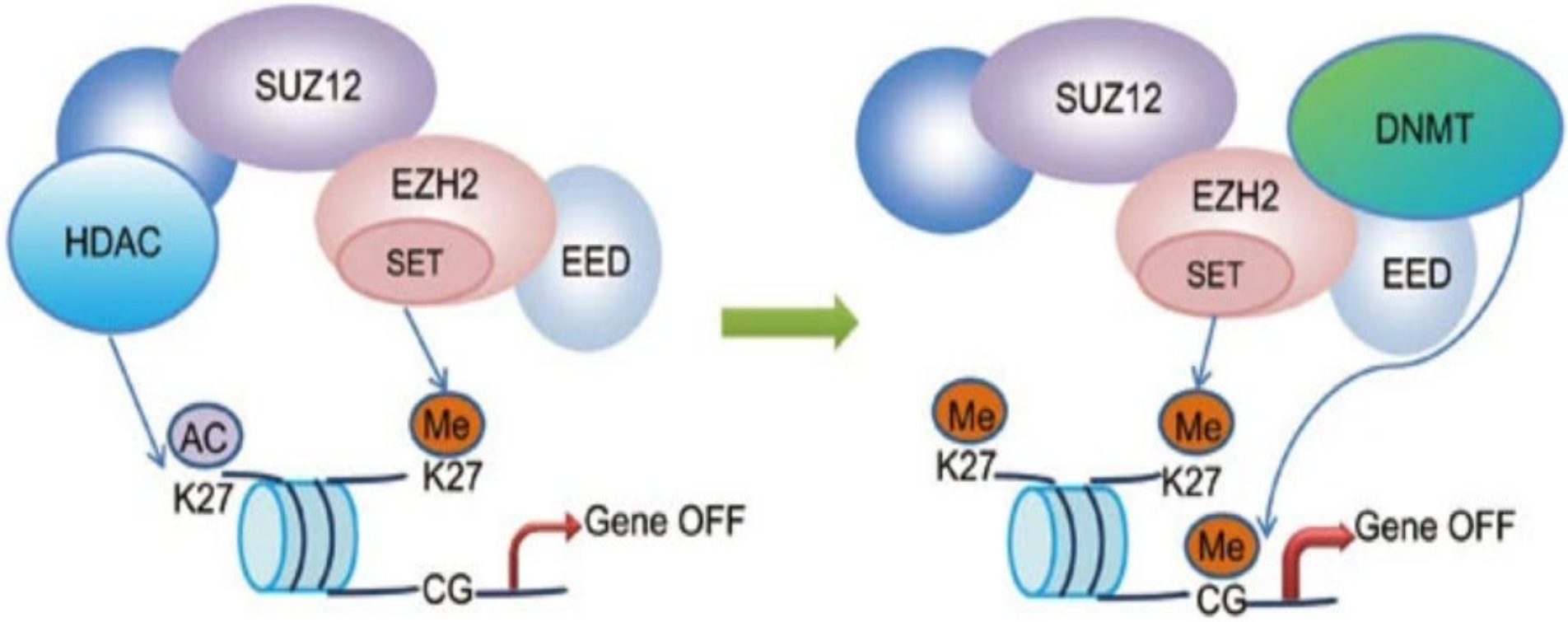
# Enhancing Tumor Suppressor Activity

- DNMT inhibitor (DNA methyl transferase inhibitors)
- HDAC inhibitors (histone deacetylases inhibitor )




| Overall mechanism of function of DNA methyltransferase inhibitors and HDAC inhibitors.

# A model for the collaboration of epigenetic silencing enzymes



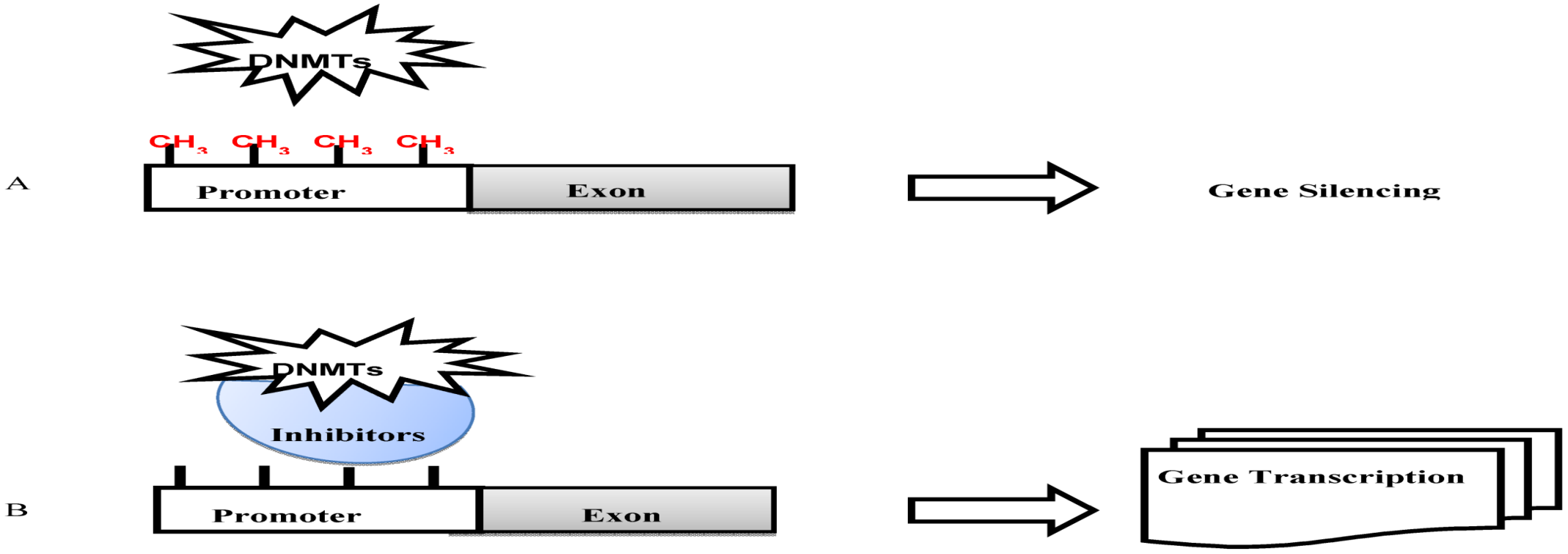

PRC2 複合體的核心、DNA 甲基轉移酶（DNMT）和組蛋白去乙酰化酶（HDAC）。在這個模型中，如果 K27 已經被乙酰化，HDAC 可能會首先去乙酰化它 (deacetylation)，然後通過 PRC2 對 K27 的甲基化使目標基因沉默。DNMT 也可能被 PRC2 招募，在對目標基因的 CpG DNA 進行甲基化後，使染色質狀態更加深度沉默。Ac，乙酰化 (Acetylation)；Me，甲基化(methylation)。

Acta Pharmacologica Sinica volume 35, pages161–174 (2014

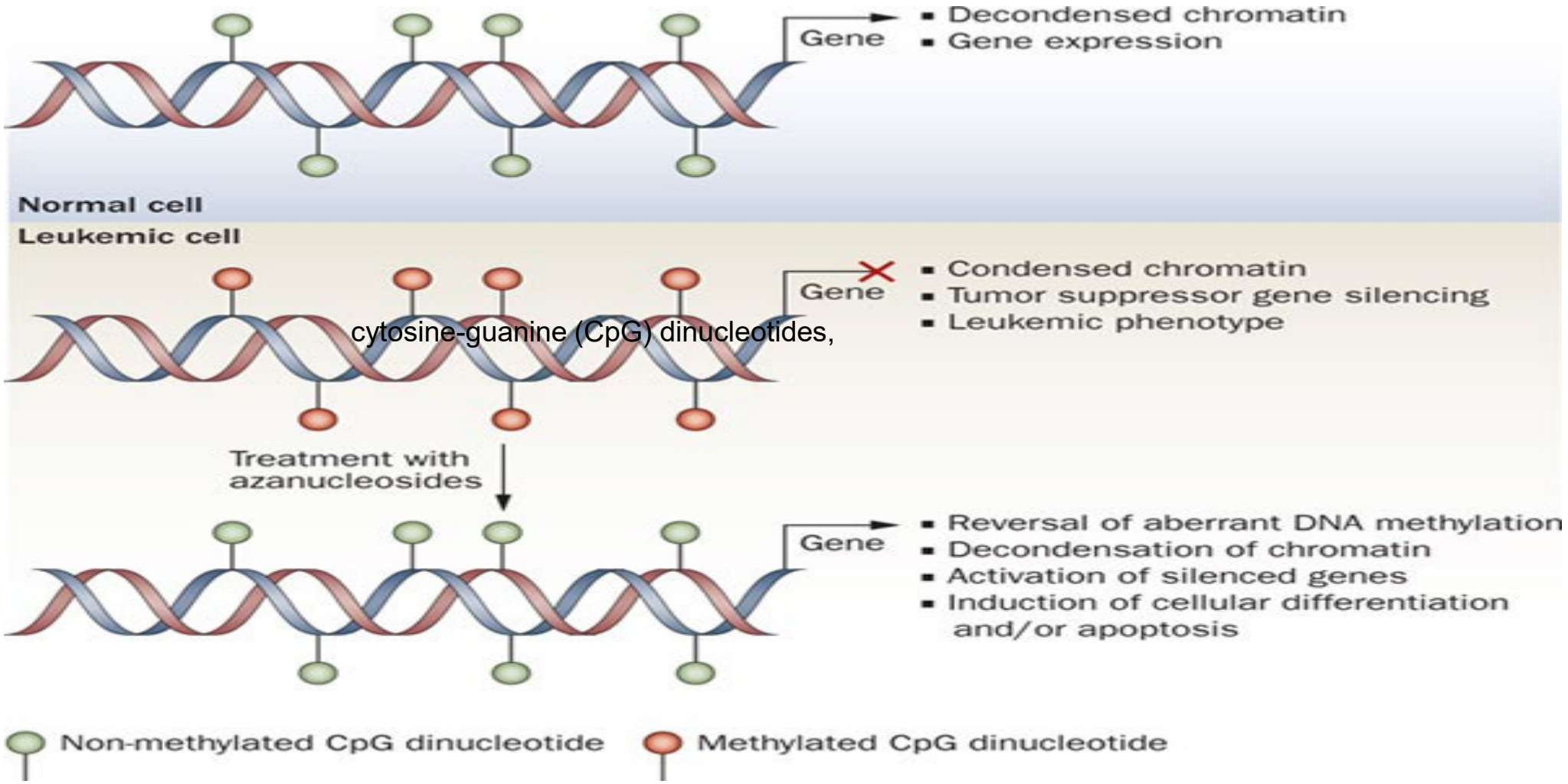
# DNA methyl transferase inhibitors (DNMT inhibitos)

**previously untreated, elderly patients (pts) unfit for chemotherapy**

- Hypomethylating agents work by desilencing epigenetically modified DNA, thus promoting the expression of silenced tumor suppressors.
- 5-azacytidine (azacitidine) and 5-aza-2'-deoxycytidine (decitabine) : higher-risk myelodysplastic syndrome (MDS).



# Proposed mechanism of action of azanucleosides




cytosine-guanine (CpG) dinucleotides,



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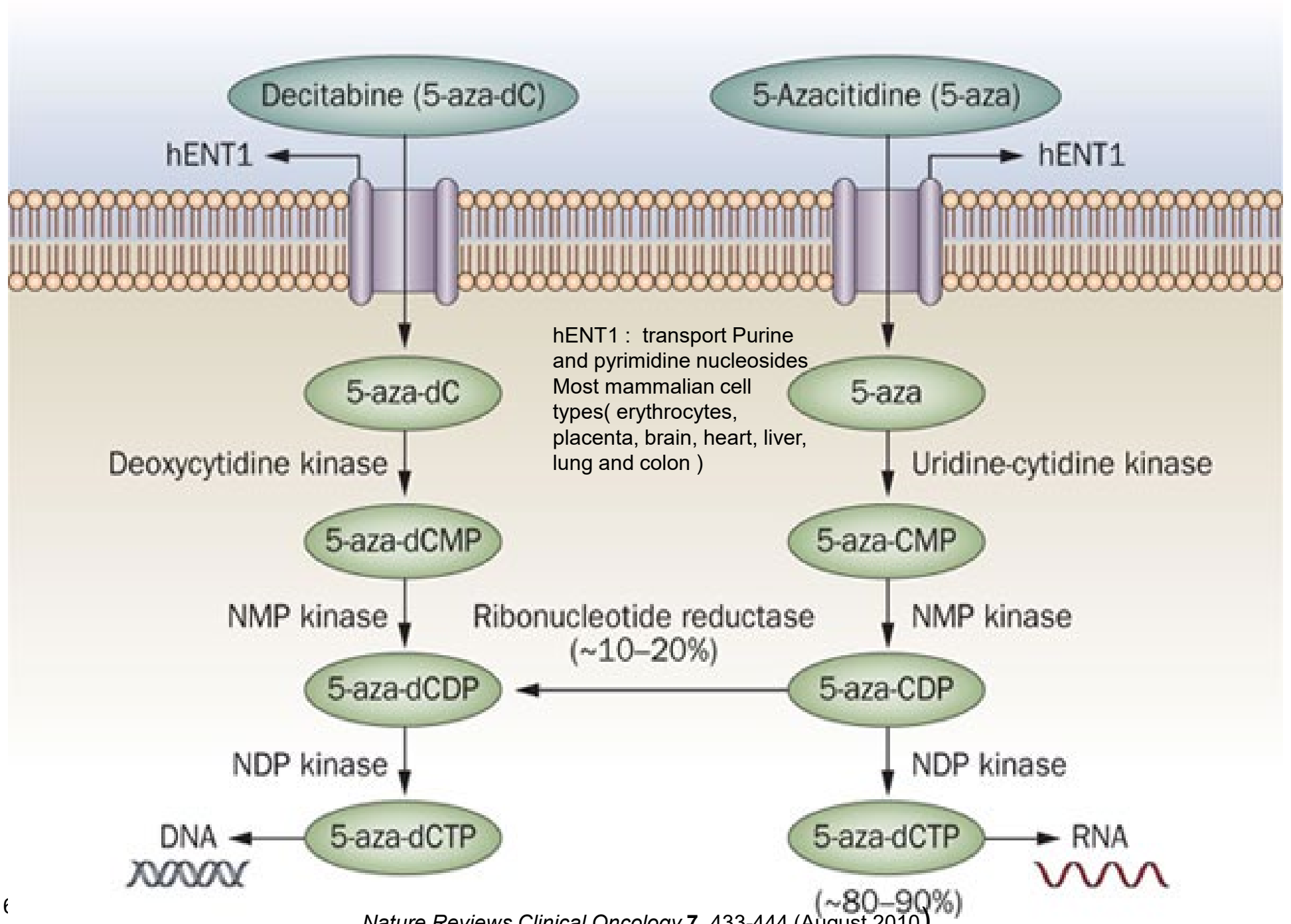
*Nature Reviews Clinical Oncology* **7**, 433-444 (August 2010)



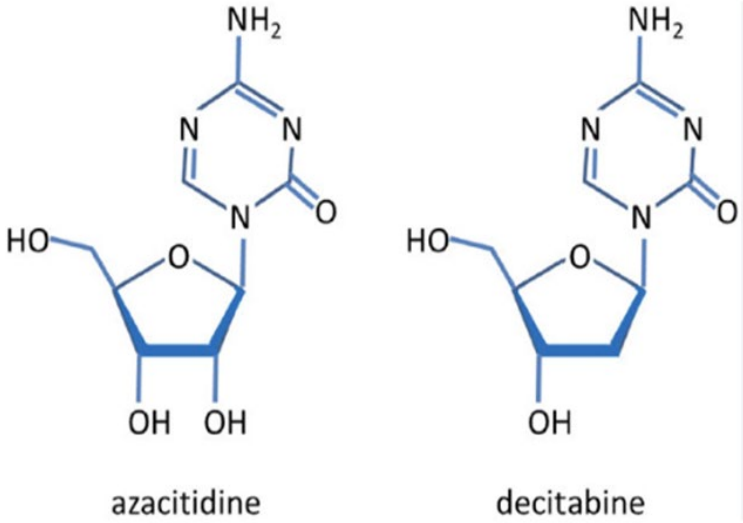

*Nature Reviews Clinical Oncology* **7**, 433-444 (August 2010)

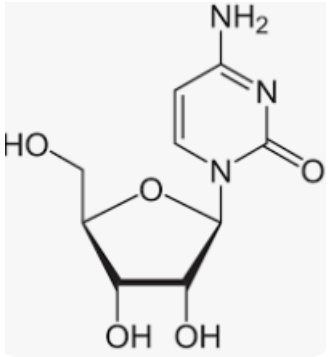
| Drug | Trial Name (Pt N) | Indication | Comparative Protocol | Comparative ORR | PFS (months) | OS (months) | Adverse Events | Source |
|---|---|---|---|---|---|---|---|---|
| **Azacitidine** (Vidaza) | CALGB 9221 (191 pts) | MDS | 75 mg/m(2)/d sc for 7 days q 28 days vs BSC | 60% vs 5% P <.001 | Median time to leukemic transformation or death 21 vs 13 months P=0.007) | 18 vs 11 months | Neutropenia, thrombocytopenia, febrile infections | J Clin Oncol. 2002 May 15;20(10):2429-40 |
| **Decitabine** (Dacogen) | DACO-016 (485 pts) | AML poor- or intermediate-risk cytogenetics. | decitabine 20 mg/m2 IV 1-hour 5 days/ 4 wks vs cytarabine 20 mg/m2 qd 10 days/ 4 wks). | 17.8% vs 7.8% ( P = .001). | 7.7 months | 7.7 vs 5.0 months; P = .108 | Neutropenia, pneumonia, fatigue | J Clin Oncol. 2012 Jul 20; 30(21): 2670–2677 |

BSC : best supportive care, MDS : Myelodysplastic Syndromes, AML : Acute Myeloid Leukemia, CMML : Chronic Myelomonocytic Leukemia

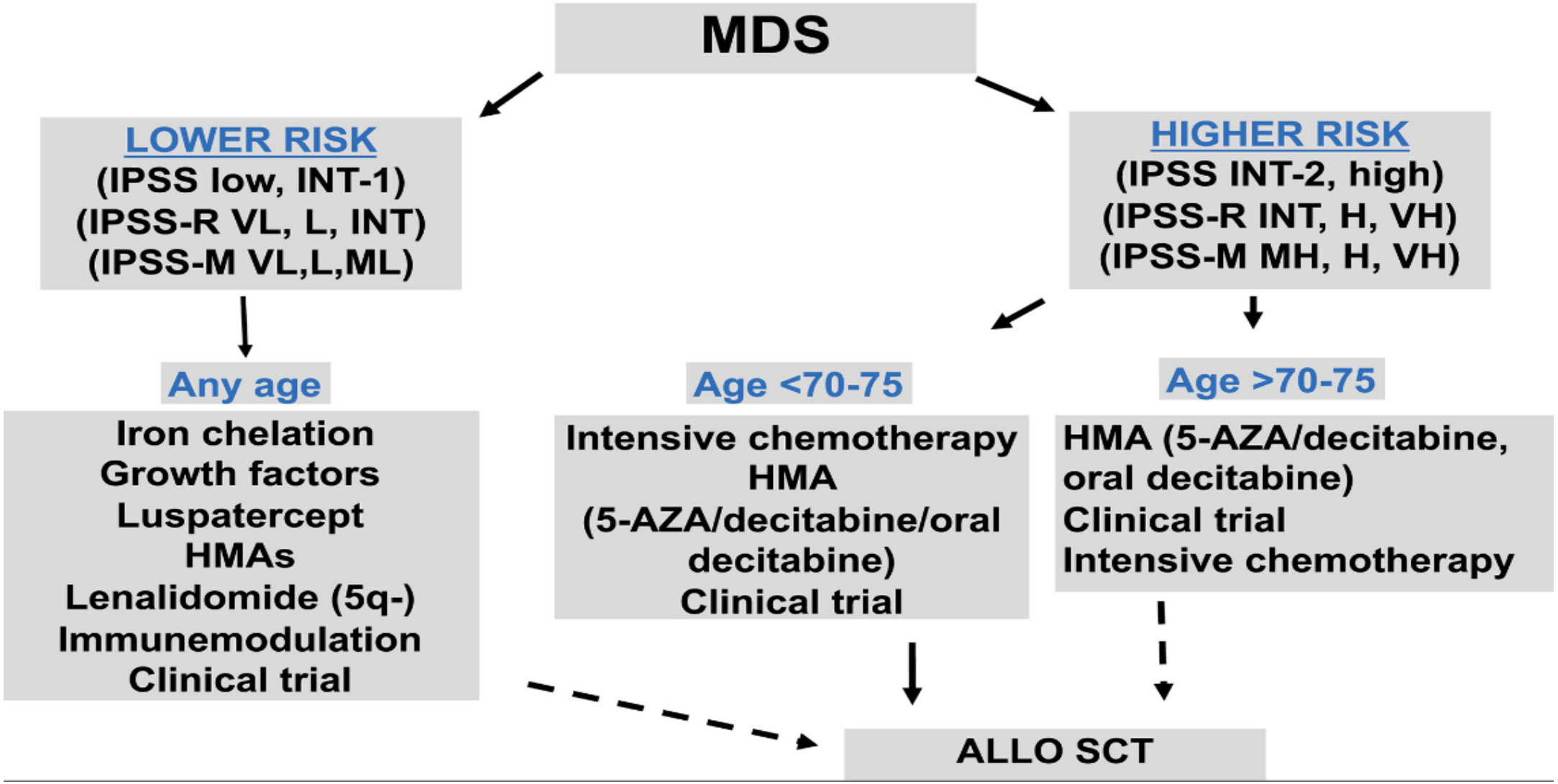
# Azacitidine for Low-/Intermediate-1 – Risk MDS

- Pyrimidine nucleoside analogue of cytidine
- Approved for use in MDS of the following subtypes
  - Refractory anemia or refractory anemia with ringed sideroblasts
    (if accompanied by neutropenia or thrombocytopenia or requiring transfusions)
  - Refractory anemia with excess blasts
  - Refractory anemia with excess blasts in transformation
  - Chronic myelomonocytic leukemia
- Causes hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow



# Proposed treatment algorithm for patients with MDS 2023






Am J Hematol.2023;98:1307–1325.

# Decitabine vs. Azacitidine in AML

| Aspect | Azacitidine | Decitabine |
|---|---|---|
| **Mechanism** | DNA + RNA incorporation | DNA incorporation only |
| **Dosing** | 75 mg/m² SC/IV daily x 7 days | 20 mg/m² IV daily x 5 or 10 days |
| **Preferred for** | MDS-AML overlap; less proliferative AML | AML with higher blast count |
| **Response rate (CR/CRi)** | ~20–30% alone<br>65–70% with venetoclax | 25–35% alone<br>60–70% with venetoclax |
| **Time to response** | Often after 3–4 cycles | Slightly faster (~2 cycles) |
| **Survival benefit** | AZA-AML-001 trial showed OS benefit trend in older AML | No OS benefit vs. supportive care (DACO-016), but useful in real-world |
| **Mutation coverage** | Also active in TP53-mutant but variable | May be more effective in TP53-mutated AML (some data) |

Blood. 2015;126(3):291–299. J Clin Oncol. 2012;30(21):2670–2677. N Engl J Med. 2020;383:617–629.

# Comparison: Azacitidine vs. Decitabine for Clinical Applications

| Category | Azacitidine (Vidaza) | Decitabine (Dacogen) |
|---|---|---|
| **Class** | Hypomethylating agent (HMA) | Hypomethylating agent (HMA) |
| **FDA-Approved Indications** | - MDS (all subtypes)<br>- AML (in adults ≥65 years unfit for intensive chemo) | - MDS<br>- AML (in adults ≥65 years unfit for intensive chemo) |
| **Dosing Schedule** | 75 mg/m² SC or IV daily x 7 days q28 days | 20 mg/m² IV daily x 5 days q28 days |
| **Administration** | Subcutaneous or IV | IV only |
| **Clinical Efficacy** | - AZA-001 trial showed improved OS in higher-risk MDS (24.5 vs. 15 months vs. conventional care).<br>- Response rate ~30–40%.<br>- Shown to delay transformation to AML. | - DACO-016 trial showed similar ORR in older AML patients but no significant OS benefit over supportive care.<br>- Response rate ~25–30%.<br>- More commonly used in AML. |
| **Use in AML** | Effective in elderly/unfit AML patients, especially in combination with **venetoclax**. | Often preferred in AML with higher blast burden; synergistic with **venetoclax**. |
| **Use in MDS** | Gold standard for higher-risk MDS. Azacitidine associated with better OS and lower AML transformation rate than decitabine in MDS patient | Also effective, but azacitidine has more robust OS data in MDS. |
| **Toxicity** | Myelosuppression, GI side effects, injection site reactions | Myelosuppression, infections, GI symptoms |
| **Clinical Considerations** | Better OS data in MDS; subcutaneous option convenient for outpatient | Shorter infusion schedule; IV only |

Lancet Oncol. 2009;10(3):223-232. J Clin Oncol. 2012;30(21):2670–2677.. Blood. 2022;140(12):1345–1377. N Engl J Med. 2020;383:617–629.

Crit Rev Oncol Hematol. 2020;147:102889.

# Azacitadine/Decitabine

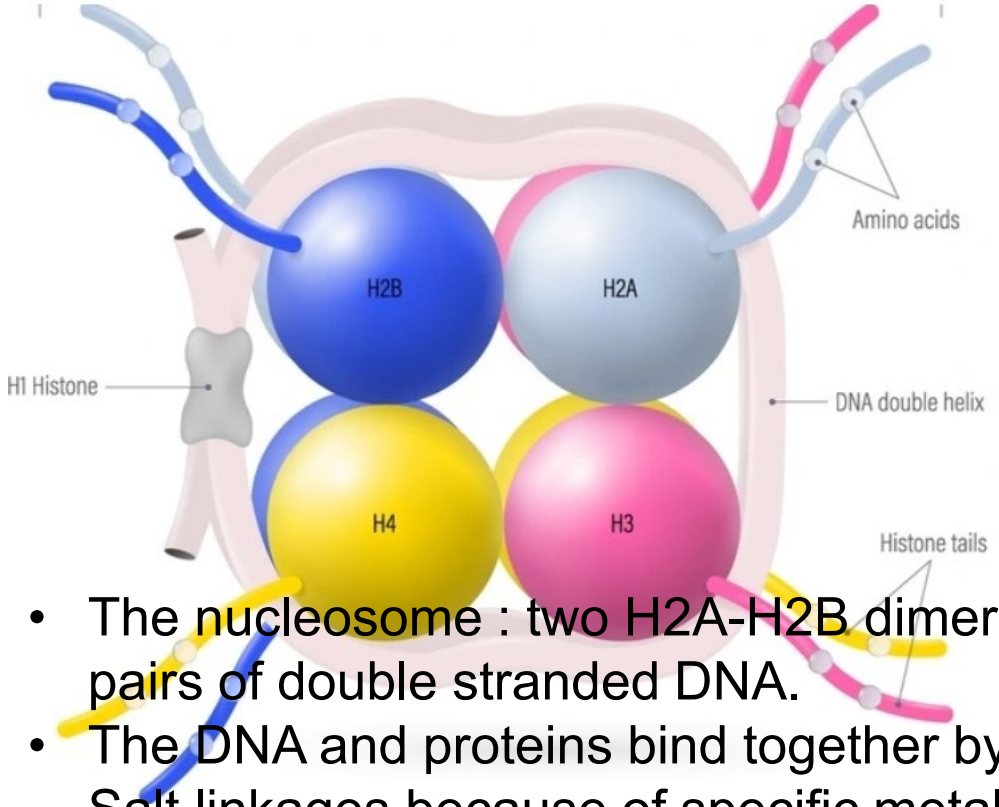
- **Indications:** are approved for higher-risk MDS and AML, ( not candidates for intensive chemotherapy).
- **Regimens:** Azacitidine : 75 mg/m²/day SC for 7 consecutive days in a 28-day cycle. Decitabine is usually given IV at 20 mg/m²/day for 5 consecutive days every 4 weeks.
- **Efficacy:**
  - In higher-risk MDS
    - Azacitidine vs observation ( ORR : 15.7% vs 0%)
    - Decitabine (15 mg/m2 IV Q 8hrs for 3 days)vs supportive ( ORR : 17% vs 0% )
  - In elderly AML patients
    - Azacitidine a median OS 10.4 vs 6.5 months with conventional care
    - Decitabine ( 20 mg/m(2) qd as a 1-hour iv infusion for 5 days ) : a median OS of 7.7 months vs 5.0 months with conventional care.(P=0.108)
- **Adverse Drug Reactions:** neutropenia, thrombocytopenia, anemia, febrile neutropenia, and gastrointestinal disorders. Azacitidine may also cause injection site reactions and constitutional symptoms.
- Both azacitidine and decitabine are effective treatment options for higher-risk MDS and AML, with comparable efficacy and safety profiles. The choice between the two agents may depend on patient-specific factors, administration preferences, and tolerability considerations.

Oncologist. 2005 Mar;10(3):176-8

Cancer . 2006 Apr 15;106(8):1794-803

Blood 2015 Jul 16;126(3):291-9,

# Histone Nucleosome (組織蛋白核小體)



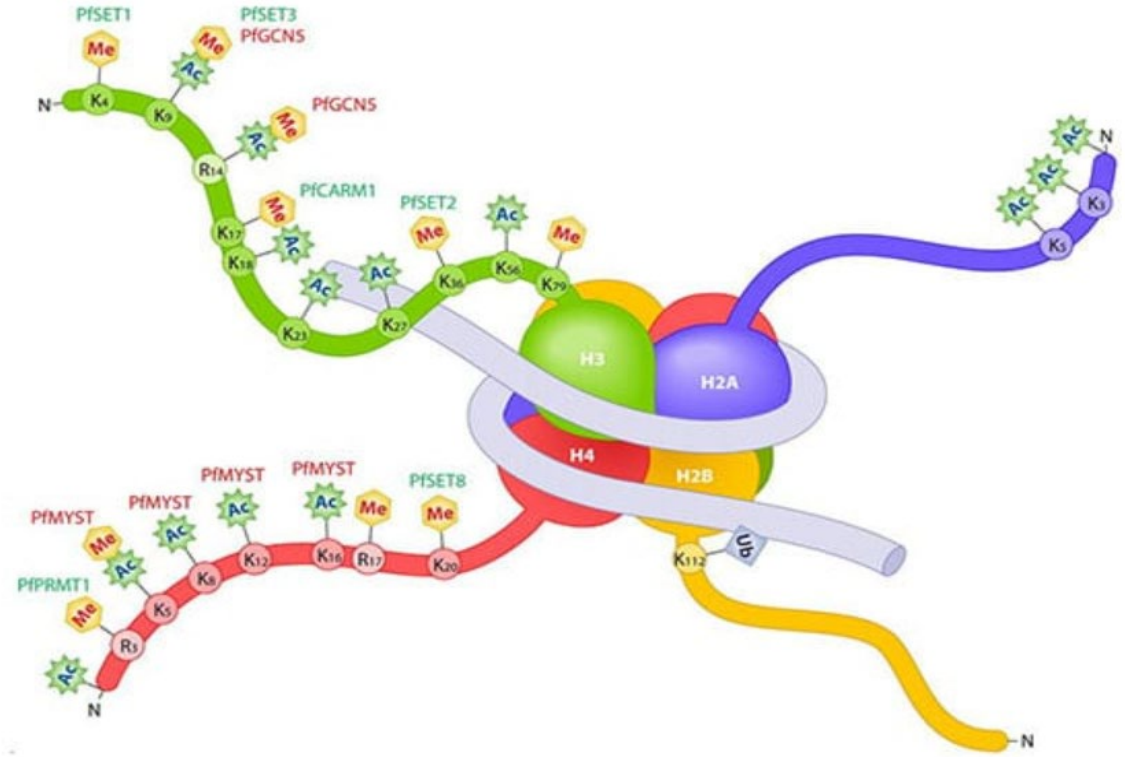



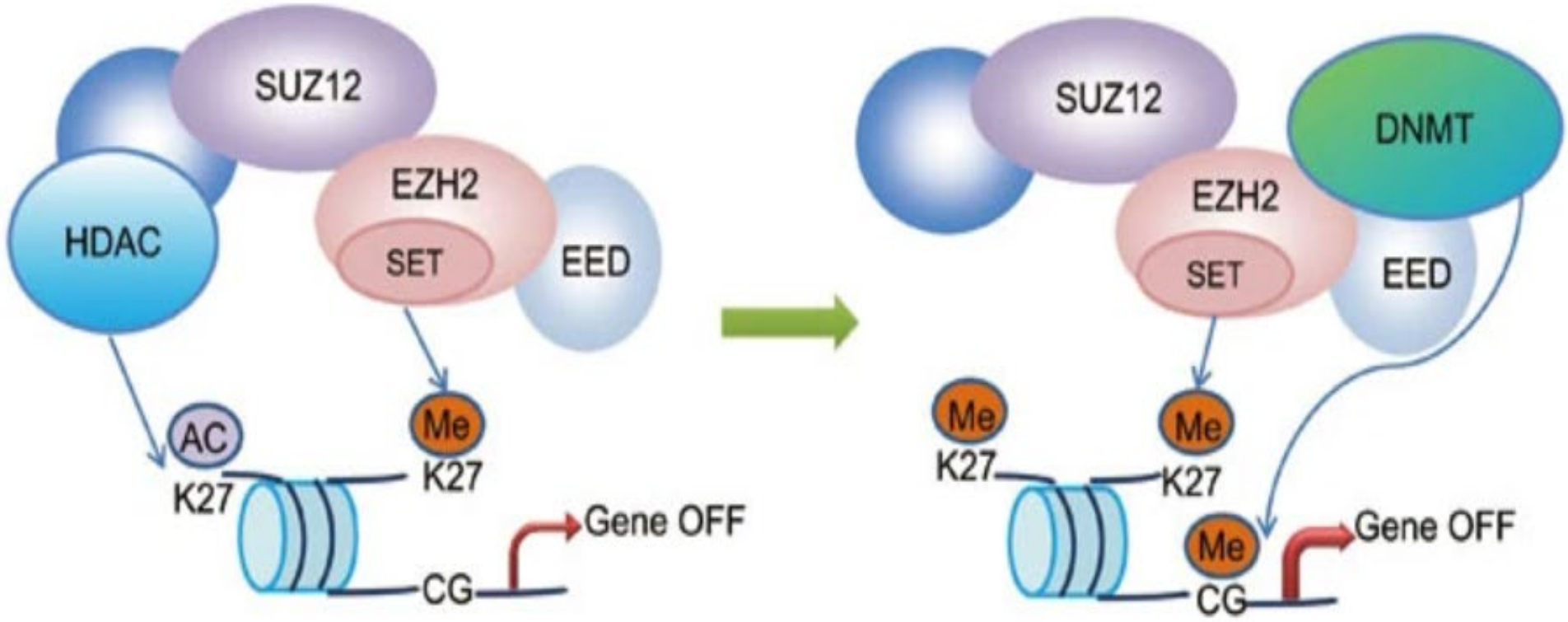

*Fig. 1. Structure of a nucleosome.*

- The nucleosome : two H2A-H2B dimers and H3-H4 tetramers) are wrapped by a stretch of 147 base pairs of double stranded DNA.
- The DNA and proteins bind together by Salt linkages (unstable ionic nature bonding). They are called Salt linkages because of specific metallic ions for example Ca++ and Mg++.
- Nucleosomes bind with the other Nucleosomes with the linker DNA ( 8 to 147 base pairs).
- Histone proteins have tails known as N-terminal tails. These tails are made up of specific amino acids and undergo various translational modifications preferably Acetylation, Phosphorylation, and Methylation with the help of these terminal tails.

# EZH2 inhibitors : target the protein Enhancer of Zeste Homolog 2 (EZH2). EZH2 is a histone methyltransferase.

- EZH2 mutations and overexpression in cancer, leading to aberrant histone methylation and silencing of tumor suppressor genes.
- Early Discoveries (2000s - 2010s)
  - The Polycomb Repressive Complex 2 (PRC2), including EZH2, was found to catalyze histone H3 lysine 27 trimethylation (H3K27me3), leading to chromatin silencing and cancer progression.
  - Somatic EZH2 gain-of-function mutations were discovered : germinal center B-cell (GCB) lymphomas, particularly follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL).
  - EZH2 overexpression: in solid tumors like prostate, breast, and ovarian cancers.
- Proof of Concept: The idea of targeting epigenetic regulators for cancer therapy gained traction.
- Selective EZH2 Inhibitors (2011-2015)
  - Tazemetostat (EPZ-6438): it selectively inhibited mutant and wild-type EZH2, leading to apoptosis in lymphoma cells.
  - Tazemetostat (Tazverik) approved for: Epithelioid sarcoma ( 2020, accelerated approval). Relapsed/refractory follicular lymphoma (FL) with EZH2 mutations (June 2020).
  - Valemetostat (DS-3201):A dual EZH1/EZH2 inhibitor was approved in Japan for adult T-cell leukemia/lymphoma (ATLL).

# A model for the collaboration of epigenetic silencing enzymes




PRC2 複合體的核心、DNA 甲基轉移酶（DNMT）和組蛋白去乙酰化酶（HDAC）。在這個模型中，如果 K27 已經被乙酰化，HDAC 可能會首先去乙酰化它，然後通過 PRC2 對 K27 的甲基化使目標基因沉默。DNMT 也可能被 PRC2 招募，在對目標基因的 CpG DNA 進行甲基化後，使染色質狀態更加深度沉默。Ac，乙酰化；Me，甲基化。

| drug Name | Trial Name/Number | Study Patient Number | Indication | Type of study | ORR | PFS | Overall Survival | ADR | Source of Journal |
|---|---|---|---|---|---|---|---|---|---|
| Tazemetostat 800 mg bid po | Study E7438-G000-101 (NCT01897571) | 99 | Relapsed or refractory follicular lymphoma (FL) with or without EZH2 mutations | Single-arm, open-label study | 69% in EZH2-mutant FL; 35% in EZH2 wild-type FL | Median PFS: 13.8 months (EZH2-mutant); 11.1 months (EZH2 wild-type) | Data not mature for overall survival | fatigue, nausea, decreased appetite, and diarrhea. Serious ADR: 37% of patients. | The Lancet Oncology, Volume 21, Issue 11, 1433 - 1442 |
| Tazemetostat 800 mg bid po | | 92( 55 died) vs 181 (104 died)(Real-World External Control Arm, ECA) | Comparison of PFS of Relapsed or Refractory Follicular Lymphoma | a Single-Arm Trial of Tazemetostvs a vs Real-World ECA third line or higher (3L+) treatments | | median PFS was 12.2 months hazard ratio : 1.31 | | | Blood (2024) 144 (Supplement 1): 6347. |

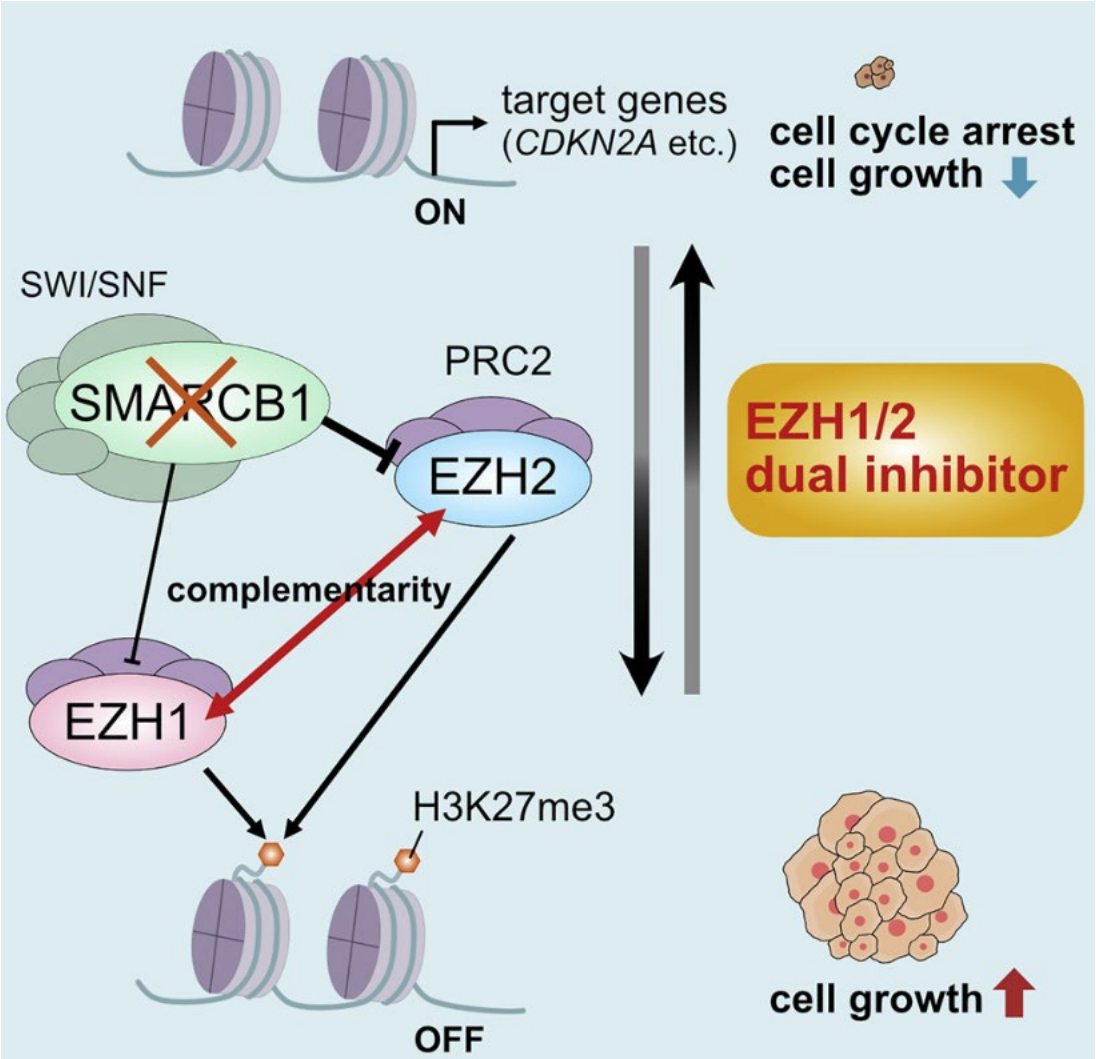
PFS was numerically longer but not significantly different between tazemetostat monotherapy and real-world physician's choice of treatment

ECA : CD20-monotherapy, bendamustine-containing regimens, and lenalidomide plus CD20.

Epithelioid sarcoma is a rare and aggressive soft-tissue sarcoma subtype. Over 90% of tumors have lost INI1 expression, leading to oncogenic dependence on the transcriptional repressor EZH2.

| Study Name | Patient Number | Indication | Comparative Protocol | Comparative ORR | Comparative PFS | Comparative Overall Survival | Adverse Events | Source |
|---|---|---|---|---|---|---|---|---|
| Study EZH-202 (Cohort 5) | 62 ( loss of INI1 expression by immunohistochemical analysis or biallelic SMARCB1 (the gene that encodes INI1) alterations | Metastatic or locally advanced epithelioid sarcoma not eligible for complete resection | Single-arm, open-label, 800 mg of Tazemetostat at 800 mg bid until disease progression or unacceptable toxicity | 26%had disease control at 32 weeks; 1.6% complete response, 13% partial response | Median PFS: 5.5 months (95% CI: 3.4–5.9) ( At a median follow-up of 13·8 months) | Median OS: 19 months (95% CI: 11–not estimable) | Most common (≥20%): pain, fatigue, nausea, decreased appetite, vomiting, constipation; Grade ≥3 ADR 48% anemia (13%), pain (7%), decreased weight (7%) | The Lancet Oncology,2020 Volume 21, Issue 11, 1423 - 1432 |

# EZH1/EZH2 Dual Inhibition




Molecular Therapy - Oncolytics, Volume 27, 14 - 25

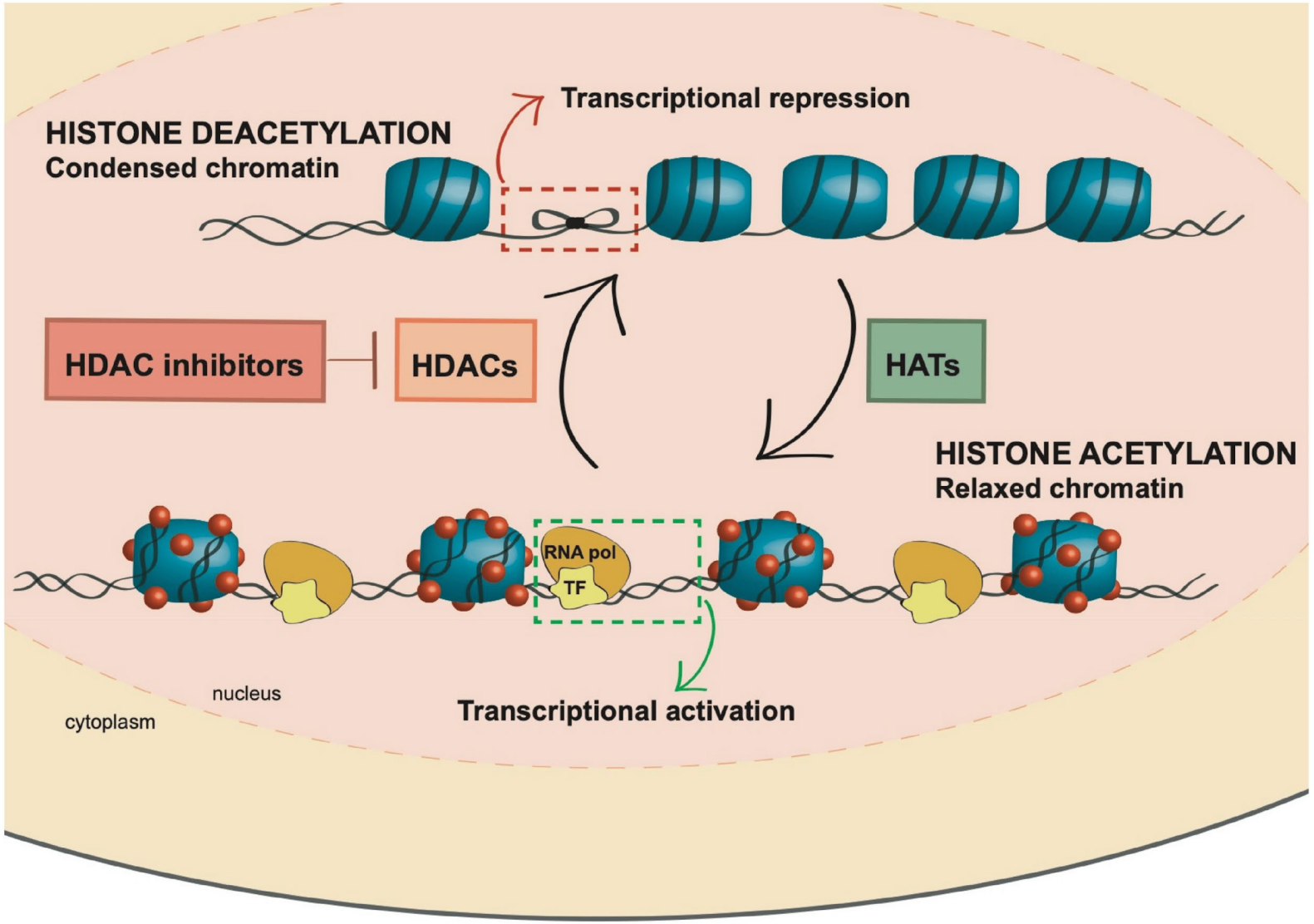
Cancer Sci
. 2017 Oct;108(10):2069-2078.

| Benefit | Mechanism | Clinical Relevance |
|---|---|---|
| **Prevents PRC2 Redundancy** | EZH1 compensates for EZH2 loss, leading to continued tumor survival when only EZH2 is inhibited | **Dual inhibition ensures stronger suppression of PRC2 activity**, leading to **more effective tumor suppression** |
| **More Effective in Hematologic Malignancies** | EZH1 is highly active in hematologic cancers (e.g., T-cell lymphomas, acute leukemia) | **Stronger anti-tumor effect** compared to EZH2-selective inhibitors |
| **Prevents Resistance to EZH2 Inhibition** | Tumors develop resistance by upregulating EZH1 when EZH2 is blocked | **Dual inhibition reduces resistance**, leading to **longer-lasting responses** |
| **Induces Stronger Apoptosis** | EZH1/2 dual inhibition causes stronger reactivation of tumor suppressor genes | **Greater anti-cancer effects in EZH2-mutated tumors** (e.g., follicular lymphoma, DLBCL) |
| **Potential Use in Solid Tumors** | EZH1 plays a role in stem-like tumor cell survival in **prostate, ovarian, and breast cancers** | Expands **therapeutic potential** beyond blood cancers |

# Summary : In clinical practice

- **Limited Efficacy Compared to Other Treatments**
  - While tazemetostat showed **moderate response rates**, particularly in **EZH2-mutant follicular lymphoma (FL)** (ORR ~69%), its effectiveness in **wild-type EZH2** patients was significantly lower (~35%).
  - **Diffuse large B-cell lymphoma (DLBCL)**, EZH2 inhibition alone has **not produced durable responses**, limiting its role in frontline therapy.
  - EZH inhibitors were approved **without a comparative RCT** (based on **single-arm phase II studies**)
- **Lack of a Predictive Biomarker Beyond EZH2 Mutation**
  - EZH2 mutations **in 15-20%** of **follicular lymphoma (FL)**
  - **No reliable biomarkers** to predict response in **wild-type EZH2** patients
- **Slow Approval in Other Indications**
  - Tazemetostat has **not yet gained FDA approval** for **solid tumors** like **sarcomas, prostate cancer, or ovarian cancer**, where preclinical data was promising.
- Other EZH inhibitors have failed in late-stage trials.
- **Competition From More Established Therapies/ more robust clinical data and a stronger survival benefit**
  - In **follicular lymphoma**, alternative targeted therapies such as:
    - **BTK inhibitors (e.g., zanubrutinib, acalabrutinib), BCL2 inhibitors (venetoclax), PI3K inhibitors (duvelisib, idelalisib)**
- **Potential Safety Concerns**
  - **relatively well tolerated**, long-term concerns about **secondary malignancies** due to epigenetic modifications are still being studied.
- Combination approaches :  are under investigation but could introduce new safety risks.

# HDAC inhibitor (HDACi) effect on chromatin remodeling



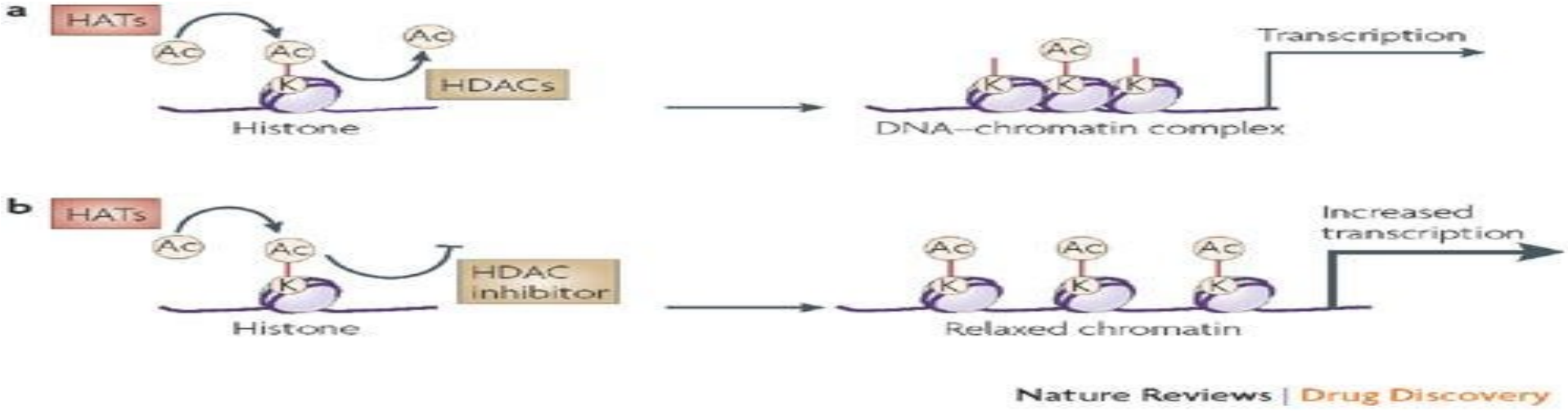

Histone deacetylases (HDACs) and histone acetyltransferases (HATs) are responsible for the balance of histone acetylation, and thereby regulate gene expression. Whereas HDACs deacetylate histones, promoting transcription repression, HATs are responsible for acetylating histones and inducing transcriptional activation. HDACi inhibits HDACs, and thus maintain an open chromatin conformation.

# Developmental history

- 1980s–1990s: Early Discoveries and Preclinical Development Role of Histone Acetylation
- Focus on Cancer: Studies in the 1990s confirmed that HDAC inhibitors could re-activate tumor suppressor genes, suggesting their use as anti-cancer agents
  - Valproic acid is studied in cancer as a low-potency HDAC inhibitor.
- 2000s: First Generation HDAC Inhibitors
  - Vorinostat (2006) : cutaneous T-cell lymphoma (CTCL).
  - Romidepsin (2009): CTCL , relapsed/refractory peripheral T-cell lymphoma (PTCL) Withdrawal: In 2021.
- 2010s: Expansion of Indications and Combination
  - Belinostat (2014): PTCL. Combining belinostat with chemotherapy : angioimmunoblastic T-cell lymphoma (AITL)
  - Panobinostat (2015): Approved for relapsed/refractory multiple myeloma, (combining with bortezomib and dexamethasone )
- Killed by brentuximab vedotin for peripheral T-cell lymphoma (PTCL)

Romidepsin was named based on its natural product origin and structure (a depsipeptide)

# HDAC (histone deacetylases ) inhibitors




- In tumors, HDACs : in favor of deacetylation and tightening of histones, leading to epigenetic silencing. DNA methylation and histone deacetylation work in concert in gene silencing because of direct binding interactions between DNMTs and HDACs.
- HDACIs are able to induce cell cycle arrest, promote differentiation, and hyperacetylate
- Vorinostat : advanced cutaneous T-cell lymphoma (CTCL) as a third-line therapy
- Belinostat : peripheral T-cell lymphoma

# FARYDAK® (panobinostat) capsules may help turn on tumor suppression in multiple myeloma

**HDAC overexpression in myeloma cells**

- ☒ Tumor suppressor gene expression
- ☒ Apoptosis

**HDAC inhibition with FARYDAK® in some myeloma cells**

- ☑ Tumor suppressor gene expression
- ☑ Apoptosis

**Histone deacetylase (HDAC) overexpression, detected across multiple myeloma cell lines, promotes a closed chromatin structure, which may reduce expression of tumor suppressor genes and increase myeloma cell growth and proliferation in vitro** [3-7]

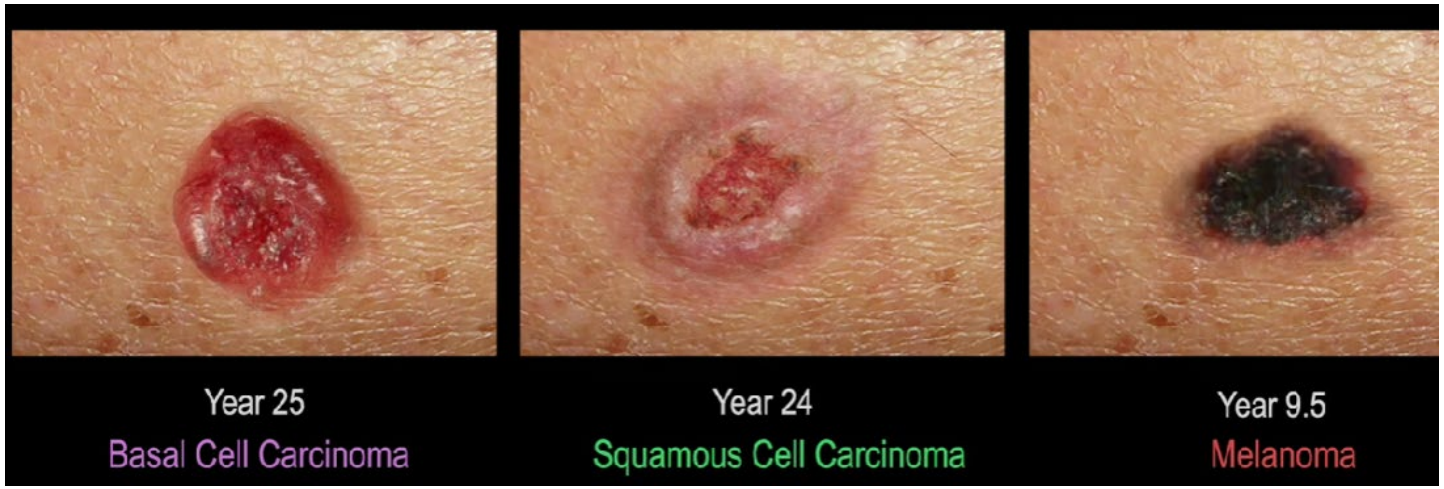
**FARYDAK, an HDAC inhibitor, may promote an open chromatin structure, increasing gene expression in vitro, including tumor suppressor genes that induce cell cycle arrest and/or apoptosis of some transformed cells** [1,3-7]

| | Romidepsin<br>Pts: 421 | Brentuximab Vedotin<br>ECHELON-2 CD 30 |
|---|---|---|
| **Indication** | Ro-CHOP Phase III Study Previously Untreated Peripheral T-Cell Lymphoma (PTCL) | phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma |
| **Comparative Regimens** | Ro-CHOP Versus CHOP | A+CHP vs CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) 6-8 cycles |
| **Overall Response Rate (ORR)** | 63% vs 60% | 59% vs 50% |
| **Median Progression-Free Survival (PFS)** | 12.0 months vs 10.2 months ( P = .096) | 5-year PFS rates were 51.4% vs 43.0% ( CHOP) (hazard ratio = 0.70), |
| **Overall Survival (OS)** | 51.8 vs 42.9 months | 5-year OS : 70.1% ( A+CHP) vs 61.0% |
| **Adverse Reactions** | thrombocytopenia (50% vs 10% ), neutropenia (49% v 33%), anemia (47% v 17%), and leukopenia (32% v 20%) | Peripheral neuropathy was resolved or improved in 72% of patients in the A+CHP arm and 78% in the CHOP arm. |
| **Source** | J Clin Oncol. 2022 Jan 20;40(3):242-251 (voluntarily withdrew the PTCL indication from the U.S. market in 2021,) | Ann Oncol . 2022 Mar;33(3):288-298. |

| Drug Name | Trial Name (Patients) | Indication | Comparative Protocol | ORR | PFS | OS | Adverse Reactions | Source |
|---|---|---|---|---|---|---|---|---|
| **Vorinostat 400 mg qd** | Olsen et al. (74) | persistent, progressive, or recurrent T-Cell Lymphoma (CTCL) | Monotherapy | 29.7% | Median: 4.9 months | | Fatigue, diarrhea, nausea, thrombocytopenia | J Clin Oncol . 2007 Jul 20;25(21):3109-15 |
| **Belinostat** 1,000 mg/m(2) iv 30-minute infusions on 1 to 5 every 21 days. | BELIEF Trial (129) | Relapsed/Refractory PTCL | Monotherapy | 26% | Median: 1.6 months | Median OS : 7.9 months | Cytopenia, dyspnea, fatigue | J Clin Oncol . 2015 Aug 10;33(23):2492-9. |
| **Panobinostat** 20 mg starting dose once every other day for 3 doses each week | PANORAMA-1 (768) | R/R multiple myeloma with one to three previous treatments. | ±Panobinostat with Bortezomib/Dexamethasone | 59.6% | 11 months (vs 6 months) | 40.3 months vs 35.8 2 previous regimens ( bortezomib and an immunomodulatory drug, m OS 25·5 vs 19·5 months | Diarrhea, fatigue, nausea, peripheral edema | Lancet Haematol . 2016 Nov;3(11):e506-e515 |

# Hedgehog Pathway Inhibitors

- 刺蝟 （Hh） 基因於 1970 年代由研究胚胎發育的研究人員首次在黑腹果蠅中發現。
- 1996年，在哺乳動物中發現了 Sonic Hedgehog （Shh） 信號通路，揭示了它在細胞分化和胚胎模式中的作用。
- 異常的 Hedgehog 信號與基底細胞癌 （BCC） 和髓母細胞瘤(Medulloblastoma)有關



# Discovery of the Hedgehog Pathway

- Mutations in PTCH1 (a negative regulator of the Hh pathway) were found to drive uncontrolled cell growth in BCC.
- The Hh pathway is tightly regulated by two transmembrane proteins, patched (PTCH), which is a negative regulator, and smoothened (SMO), a positive regulator
- Drug discovery efforts targeted Smoothened (SMO), a key activator of the Hh pathway, leading to the first generation of inhibitors.
- First-Generation Hedgehog Pathway Inhibitors (2006-2012) : Vismodegib (Erivedge®) in 2012 for advanced basal cell carcinoma (BCC).
- Sonidegib (Odomzo®) : locally advanced BCC (2015)
- Glasdegib (Daurismo®) : AML combined with low-dose cytarabine. aged ≥ 75 years or with comorbidities precluding intensive induction chemotherapy.

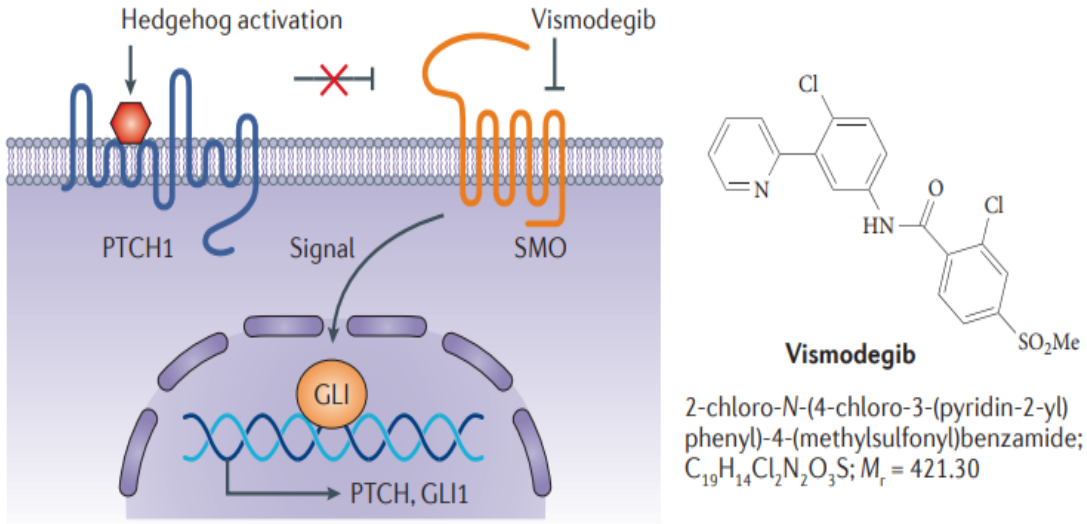


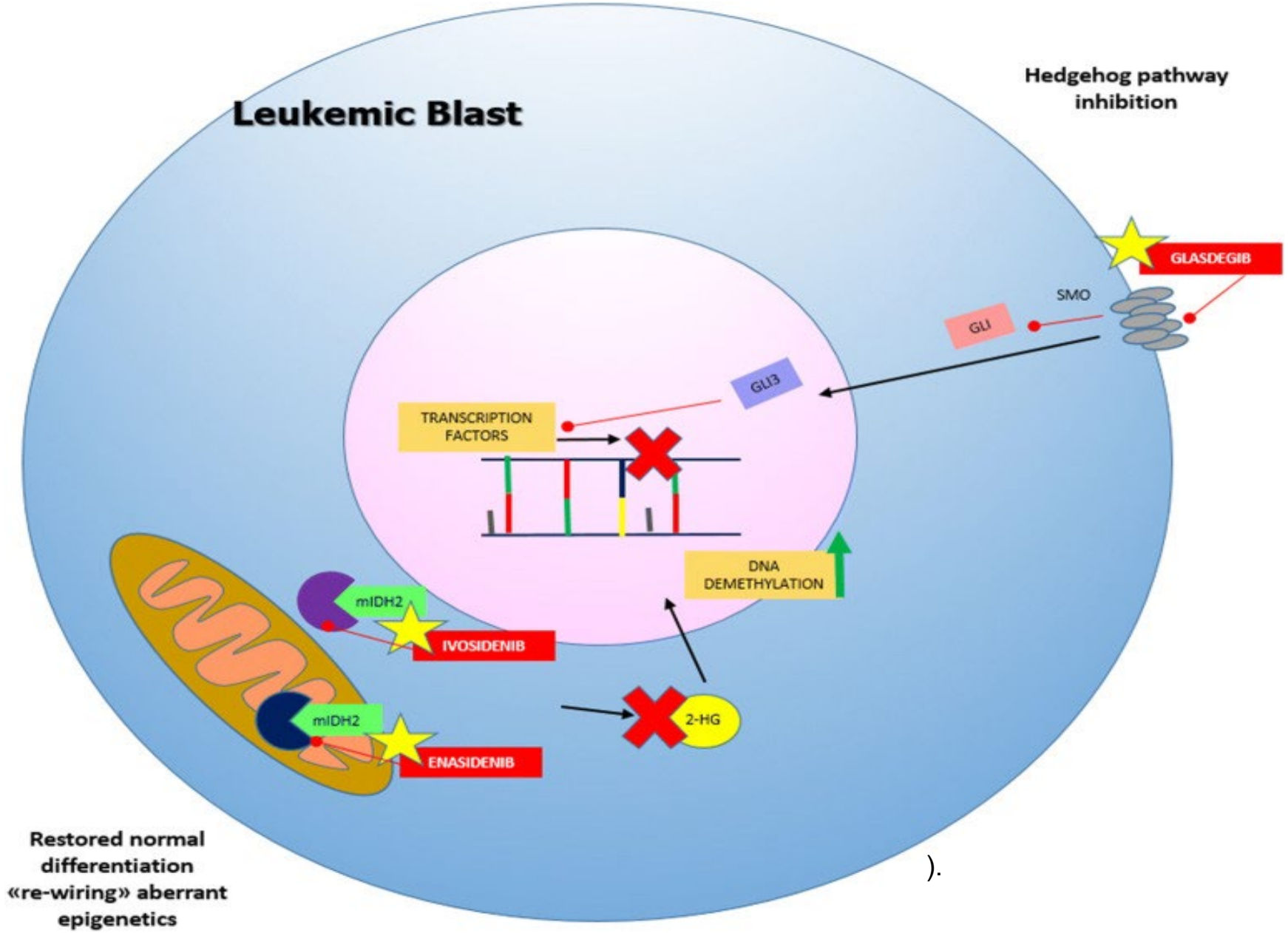

Figure 1 | **Hedgehog signalling pathway and vismodegib. a** | Binding of a Hedgehog ligand to the 12-transmembrane receptor Patched homologue 1 (PTCH1) prevents PTCH1-mediated inhibition of signalling by the seven-transmembrane protein Smoothened homologue (SMO), leading to activation of the GLI family of transcription factors and the regulation of target genes[2,5]. Vismodegib inhibits this pathway by binding to SMO. **b** | Structure of vismodegib, which was discovered through optimization of a class of 2-pyridyl amides[3].

Nat Rev Drug Discov 11, 437–438 (2012

# Acute myeloid leukemia (AML)

a complex disease characterized by genetic and clinical heterogeneity and high mortality

- Traditional chemotherapy : 3+7
- FLT3 inhibitors midostaurin and gilteritinib
- CPX-351 (liposomal cytarabine and daunorubicin)
- Gemtuzumab ozogamicin (GO, anti-CD33 monoclonal antibody conjugated with calicheamicin)
- IDH1/IDH2 inhibitors ivosidenib and enasidenib
- Hedgehog inhibitor Glasdegib
- BCL-2 inhibitor venetoclax.

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Leukemia . 2019 Feb;33(2):379-389

| Drug | Trial Name | Study Patient Number | Indication | Comparative Protocol | Comparative ORR | Comparative PFS | Comparative OS | Adverse Events | Source |
|---|---|---|---|---|---|---|---|---|---|
| Vismodegib | ERIVANCE | 104 | Metastatic and locally advanced basal cell carcinoma | Single-arm study | mBCC: 30.3%<br>laBCC: 42.9% | mBCC: 9.5 months<br>laBCC: 12.9 months | Not reached | Muscle spasms (68%), alopecia (63%), dysgeusia (51%), weight loss (46%), fatigue (36%) | NEJM 2012;366(23):2171-2179. |
| Sonidegib | BOLT | 230 | Locally advanced and metastatic basal cell carcinoma | Randomized (200 mg vs. 800 mg) | laBCC: 44% (200 mg), 38% (800 mg)<br>mBCC: 15% (200 mg), 17% (800 mg) | laBCC: 22.1 months (200 mg) | Not reached | Muscle spasms (54%), alopecia (49%), dysgeusia (44%), nausea (38%), fatigue (35%) | Lancet Oncol. 2015;16(6):716-728. |
| Glasdegib | BRIGHT 1003 | 115 | Newly diagnosed acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome | Randomized (LDAC ± glasdegib) | 17% (glasdegib + LDAC) vs. 2.3% (LDAC alone) | 4.9 months (glasdegib + LDAC) vs. 2.3 months (LDAC alone) | 8.8 months (glasdegib + LDAC) vs. 4.9 months (LDAC alone) | Anemia (43%), fatigue (36%), hemorrhage (29%), febrile neutropenia (27%), thrombocytopenia (27%) | Leukemia. 2019;33(2):379-389. |

*Note: mBCC = metastatic basal cell carcinoma; laBCC = locally advanced basal cell carcinoma; LDAC = low-dose cytarabine.*
These studies highlight the efficacy and safety profiles of Hedgehog pathway inhibitors across different cancer types.

# Comparison of Vismodegib and Sonidegib in Clinical Practice

| Feature | Vismodegib (Erivedge®) | Sonidegib (Odomzo®) |
|---|---|---|
| **FDA Approval** | 2012 | 2015 |
| **Indication** | Advanced **Basal Cell Carcinoma (BCC)** (metastatic or locally advanced) | **Locally Advanced BCC** in patients not candidates for surgery/radiotherapy |
| **Trial Data** | **ERIVANCE** (mBCC: 30.3% ORR, laBCC: 42.9% ORR) | **BOLT** (laBCC ORR: 44% with 200 mg dose) |
| **Dosing** | **150 mg orally once daily** | **200 mg orally once daily** |
| **Half-Life** | ~4 days | ~28 days (longer duration) |
| **Metabolism** | Primarily **CYP3A4**, also involves CYP2C9 | Mainly **CYP3A4** |
| **Common Adverse Effects** | Muscle spasms (68%), alopecia (63%), dysgeusia (51%), weight loss (46%) | Muscle spasms (54%), alopecia (49%), dysgeusia (44%), nausea (38%) |
| **Teratogenicity** | High risk (Boxed warning for embryo-fetal toxicity) | High risk (Boxed warning for embryo-fetal toxicity) |
| **Resistance Concerns** | Resistance mutations in **SMO** reported in some cases | Similar resistance mechanisms, but long half-life may help maintain efficacy |
| **Food Effect** | No significant effect | **Food increases absorption**, recommended **fasting state** |

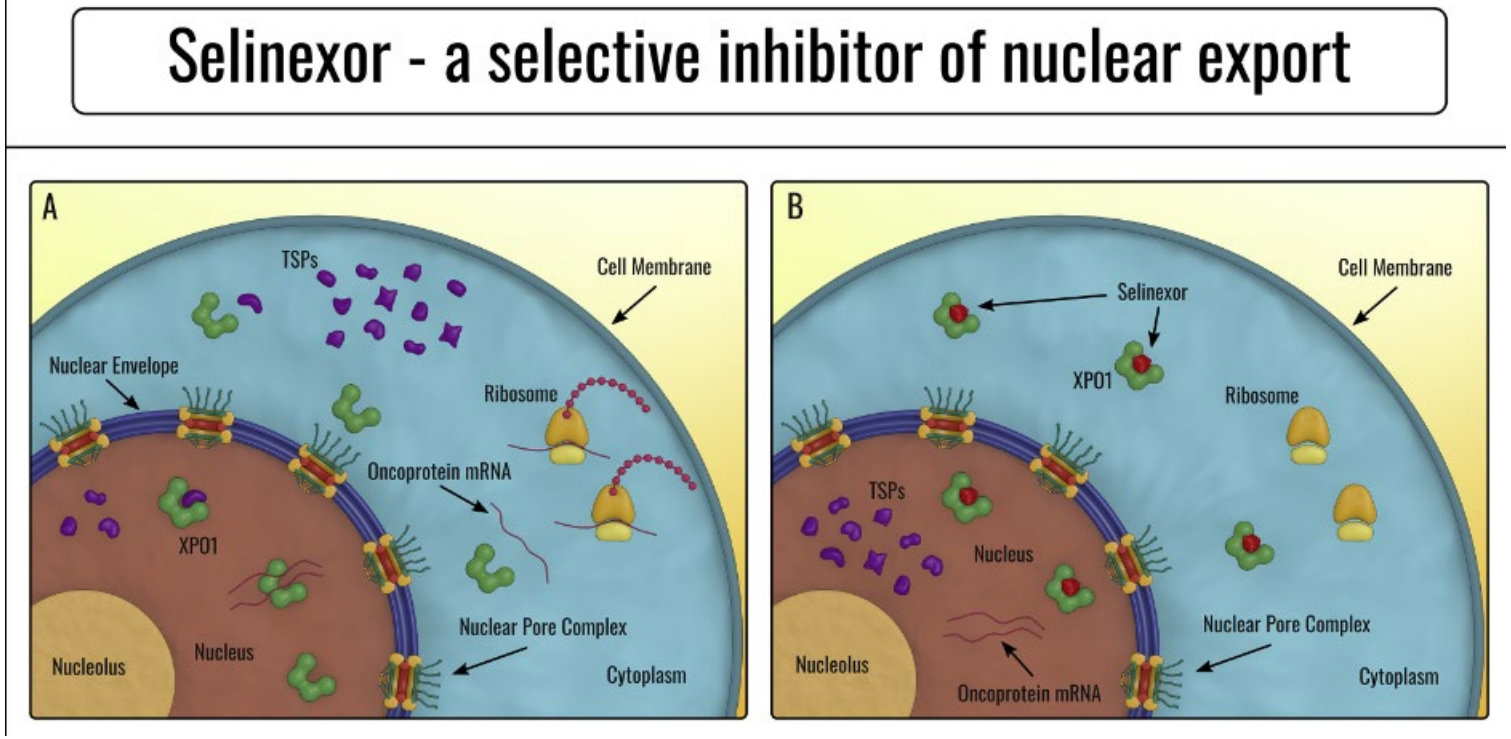
# Conclusion: Hedgehog Pathway Inhibitors in Clinical Practice

- **Key Clinical Roles of Hedgehog Inhibitors**
  - **Vismodegib & Sonidegib**: Effective for **locally advanced and metastatic BCC**, particularly in patients **ineligible for surgery or radiation**.
  - **Glasdegib**: Used in **AML** as part of combination therapy with low-dose cytarabine (LDAC), targeting **leukemic stem cells** to improve chemotherapy outcomes.
- **Mechanistic Differences in Clinical Use**
  - **Vismodegib and Sonidegib target tumor cells** in **solid tumors** (BCC).
  - **Glasdegib targets leukemia stem cells**, disrupting the **tumor microenvironment** in hematologic malignancies (AML).
- **Challenges & Limitations**
  - **Drug Resistance**: Mutations in **SMO (Smoothened)** can lead to **resistance**.
  - **Adverse Effects**: **muscle spasms, alopecia, dysgeusia, and fatigue**
  - **Teratogenicity**: **warning for embryo-fetal toxicity**
- **Clinical Impact Summary**
  - **Hedgehog inhibitors provide targeted therapy options** where conventional treatments are limited.

# XPO1 inhibitor

Selinexor (XPOVIO) : selective inhibitor of nuclear export: Unselective bullet for blood cancers

- **XPO1 (Exportin 1)**, also known as **CRM1(**chromosome maintenance 1 protein (CRM1) **)**, is a nuclear export protein responsible for transporting various tumor suppressor proteins (e.g., p53, p21, Rb) and growth regulatory proteins from the nucleus to the cytoplasm.
- Overexpression of XPO1 is found in many cancers and is associated with poor prognosis.
- By **inhibiting XPO1,** Tumor suppressor proteins are retained in the nucleus, enhancing their ability to induce cell cycle arrest and apoptosis in malignant cells.
- Selinexor (XPOVIO), a selective inhibitor of nuclear export (SINE)
  - R/R multiple myeloma and R/R diffuse large B-cell lymphoma.




Exportin 1 protein (XPO1) regulates nuclear export of key tumor suppressor proteins (p53, p73, FOXO, pRB, BRCA1, and PP2A), growth regulatory and anti-inflammatory proteins as well as oncoprotein mRNAs. Malignant cells that overexpress XPO1 move these molecules out of the cell's nucleus. Therefore, tumor suppressor proteins (TSPs) lose their ability to identify and initiate the death of cancer cells and growth regulatory proteins along with oncoproteins (oncoprotein mRNAs are translated into oncoproteins in cytoplasm) which allow cancer cells to grow uncontrollably.

Blood Reviews 46 (2021) 100758

| Trial Name | Patient Number | Indication | Comparative Protocol | Comparative ORR | Comparative PFS | Comparative OS | Dose and Schedule | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| STORM Part 2 | 122 | Relapsed/Refractory MM (penta-refractory) | Selinexor (80 mg) + Dexamethasone (20 mg) twice weekly | ORR: 26.2% | Median PFS: 3.7 months | Median OS: 8.6 months | Selinexor 80 mg + Dexamethasone 20 mg twice weekly | Nausea, fatigue, decreased appetite, diarrhea, thrombocytopenia, anemia |
| BOSTON | 402 | Relapsed/Refractory MM (≥1 prior therapy) | Selinexor (100 mg) + Bortezomib (1.3 mg/m²) + Dex (20 mg) weekly vs. Bortezomib (1.3 mg/m²) + Dex (20 mg) twice weekly | ORR: 76.4% (SVd) vs. 62.3% (Vd) | Median PFS: 13.9 months (SVd) vs. 9.5 months (Vd) | Median OS: Not reached | Selinexor 100 mg weekly; Bortezomib 1.3 mg/m² weekly; Dex 20 mg twice weekly | Thrombocytopenia, fatigue, nausea, anemia, diarrhea |
| STOMP SPd Arm | 48 (28 in SPd-40; 20 in SPd-60) | Relapsed/Refractory MM (≥2 prior therapies) | Selinexor (40 mg or 60 mg) + Pomalidomide (4 mg) + Dex (40 mg) weekly | ORR: 50% (SPd-40) vs. 65% (SPd-60) | Median PFS: 18.4 months (SPd-40) vs. 9.5 months (SPd-60) | 24-month OS: 64.2% (SPd-40) vs. 51.1% (SPd-60) | SPd-40: Selinexor 40 mg weekly; SPd-60: Selinexor 60 mg weekly; Pomalidomide 4 mg daily (days 1-21); Dex 40 mg weekly | Neutropenia, anemia, thrombocytopenia, fatigue, nausea, diarrhea |

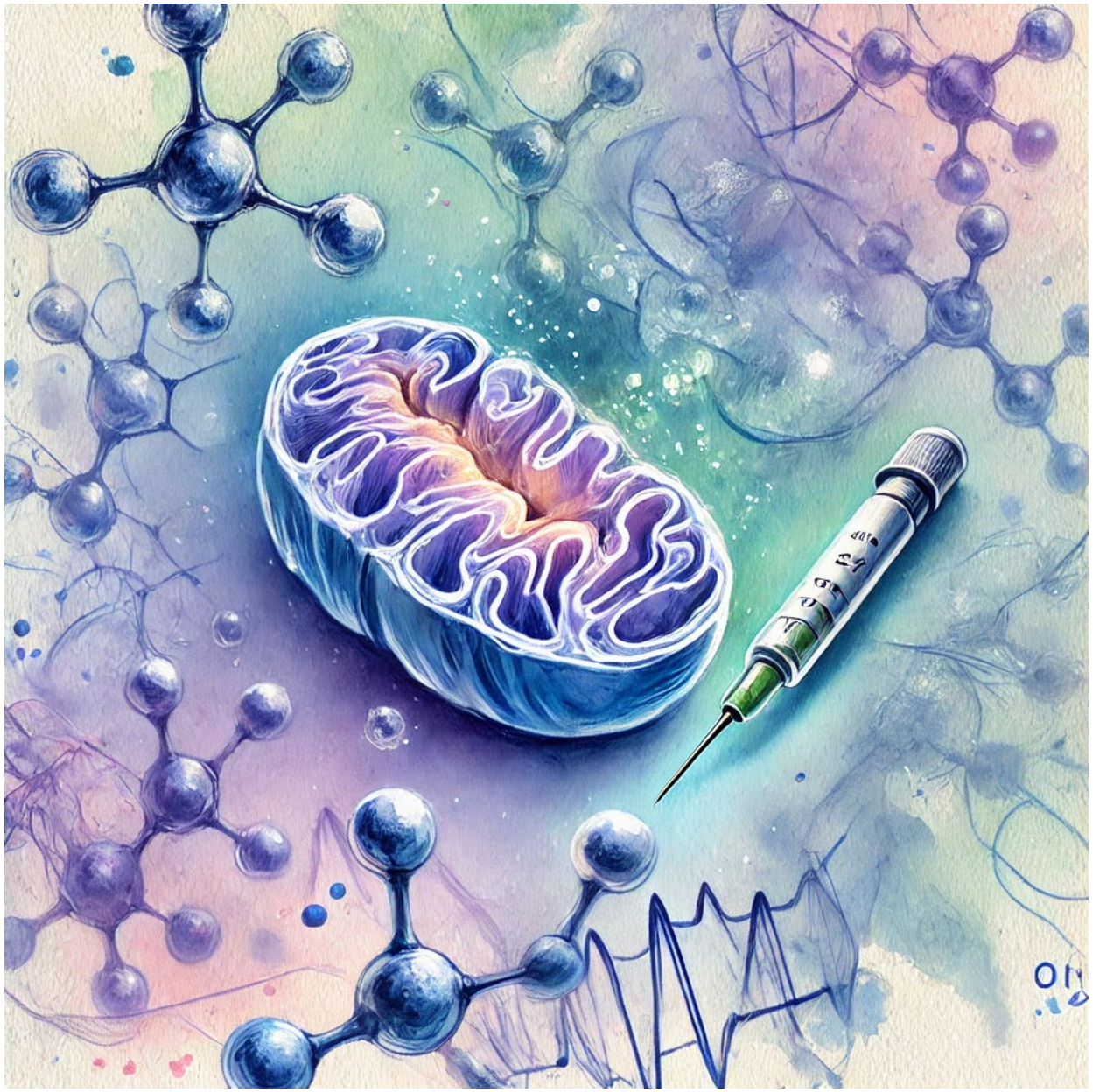
# Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial

| Trial Name | Pt Number | Indication | Dose schedule | ORR | PFS | OS | Adverse Events |
|---|---|---|---|---|---|---|---|
| SADAL | 127 | Relapsed/Refractory Diffuse Large B-Cell Lymphoma (R/R DLBCL) | Selinexor 60 mg orally on days 1 and 3 weekly | ORR: 28%<br>CR :17% | Median PFS: 2.6 months | Median OS: 9.1 months | Thrombocytopenia (56%), neutropenia (25%), anemia (23%), fatigue (11%), hyponatremia (8%), nausea (6%) |

Lancet Haematol. 2020 Jul;7(7):e511-e522.

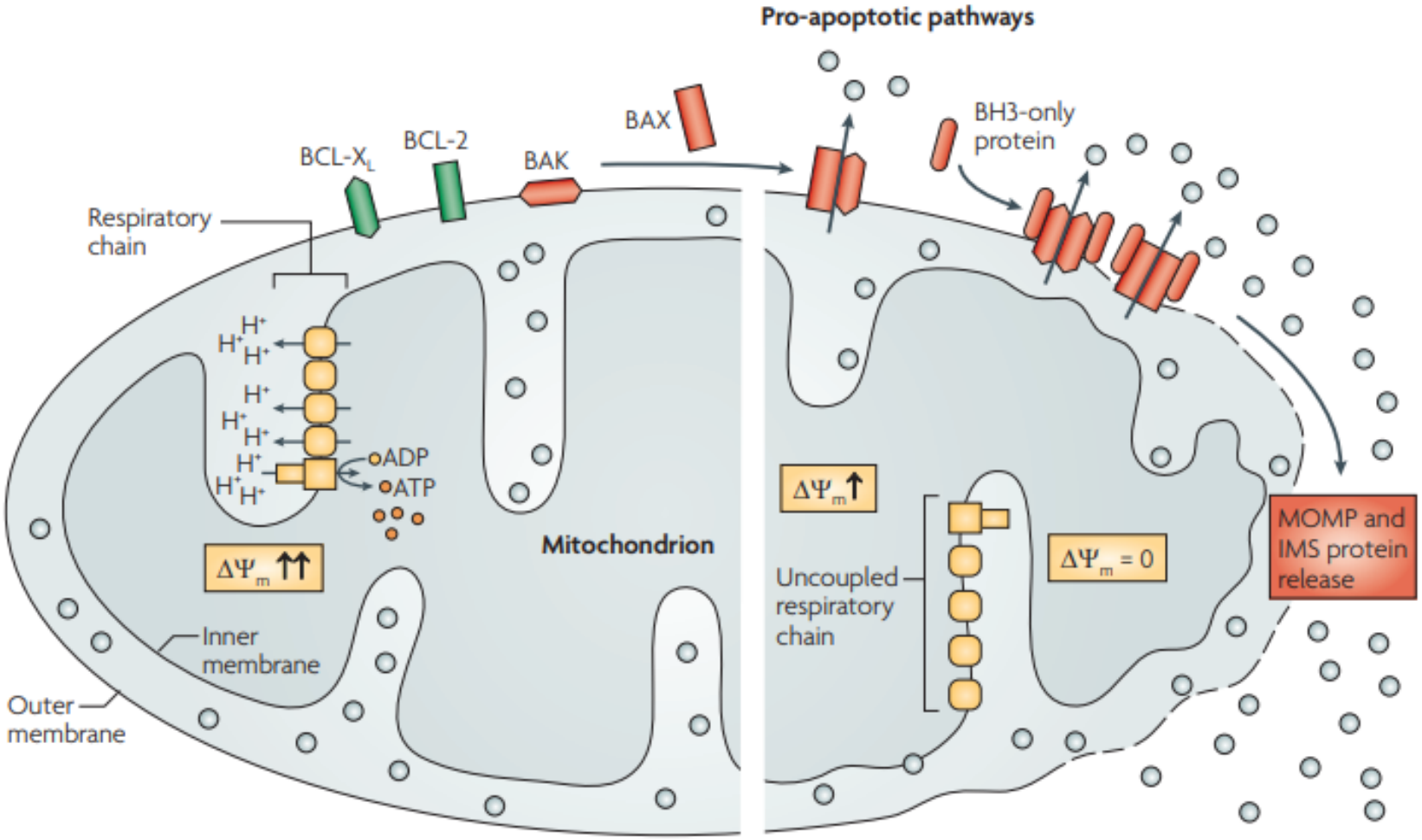
# Clinical Application and Role

- Novel Mechanism of Action
- Monotherapy Approval: Unlike many other lymphoma treatments that require combination therapy, Selinexor was approved as a single-agent therapy.
- Potential for Combination Therapy .
- Adverse Events: While effective, Selinexor is associated with hematologic toxicities, necessitating careful patient monitoring and dose adjustments.
- Ongoing research may further refine its role in combination regimens.



# Mitochondria

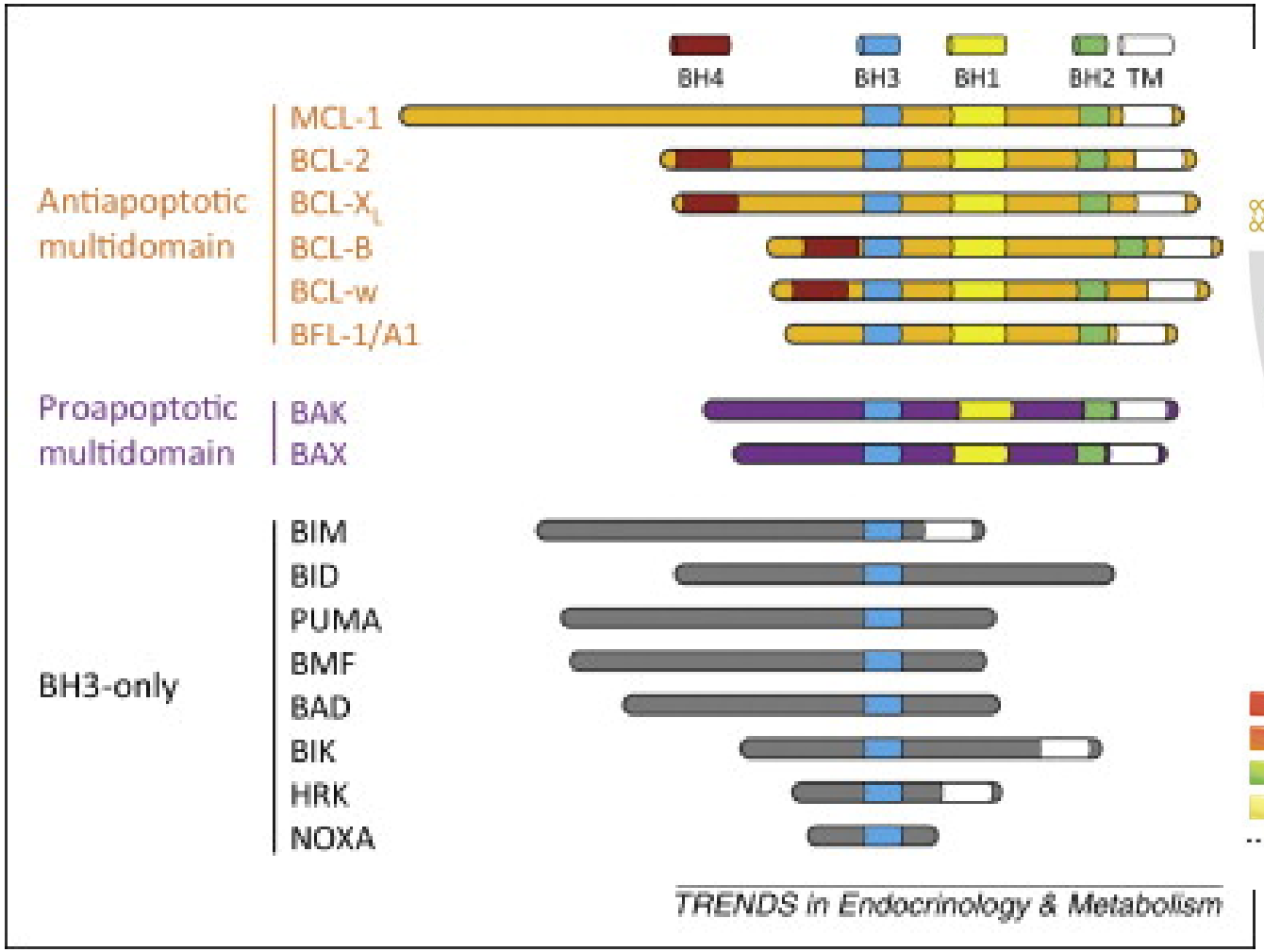
- BCL2 Inhibitors : venetoclax
- IDH1 inhibitors : Ivosidenib (Tibsovo)
- IDH2 Inhibitors : Enasidenib (Idhifa)

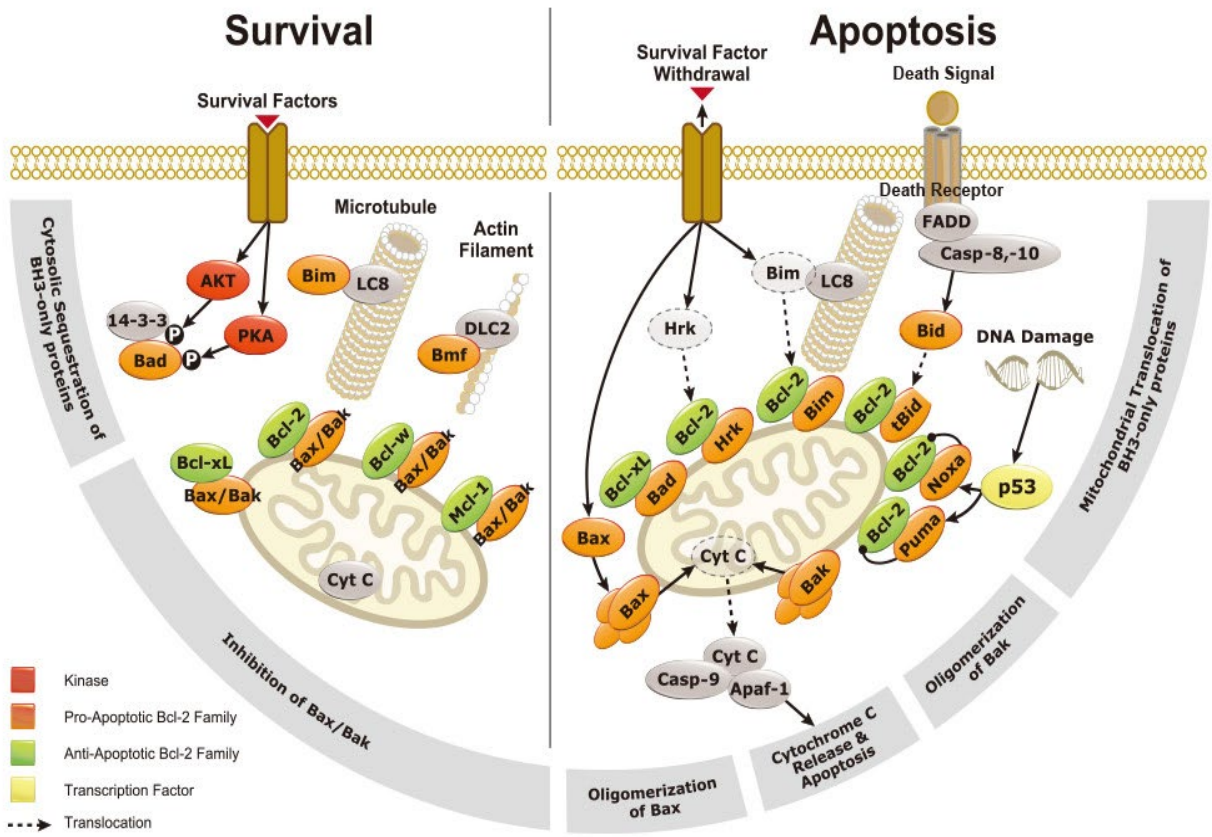


# Developmental history of BCL-2

- **Discovery of BCL-2 gene :** discovered in the 1980s in follicular lymphoma (overexpressed due to chromosomal translocation)
- **Understanding Apoptotic Pathways**
  - BCL-2 was found as a larger family of proteins that regulate the balance between cell survival and death
  - Anti-apoptotic (e.g., BCL-2, BCL-XL) and pro-apoptotic (e.g., BAX, BAK) members.
- **The Concept of BH3 Mimetics:** By the early 2000s
  - blocking the interaction between BCL-2 and pro-apoptotic proteins could promote apoptosis in cancer cells.
  - BH3 mimetics, small molecules that mimic the action of pro-apoptotic proteins, targeting BCL-2.
- **Development of Venetoclax (ABT-199)**
  - **Breakthrough in Selectivity:** Venetoclax selectively inhibits BCL-2 without affecting BCL-XL, reducing the risk of thrombocytopenia (a side effect associated with BCL-XL inhibition).
  - **Preclinical Studies:** chronic lymphocytic leukemia (CLL) and other BCL-2-dependent cancers.
  - **Clinical Trials:** venetoclax to be highly effective in CLL, particularly in patients with 17p deletion, which is associated with poor prognosis.
- **FDA Approval and Clinical Use (2016 Onwards)**

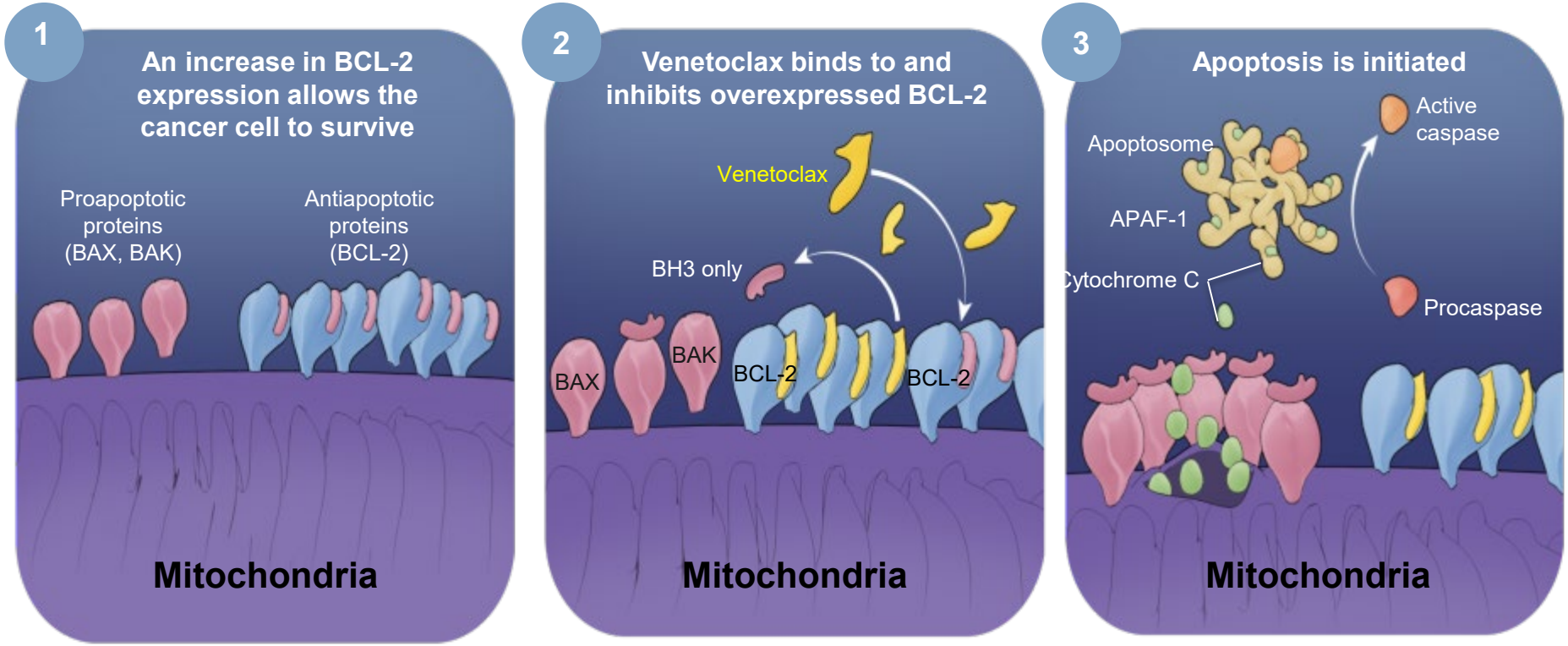
# Classifications of BCL-2 proteins according to conserved BCL-2 homology (BH) domains



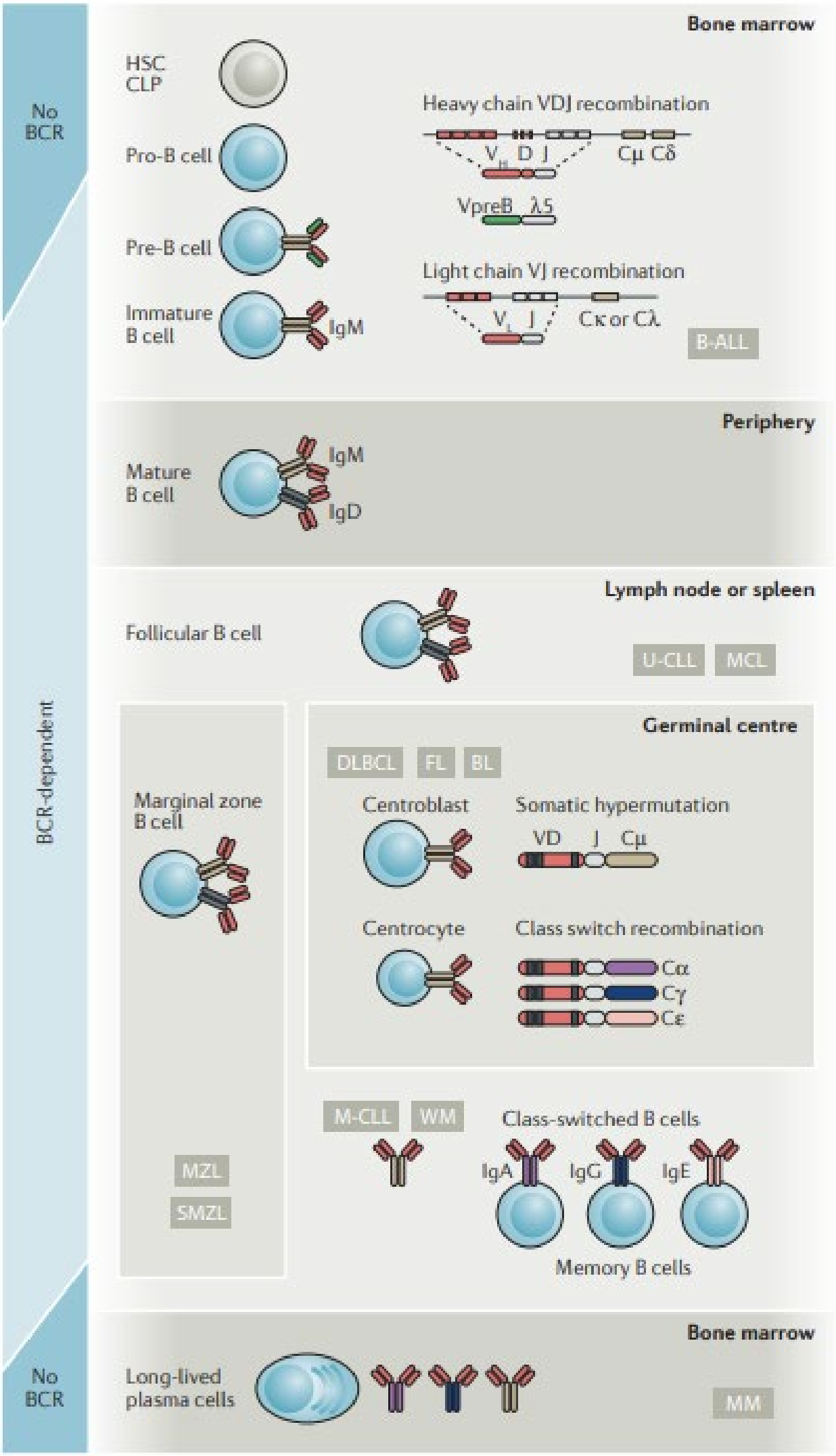

https://doi.org/10.1016/j.tem.2015.02.004

# Venetoclax: B-cell lymphoma-2 (Bcl-2) protein




Kumar S, et al. ASCO 2015. Abstract 8576.
Reproduced with permission.

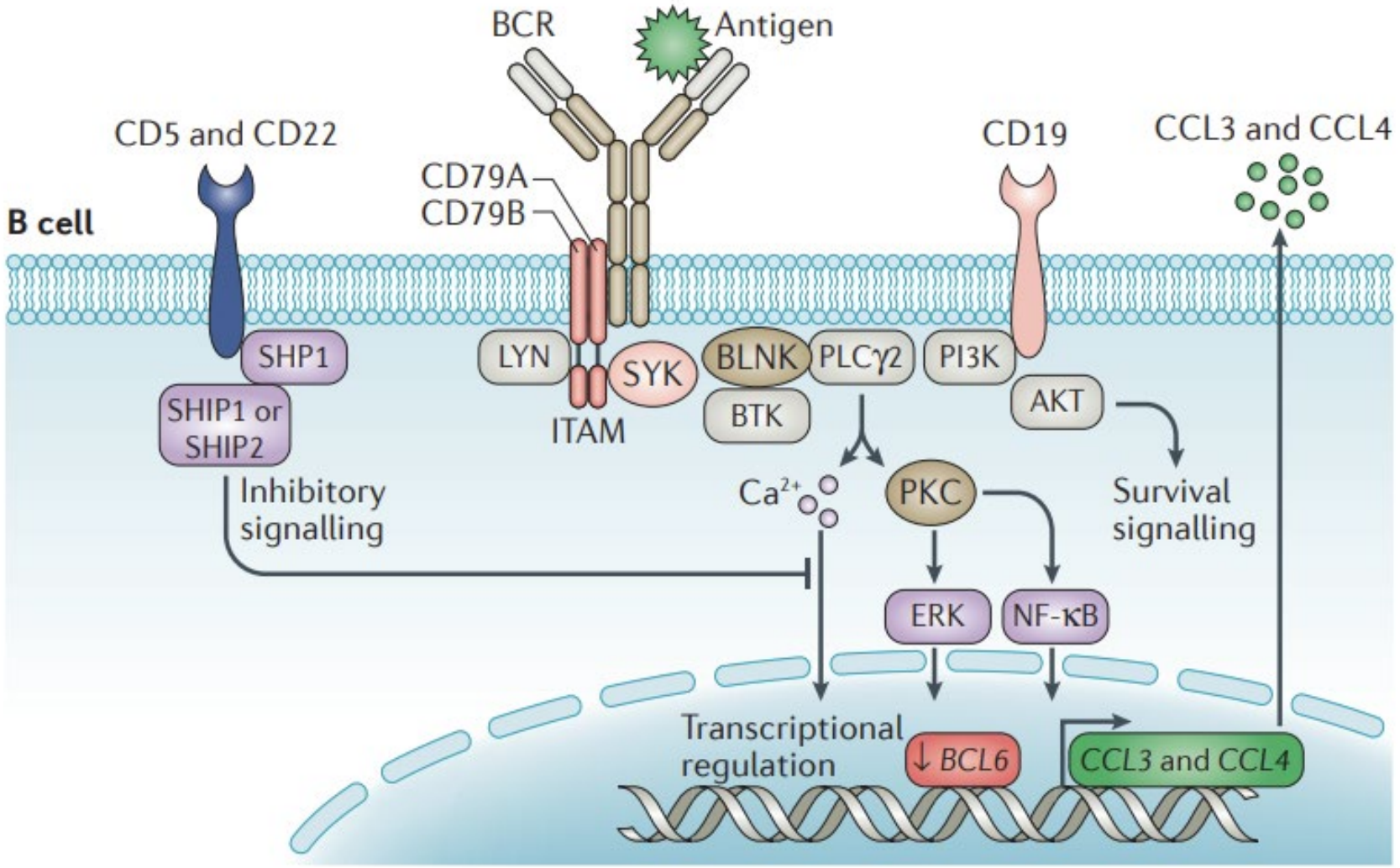
Cytochrome C is critical for both **energy production** and the regulation of **cell death**.




Nat Rev Cancer . 2018 Mar;18(3):148-167

SMZL stands for Splenic Marginal Zone Lymphoma unmutated (U-CLL) or mutated (M-CLL)

# The B cell receptor signalling pathway




Nat Rev Cancer . 2018 Mar;18(3):148-167

# BCL2-inhibitor : Venetoclax

**Targeting BCL-2 Overexpression:**

•**BCL-2** (B-cell lymphoma 2) is a protein that regulates cell death (apoptosis) and is frequently overexpressed in many B-cell malignancies. **Effectiveness Across a Range of B-Cell Neoplasms:**

•Venetoclax has shown efficacy in several B-cell cancers, including:

- **Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL)**: high BCL-2 expression .(17p deletions or TP53 mutations)
- **Acute Myeloid Leukemia (AML)**: Venetoclax in combination with other agents (like hypomethylating agents) to treat elderly or unfit AML patients, who often have BCL-2 overexpression.
- **Diffuse Large B-Cell Lymphoma (DLBCL)**: with BCL-2 rearrangements.
- **Mantle Cell Lymphoma (MCL)**: BCL-2 expression is common in MCL, in refractory or relapsed cases.
- **Follicular Lymphoma (FL)**: Venetoclax is explored in combination therapies due to its activity in this indolent B-cell lymphoma.
- **Multiple Myeloma**: particularly in patients with t(11;14) translocations, which upregulate BCL-2.

**3. Synergy with Other Therapies:** :

- **BTK inhibitors (e.g., ibrutinib)**: Combining venetoclax with BTK inhibitors (which block survival signals in B-cells) enhances the depth of response, especially in CLL.
- **Monoclonal antibodies (e.g., rituximab, obinutuzumab)**: alongside anti-CD20 antibodies ( CLL and DLBCL).
- **Chemotherapy**: Venetoclax can sensitize cancer cells to chemotherapy ( DLBCL).

**4. Minimal Overlap in Toxicity:**

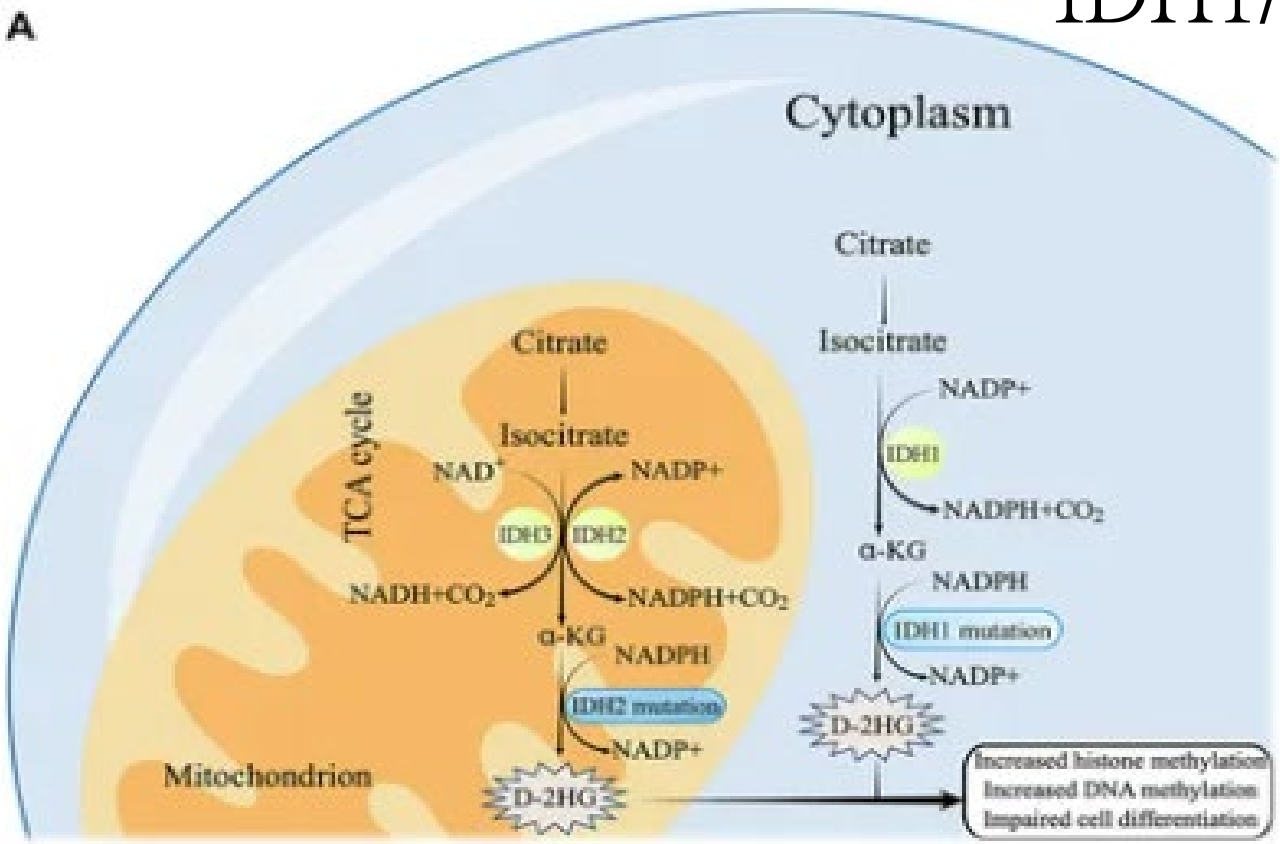
| Trial Name | Study Patients (n) | Indication | Comparative Protocol | Comparative ORR (%) | PFS (months) | Comparative Overall Survival (months) | Adverse Events | Source |
|---|---|---|---|---|---|---|---|---|
| MURANO (NCT02005471) | 389 | Relapsed/Refractory CLL | Venetoclax + Rituximab vs BR | 92% vs 72% (BR arm) | 23.3 vs 17.0 (BR arm) | 82.1% 2-year OS vs 62.2% | Neutropenia, diarrhea, URI | Blood. 2018; 132(23): 2446–2455 |
| CLL14 (NCT02242942) | 432 | Treatment-Naïve CLL<br>Clb : Chlorambucil | Venetoclax + Obinutuzumab vs Clb + Obinutuzumab | 85% vs 71% | 34.4 vs 27.3 (Clb arm) | Not reached (Venetoclax arm) | Neutropenia, febrile neutropenia, thrombocytopenia | N Engl J Med. 2020; 382: 2226-2234 |
| BELLINI (NCT02755597) | 291 | Relapsed/Refractory Multiple Myeloma | Venetoclax + Bortezomib vs Placebo + Bortezomib | 82% vs 68% | 22.4 vs 11.5 | Not reached (Venetoclax arm) | Neutropenia, diarrhea, URI , anemia | Lancet Oncol. 2020; 21: 1630-1642 |
| M14-358 (NCT02203773) | 145 | Relapsed/Refractory AML (IDH1/IDH2 mutation) | Venetoclax + Azacitidine vs Azacitidine | 67% vs 28% | 14.7 vs 7.2 (Azacitidine arm) | 17.5 vs 12.0 | Neutropenia, febrile neutropenia, nausea | Blood. 2019; 133(15): 1569-1579 |
| VIALE-A (NCT02993523) | 431 | Newly Diagnosed AML (unfit for intensive chemo) | Venetoclax + Azacitidine vs Azacitidine | 66% (Venetoclax arm) vs 28% (Azacitidine arm) | 14.7 (Venetoclax arm) vs 4.3 (Azacitidine arm) | 14.2 (Venetoclax arm) vs 9.6 (Azacitidine arm) | Neutropenia, febrile neutropenia, thrombocytopenia | N Engl J Med. 2020; 383: 617-629 |

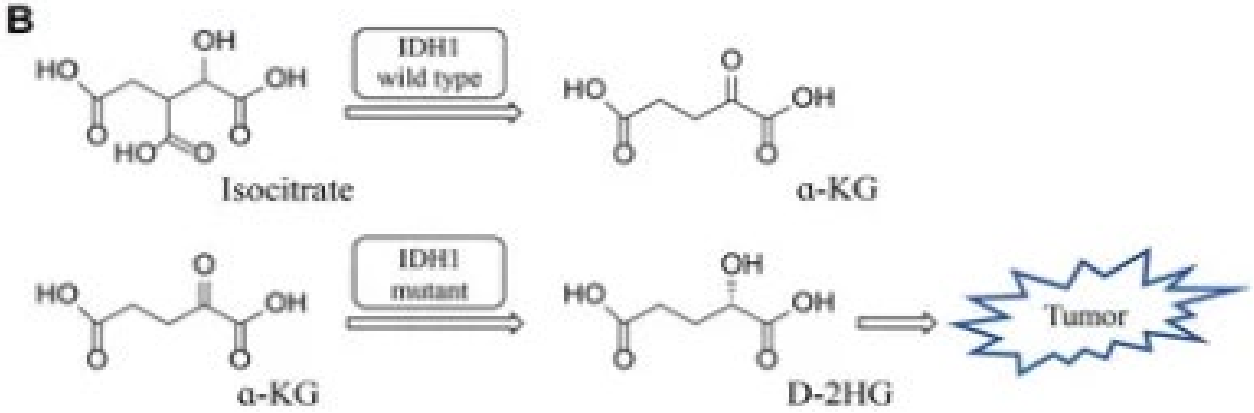
# Clinical Impact Summary ( BCL-2 Inhibitors)

- Key Clinical Roles of BCL-2 Inhibitors (Venetoclax)
  - effective in CLL, AML, and mantle cell lymphoma (MCL).
- Clinical Benefits and Impact
  - High Efficacy: Venetoclax, especially when combined with rituximab (CLL) or azacitidine (AML), has shown deep remissions and durable responses.
  - Chemo-Free Regimens: Allows targeted therapy approaches, reducing reliance on chemotherapy.
  - Overcomes Chemotherapy Resistance: Particularly effective in TP53-mutated and relapsed/refractory CLL and AML.
- **Challenges & Limitations**
  - ⚠ **Tumor Lysis Syndrome (TLS)**: Due to rapid tumor cell apoptosis (**careful dose escalation and monitoring)**.
  - ⚠ **Acquired Resistance**: Resistance mechanisms (e.g., **BCL-2 mutations**, upregulation of MCL-1, BCL-xL) can lead to **treatment failure**.
  - ⚠ **Combination Strategies Needed**: To prevent resistance, **combination therapy with BTK inhibitors (ibrutinib), hypomethylating agents (HMA),** is being explored.
  - ⚠ **Limited Solid Tumor Efficacy**: Unlike in hematologic cancers, BCL-2 inhibitors have **shown limited success in solid tumors** due to **redundant apoptosis pathways**.

Figure 2

# IDH1/2 inhibitors




- To inhibit the mutated forms of the IDH1/2 enzymes, which are involved in cellular metabolism.
  In mutant cells, these enzymes produce an oncometabolite called 2-hydroxyglutarate (2-HG).
- Elevated 2-HG levels inhibit various dioxygenases, including those involved in DNA and histone demethylation (such as TET enzymes), leading to widespread epigenetic changes.
- IDH1/2 inhibitors indirectly restore normal epigenetic regulation by reducing 2-HG production.

Mutations in isocitrate dehydrogenase genes (IDH1 and IDH2) are common in acute myeloid leukemia (AML), occurring in up to 30% of AML cases

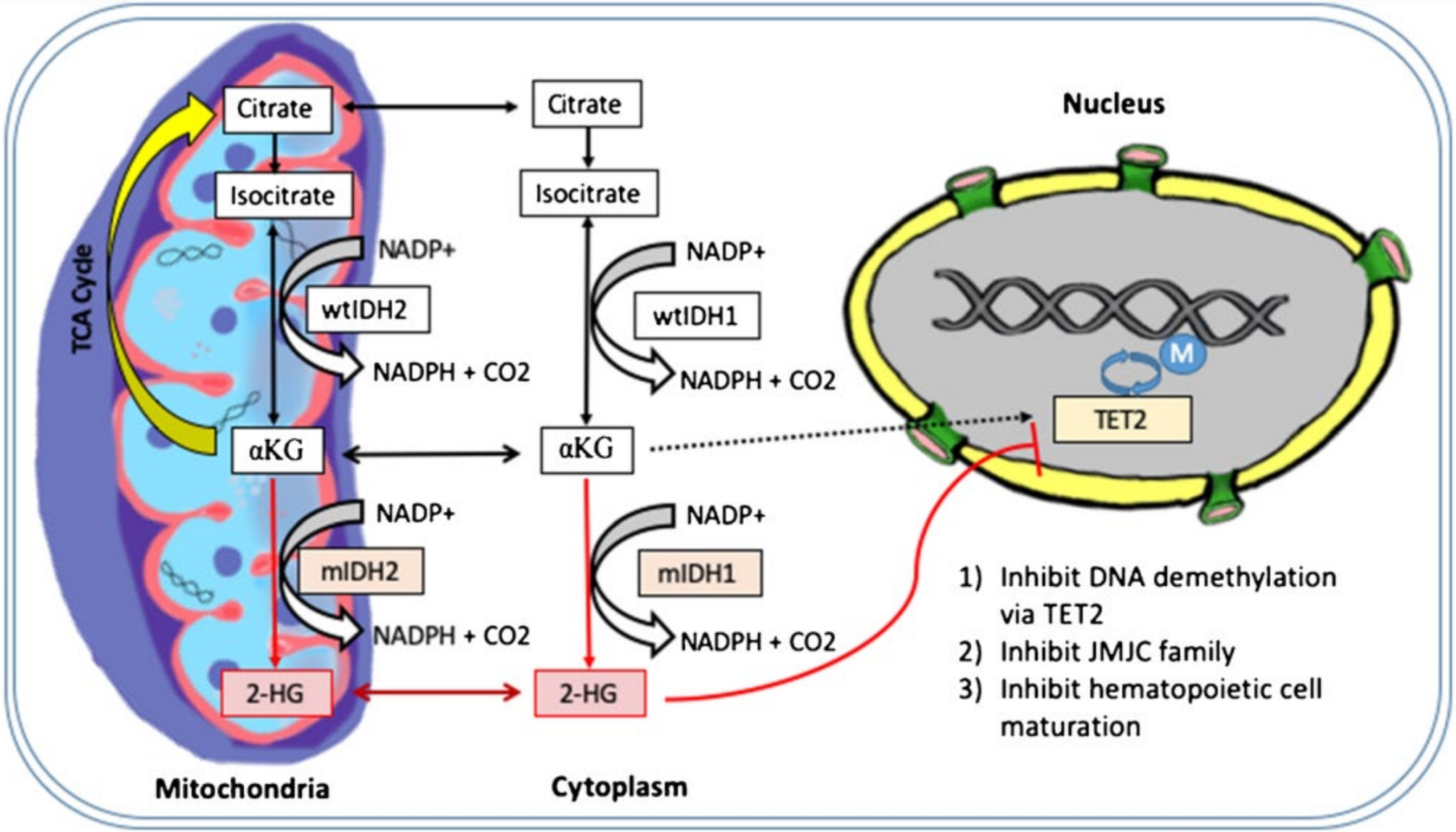



**Fig. 1.** Mutant IDH1 and IDH2 (mIDH1 and mIDH2) produce the oncometabolite 2-hydroxyglutarate (2-HG) , which inhibits TET2 function and th Jumonji-C domain-containing (JMJC) family of histone lysine demethylases to block normal hematopoietic cell maturation

# IDH2 (mutant isocitrate dehydrogenase 2 enzyme) inhibitors

- Enasidenib is a selective inhibitor of the mutant isocitrate dehydrogenase 2 (IDH2) enzyme.
- IDH2 plays a role in the citric acid cycle, converting isocitrate to α-ketoglutarate (α-KG).
- In cells with IDH2 mutations, the enzyme produces an oncometabolite called 2-hydroxyglutarate (2-HG) instead of α-KG. Accumulation of 2-HG leads to DNA and histone hypermethylation, which impairs cellular differentiation and contributes to the development of cancer, particularly acute myeloid leukemia (AML).

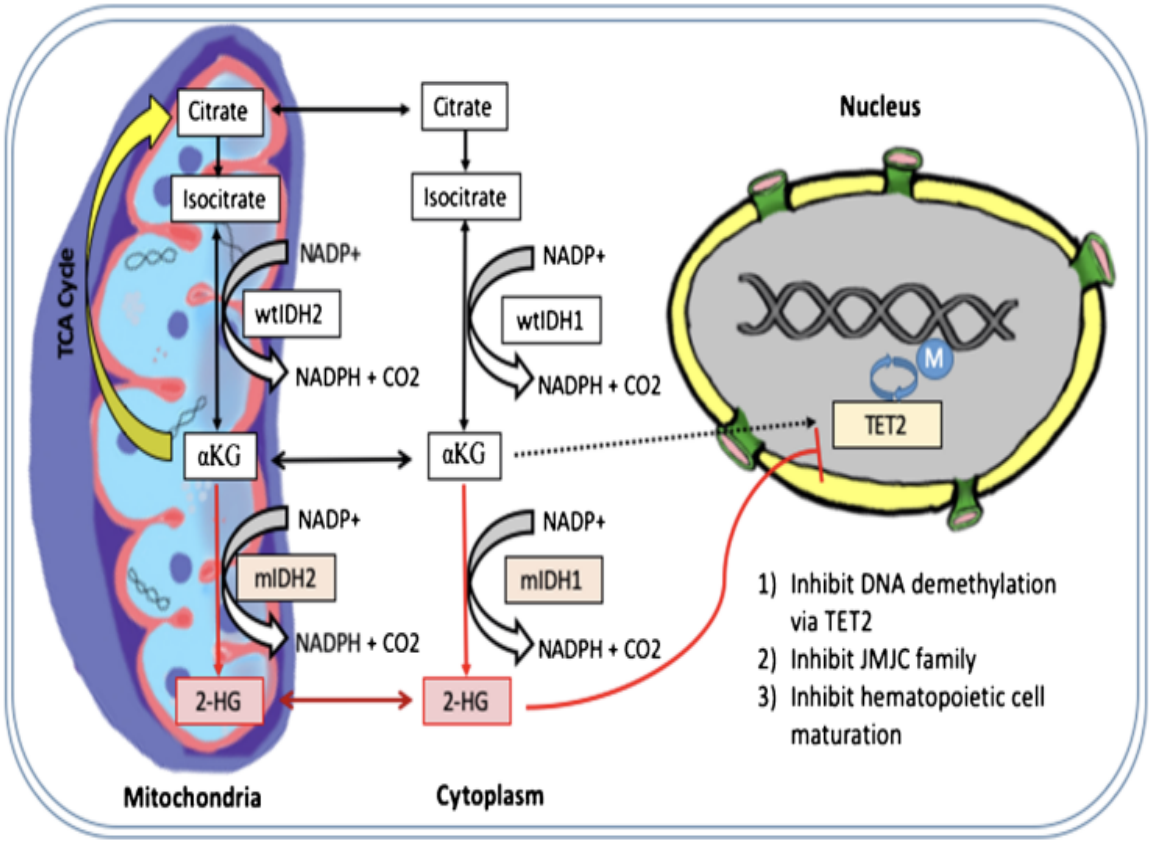
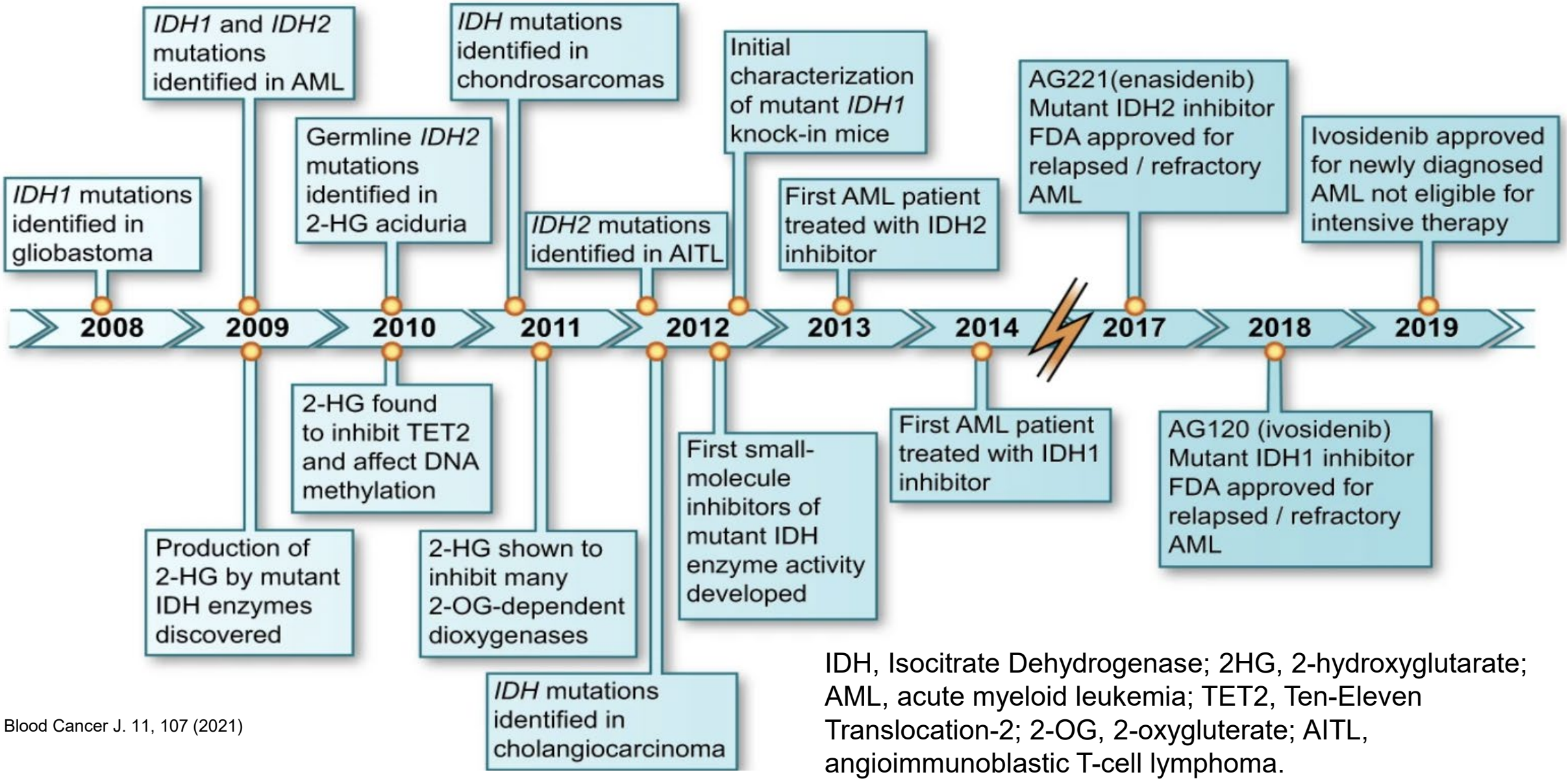


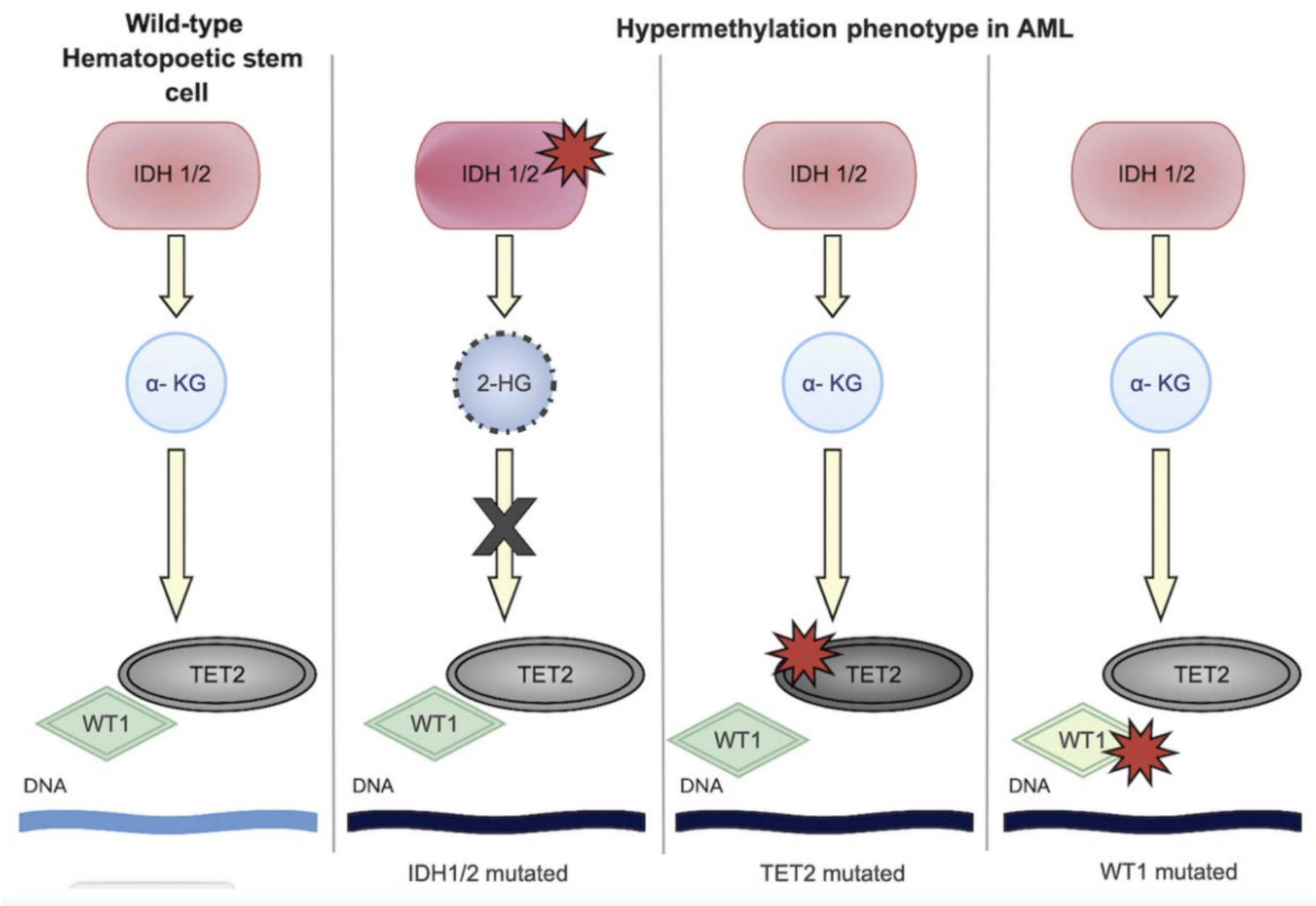

**Fig. 1.** Mutant IDH1 and IDH2 (mIDH1 and mIDH2) produce the oncometabolite 2-hydroxyglutarate (2-HG) , which inhibits TET2 function and the Jumonji-C domain-containing (JMJC) family of histone lysine demethylases to block normal hematopoietic cell maturation

# A timeline depicting the decade of progress in IDH-mutated malignancies




Blood Cancer J. 11, 107 (2021)

IDH, Isocitrate Dehydrogenase; 2HG, 2-hydroxyglutarate; AML, acute myeloid leukemia; TET2, Ten-Eleven Translocation-2; 2-OG, 2-oxygluterate; AITL, angioimmunoblastic T-cell lymphoma.




WT1 (Wilms Tumor 1 protein) acts as a transcription factor that recruits TET2 (Ten-Eleven Translocation 2 protein) to DNA, allowing TET2 to modify DNA methylation patterns and regulate gene expression, essentially functioning as a tumor suppressor by controlling cell growth and differentiation; mutations in either WT1 or TET2 are often linked to the development of certain cancers, particularly acute myeloid leukemia (AML).

| Feature | IDH1 Inhibitors | IDH2 Inhibitors |
|---|---|---|
| **Target Enzyme** | Mutant **IDH1** | Mutant **IDH2** |
| **Mutation Location** | **Cytoplasm** | **Mitochondria** |
| **Approved Drugs** | **Ivosidenib (Tibsovo)** | **Enasidenib (Idhifa)** |
| **FDA-Approved Indications** | - AML with IDH1 mutation (newly diagnosed & relapsed/refractory)<br>- IDH1-mutated **cholangiocarcinoma**<br>- IDH1-mutated **gliomas** (investigation) | - AML with IDH2 mutation (relapsed/refractory) |
| **Mechanism of Action** | Inhibits IDH1 mutant enzyme to restore normal differentiation | Inhibits IDH2 mutant enzyme to restore normal differentiation |
| **Metabolite Reduction** | Decreases **(R)-2-HG** production from IDH1 | Decreases **(R)-2-HG** production from IDH2 |
| **Response Rate (AML)** | ORR ~42% (monotherapy) | ORR ~40% (monotherapy) |
| **Metabolism** | Primarily hepatic (CYP3A4)主要肝臟 (CYP3A4) | Hepatic (UGT1A1 metabolism) 肝臟 (UGT1A1 代謝) |
| **Half-Life** | ~93 hours | ~137 hours |

# IDH1 inhibitors (Ivosidenib)

| Trial Name (Study Patient Number) | Indication | comparative Protocol | Comparative ORR | Comparative PFS | Comparative OS | Adverse Events | Source of Journal |
|---|---|---|---|---|---|---|---|
| **AG120-C-001 (174 patients)** | Relapsed/Refractory AML with IDH1 mutation | Ivosidenib vs. Conventional Care | 30.4% vs. 10.8% | 2.8 months vs. 1.9 months | 9.0 months vs. 4.7 months | Differentiation syndrome, QT prolongation, leukocytosis | New England Journal of Medicine 2018; 378(25): 2386-2398 |
| **AGILE (386 patients)** | Newly Diagnosed AML with IDH1 mutation | Ivosidenib + Azacitidine vs. Azacitidine Alone | 42% vs. 13% | 5.3 months vs. 2.7 months | 12.4 months vs. 8.9 months | Differentiation syndrome, fatigue, nausea | Lancet Oncology 2021; 22(9): 1444-1456 |
| **ClarIDHy (146 patients)** | Advanced Cholangiocarcinoma with IDH1 mutation | Ivosidenib vs. Placebo | 2.4% vs. 0% | 2.7 months vs. 1.4 months | 10.8 months vs. 9.7 months | Nausea, diarrhea, fatigue | Lancet Oncology 2020; 21(6): 796-807 |
| **NCT02073994 (125 patients)** | Glioma with IDH1 mutation | Ivosidenib vs. Conventional Care | 11% vs. 5% | 3.8 months vs. 1.7 months | 13.6 months vs. 7.8 months | Nausea, diarrhea, fatigue, QT prolongation | Neuro-Oncology 2021; 23(9): 1553-1562 |

# IDH2 inhibitors (mutant isocitrate dehydrogenase 2 enzyme) inhibitors : Enasidenib )

| Trial Name (Study Patient Number) | Indication | Comparative Protocol | Comparative ORR | Comparative PFS | Comparative Overall Survival | Adverse Events | Source of Journal |
|---|---|---|---|---|---|---|---|
| **AG221-C-001 (258 patients)** | Relapsed/Refractory AML with IDH2 mutation | Enasidenib vs. Conventional Care | 19.3% vs. 14.3% | 2.9 months vs. 2.0 months | 8.8 months vs. 6.1 months | Differentiation syndrome, leukocytosis, hyperbilirubinemia | Lancet Oncology 2017; 18(7): 1061-1075 |
| **AG221-C-002 (101 patients)** | Untreated AML with IDH2 mutation (Elderly) | Enasidenib + Azacitidine vs. Azacitidine Alone | 53% vs. 12% | 6.4 months vs. 3.4 months | 22.9 months vs. 11.9 months | Differentiation syndrome, nausea, hyperbilirubinemia | Blood 2019; 134(1): 31-42 |
| **IDHENTIFY (252 patients)** | Relapsed/Refractory AML with IDH2 mutation | Enasidenib vs. Conventional Care | 23.7% vs. 13.4% | 3.7 months vs. 2.6 months | 10.8 months vs. 6.2 months | Differentiation syndrome, nausea, vomiting | J Clin Oncol 2021; 39(3): 266-277 |
| **AGILE (387 patients)** | Newly Diagnosed AML with IDH2 mutation | Enasidenib + Azacitidine vs. Azacitidine Alone | 37% vs. 13% | 4.7 months vs. 2.7 months | 15.7 months vs. 10.0 months | Differentiation syndrome, fatigue, decreased appetite | Leukemia 2022; 36(6): 1642-1653 |

# Differentiation syndrome

- Can be fatal.
- Symptoms :  fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction.
- Management : corticosteroid therapy and hemodynamic monitoring until symptom resolution.

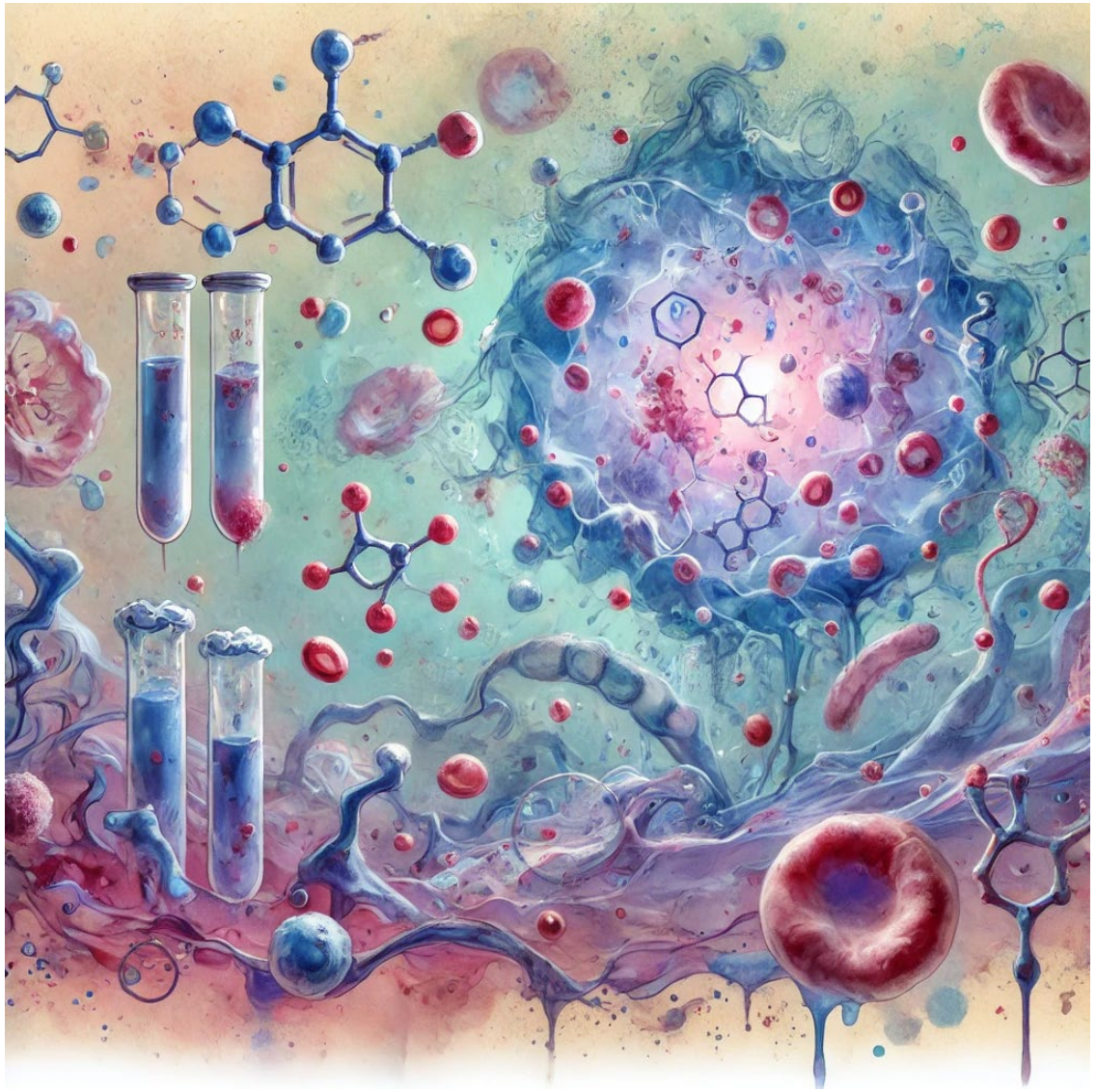
| Adverse Event | IDH1 Inhibitors (Ivosidenib) | IDH2 Inhibitors (Enasidenib) | Management |
|---|---|---|---|
| **Differentiation Syndrome (DS)** | ~30% incidence | ~14% incidence | **Corticosteroids (Dexamethasone 10 mg IV/PO q12h for ≥3 days), diuretics**, hold treatment if severe |
| **QT Prolongation** | Common (Monitor ECG) | Less frequent | Regular ECG monitoring, **correct electrolytes (K+, Mg2+, Ca2+)** |
| **Hepatotoxicity** | Mild to moderate | Risk of **indirect hyperbilirubinemia** (due to UGT1A1 inhibition) | **Hold treatment for Grade 3+ hepatotoxicity**, supportive care |
| **Leukocytosis** | May occur (transient increase in WBCs) | Less common | **Hydroxyurea** for WBC control if needed |
| **GI Symptoms (Nausea, Diarrhea, Vomiting)** | Mild | Common (especially diarrhea) | Supportive care: **antiemetics, hydration, loperamide for diarrhea** |

# Summary of IDH1 and IDH2 Inhibitors in Clinical Practice

- IDH1 and IDH2 inhibitors used in acute myeloid leukemia (AML) with IDH1 or IDH2 mutations.
  - by inhibiting mutant IDH enzymes, reducing 2-hydroxyglutarate (2-HG) accumulation, and allowing leukemic cells to differentiate into normal blood cells.
- Indications and Patient Selection (Requires molecular testing for IDH1/2 mutations.)
  - Ivosidenib (IDH1 Inhibitor) 500 mg qd : Relapsed/Refractory AML with IDH1 mutations, Newly diagnosed AML (unfit for intensive chemotherapy)
  - Enasidenib (IDH2 Inhibitor) 100 mg qd : Relapsed/Refractory AML with IDH2 mutations
- **Response Rates:**
  - Ivosidenib: **30–40%** complete remission (CR) in IDH1-mutant AML
  - Enasidenib: **20–40%** complete remission (CR) in IDH2-mutant AML
- **Overall Survival:**
  - Improved survival in patients responding to treatment.
- **Duration of Response:**
  - **6–12 months** on average, with some long-term responders.

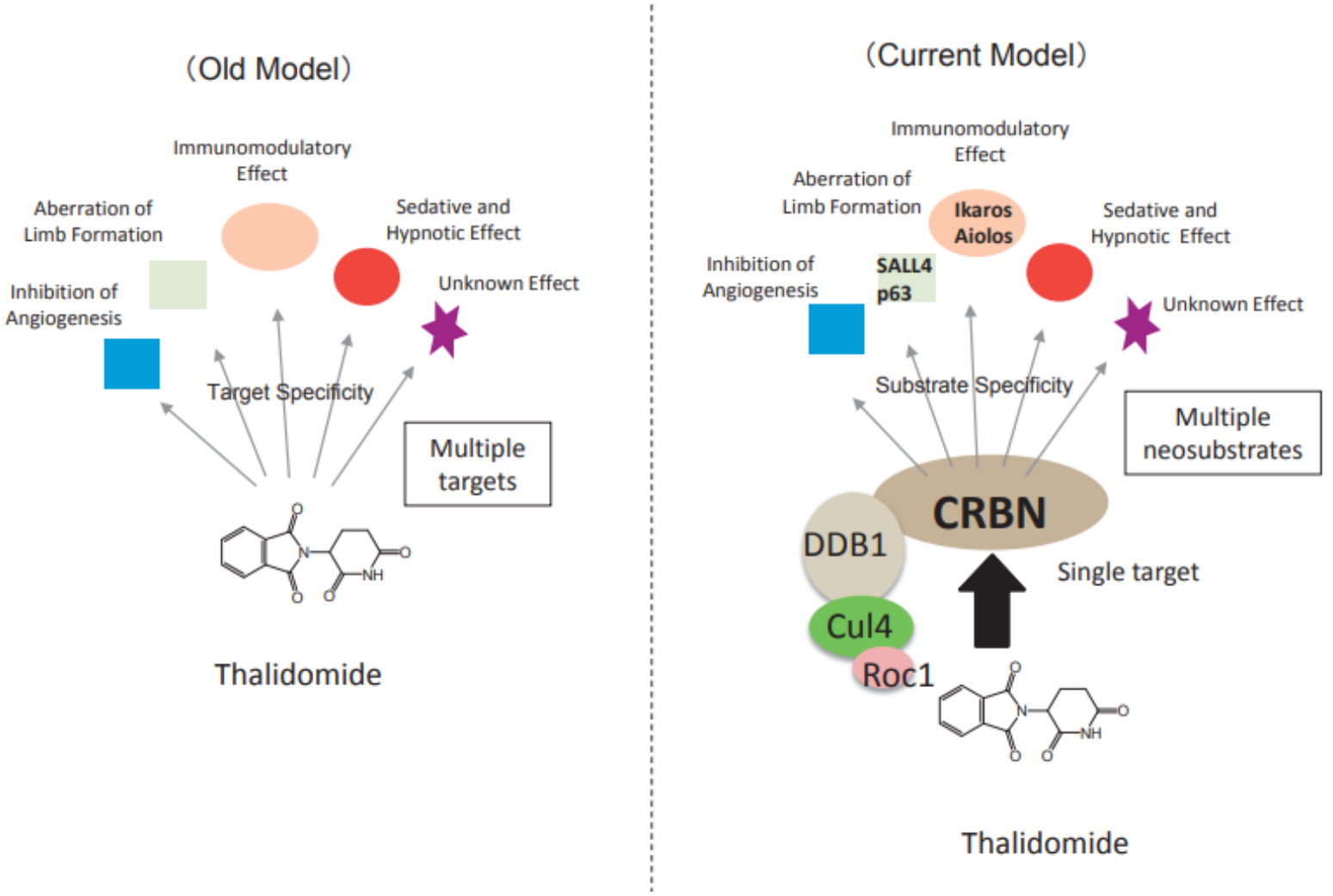
# Cytoplasm

- KRAS Inhibitors
- Proteasome inhibitors : (multiple myeloma )
- IMiDS
- STAMP Inhibitors



# Developmental History of Immunomodulatory Drugs (IMiDs)

- The Thalidomide Tragedy and Rebirth (1950s–1990s)
  - 1950s: Thalidomide was initially developed in Germany (1953) as a sedative and was widely used for morning sickness in pregnant women.
  - 1960s: cause severe birth defects, leading to phocomelia (limb malformations) in newborns. This resulted in a global ban.
  - 1990s: Dr. Judah Folkman and Bart Barlogie, for its anti-angiogenic and immunomodulatory properties in treating multiple myeloma (MM) and leprosy.
- FDA Approval and Expansion of IMiDs (2000s)
  - 2003: Thalidomide received accelerated approval for relapsed/refractory MM based on studies showing improved survival in combination with dexamethasone.
  - 2005: Lenalidomide (Revlimid), a structural analog of thalidomide, was FDA-approved for myelodysplastic syndromes (MDS) and multiple myeloma.Compared to thalidomide, lenalidomide had fewer neurotoxic effects and enhanced anti-tumor activity.
- Next-Generation IMiDs and Expanding Applications (2010s–Present)
  - 2013: Pomalidomide (Pomalyst) was approved for relapsed/refractory multiple myeloma (RRMM) after lenalidomide and bortezomib failure.
  - 2019–2020: Research into novel cereblon-modulating drugs led to the fourth-generation IMiDs, including Iberdomide (CC-220) and Mezigdomide (CC-92480), designed for enhanced anti-myeloma effects.
  - 2022: Iberdomide and Mezigdomide entered clinical trials for lenalidomide- and pomalidomide-refractory MM.

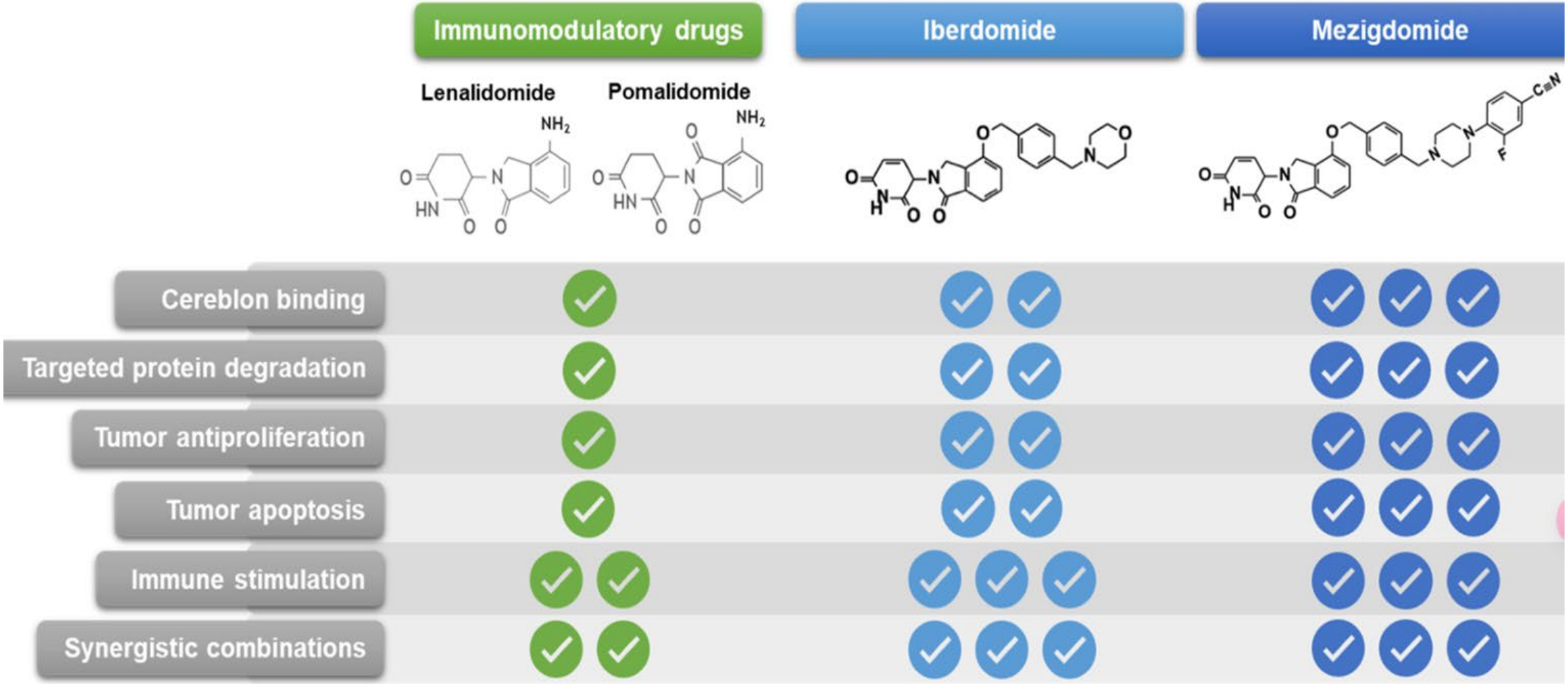



Proposed thalidomide mechanisms of action. Previously, it was thought that thalidomide has multiple targets, resulting in pleiotropic effects. However, it is now believed that thalidomide has a sole target (CRBN). Binding of IMiDs to CRL4CRBN causes breakdown of multiple neosubstrates such as Ikaros and SALL4, resulting in various effects.

Proc. Jpn. Acad., Ser. B 96 (2020)

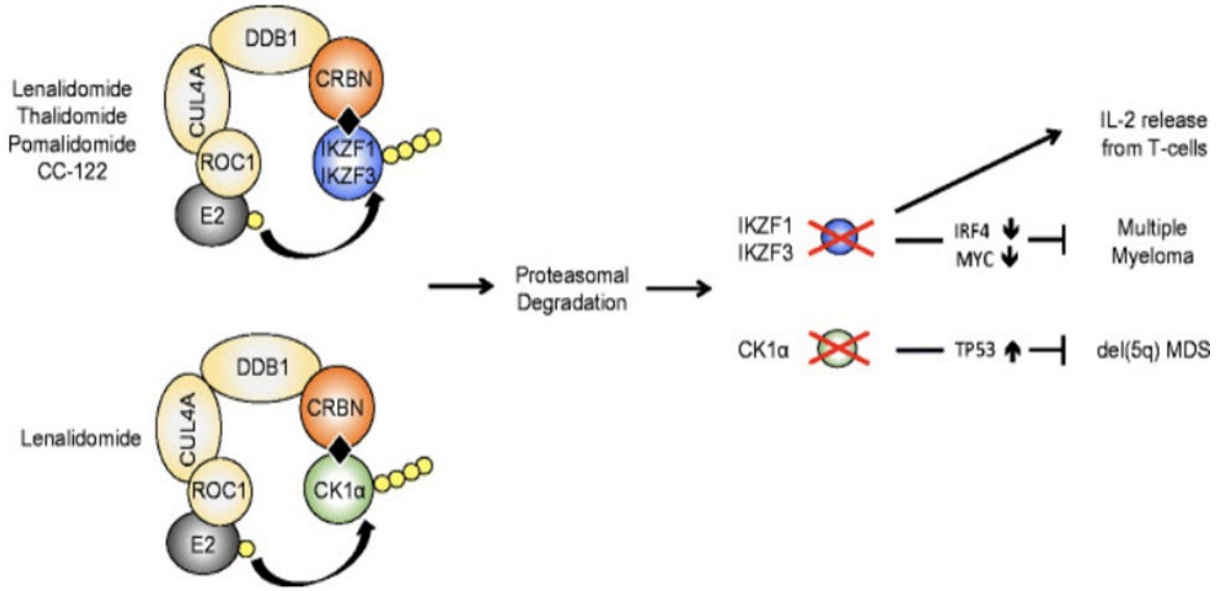
# Summary of Key FDA Approvals

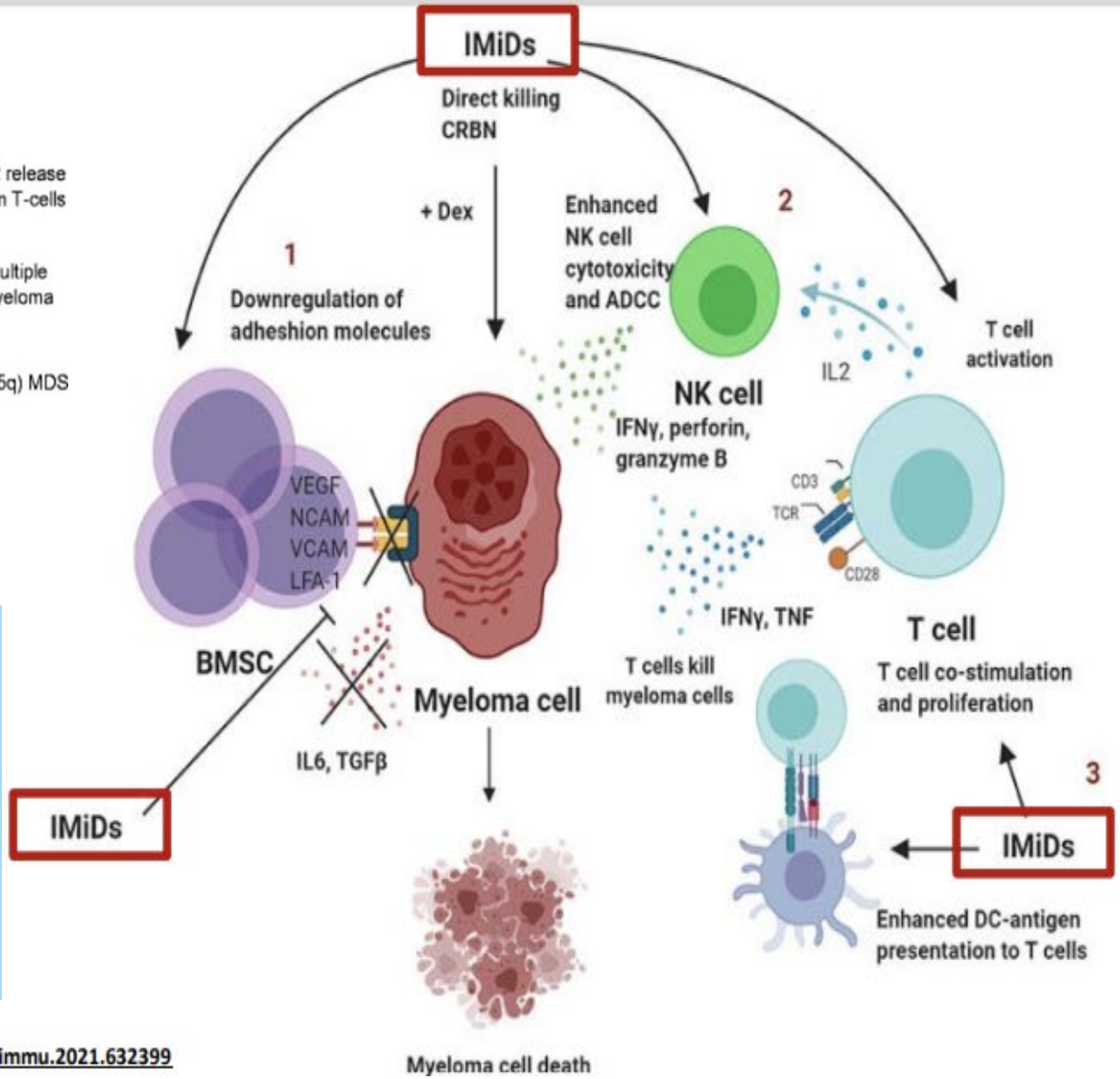
| Drug | FDA Approval Year | Indication |
|---|---|---|
| **Thalidomide** | 1998 | ENL, MM (restricted use) |
| **Lenalidomide (Revlimid)** | 2005 | MM, MDS, NHL |
| **Pomalidomide (Pomalyst)** | 2013 | RRMM |
| **Iberdomide (CC-220)** | In Trials | Advanced MM |
| **Mezigdomide (CC-92480)** | In Trials | RRMM |




Cancers 2024, 16(6), 1166

# Immunomodulatory Drugs (IMiD)

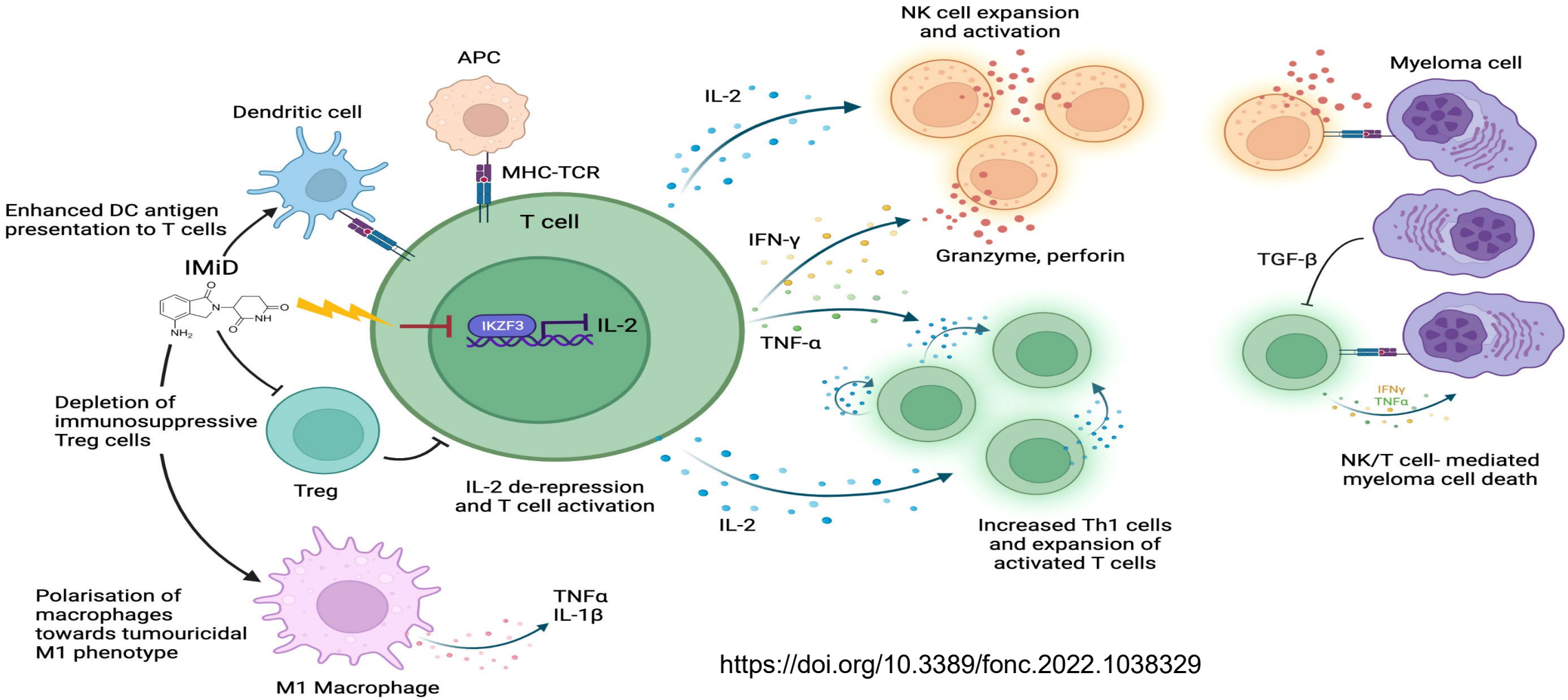



IMiDs bind to CRBN and increase its affinity to IKZF1(Ikaros) and IKZF3(Aiolos), . This results in ubiquitination and proteasomal degradation of both lymphoid transcription factors. Inactivation of IKZF1 and IKZF3 is responsible for IL-2 release from T cells and growth inhibition of multiple myeloma cells. CK1α is specifically recruited to CRBN by lenalidomide. Del(5q) MDS cells are highly sensitive to CK1α degradation due to CK1α haploinsufficiency

Image Source: D'Souza C, et al. *Front Immunol.* 2021; https://doi.org/10.3389/fimmu.2021.632399

# Mechanism




https://doi.org/10.3389/fonc.2022.1038329

- Cereblon (CRBN) Binding: They target cereblon, leading to ubiquitination and degradation of key tumor-supportive proteins.
- T-Cell Activation & Immune Modulation: They enhance IL-2 production and activate NK cells, increasing anti-myeloma activity.
- Anti-Angiogenic Effects: IMiDs inhibit VEGF, reducing tumor blood supply.

| Drug | Trial Name (Pt N) | Indication | Comparative Protocol | Comparative ORR (%) | Comparative PFS (months) | Comparative OS (months) | Adverse Events | Source of Journal |
|---|---|---|---|---|---|---|---|---|
| Thalidomide | 1999 (n=84) | R/R multiple myeloma (RRMM) | Single-arm | 32% (Thalidomide alone) | NA | 13.0 (single arm) | Peripheral neuropathy, constipation, sedation, thromboembolism | NEJM 1999;341:1565–1571 |
| Lenalidomide | MM-009 & MM-010, (n=353 & 351) | R/RMM after at least one prior therapy | Lenalidomide + Dex vs Dexamethasone alone | 60.6% vs 21.9% | 11.1 vs 4.7 | 29.6 vs 20.2 | Neutropenia, thrombosis, fatigue, rash | NEJM 2007;357:2123–2132 |
| Pomalidomide | MM-003, JCO 2013 (n=455) | R/RMM after ≥2 prior therapies including lenalidomide & bortezomib | Pomalidomide + Low-dose Dex vs High-dose Dex | 31% vs 10% | 4.0 vs 1.9 | 12.7 vs 8.1 | Neutropenia, anemia, thrombocytopenia, fatigue | J Clin Oncol 2013;31(23):2691–2697 |

| Drug Class | Examples | Mechanism/Role |
|---|---|---|
| **Proteasome Inhibitors (PI)** | Bortezomib (V), Carfilzomib (K), Ixazomib | Block protein degradation; apoptosis |
| **IMiDs / CELMoDs** | Lenalidomide (R), Pomalidomide (P), Iberdomide (new) | Enhance T cell/NK function, degrade Ikaros/Aiolos |
| **Steroids** | Dexamethasone | Anti-inflammatory; enhance MM drug efficacy |
| **Monoclonal antibodies** | Daratumumab (anti-CD38), Isatuximab (anti-CD38), Elotuzumab (anti-SLAMF7) | ADCC, CDC, direct cytotoxicity |
| **XPO1 Inhibitor** | Selinexor | Nuclear export inhibition; induces apoptosis |
| **Alkylators** | Cyclophosphamide, Melphalan | DNA cross-linking; used in ASCT or elderly |
| **Bispecifics / CAR-T** | Teclistamab (BCMA × CD3), Ide-cel | Redirect immune cells to MM |

| Protocol | Candidate Situation | Overall Response Rate (ORR) | Median Progression-Free Survival (PFS) | Combination Components |
|---|---|---|---|---|
| VRd | Newly diagnosed, transplant-eligible | 89–97% | >4 years | Bortezomib + Lenalidomide + Dexamethasone |
| KRd | Relapsed, 1–3 prior therapies | 87.1% | 26.3 months | Carfilzomib + Lenalidomide + Dexamethasone |
| Dara-VRd | Newly diagnosed, transplant-eligible | 87.9% CR or better | 84.3% at 48 months | Daratumumab + Bortezomib + Lenalidomide + Dexamethasone |
| IRd | Relapsed/refractory, ≥1 prior therapy | 78% | 20.6 months | Ixazomib + Lenalidomide + Dexamethasone |
| Dara-Rd | Relapsed/refractory, 1–3 prior therapies | 93% | Not reached (13.5-month follow-up) | Daratumumab + Lenalidomide + Dexamethasone |
| Elo-Rd | Relapsed/refractory, 1–3 prior therapies | 79% | 19.4 months | Elotuzumab + Lenalidomide + Dexamethasone |
| SVd | Relapsed/refractory, 1–3 prior therapies | 76.4% | 13.9 months | Selinexor + Bortezomib + Dexamethasone |
| Carvykti | Relapsed/refractory, ≥1 prior therapy | N/A | 45% reduction in death risk | Ciltacabtagene Autoleucel (CAR-T) |
| Blenrep + BorDex | Relapsed/refractory, ≥1 prior therapy | N/A | 42% reduction in death risk | Belantamab Mafodotin + Bortezomib + Dexamethasone |

# Specifically Targeting the ABL Myristoyl Pocket (STAMP) inhibitor

an allosteric inhibitor ( 變構抑制劑)

- asciminib (Scemblix), for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML).

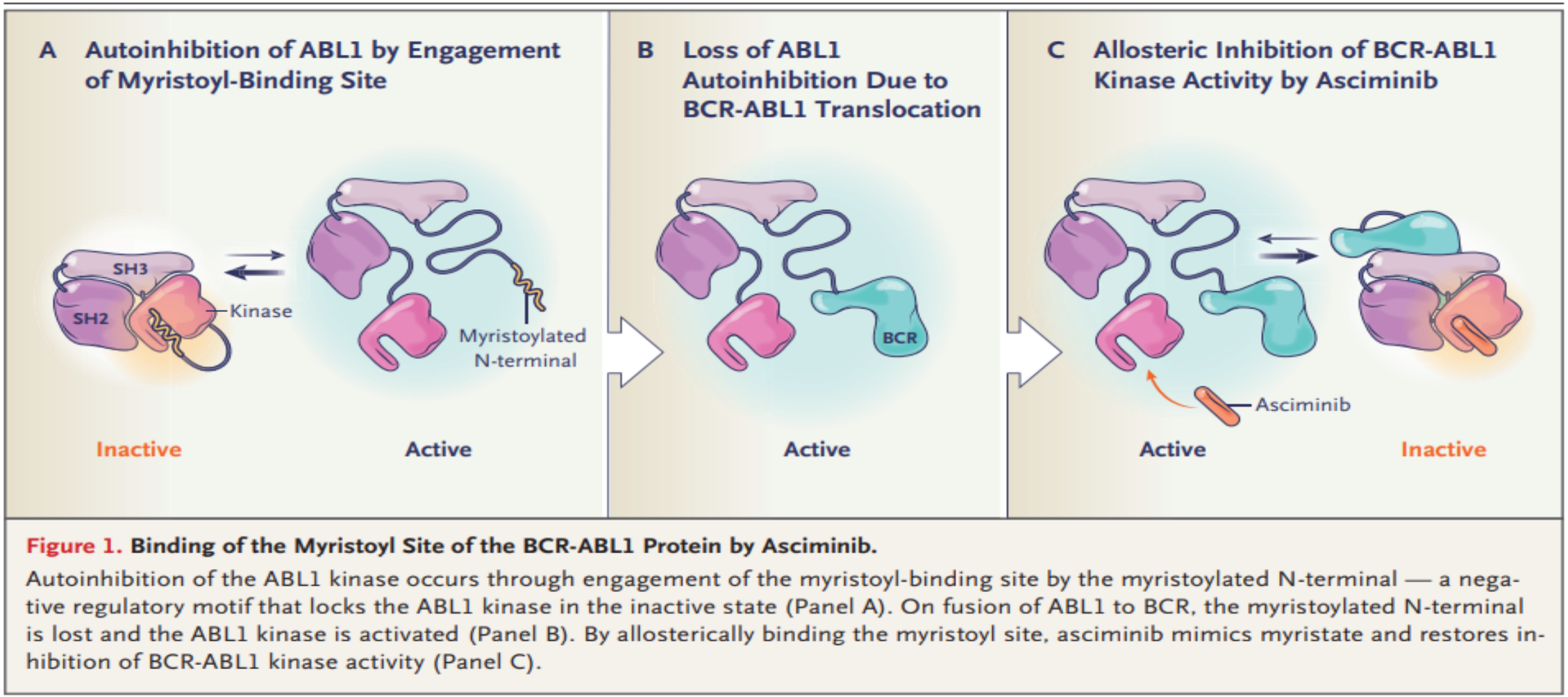



**Figure 1. Binding of the Myristoyl Site of the BCR-ABL1 Protein by Asciminib.**

Autoinhibition of the ABL1 kinase occurs through engagement of the myristoyl-binding site by the myristoylated N-terminal — a negative regulatory motif that locks the ABL1 kinase in the inactive state (Panel A). On fusion of ABL1 to BCR, the myristoylated N-terminal is lost and the ABL1 kinase is activated (Panel B). By allosterically binding the myristoyl site, asciminib mimics myristate and restores inhibition of BCR-ABL1 kinase activity (Panel C).

N Engl J Med 2019;381:2315-2326

| Study Name | Patient Number | Indication | Study Design | Overall Response Rate (ORR) | Progression-Free Survival (PFS) | Overall Survival (OS) | Adverse Events | Source |
|---|---|---|---|---|---|---|---|---|
| **ASCEMBL (NCT03106779)** | 233 | Ph+ CML in chronic phase (CP), previously treated with ≥2 TKIs | Phase III, multicenter, open-label, randomized | Major Molecular Response (MMR) at 24 weeks: 25.5% for asciminib 40mg bid vs. 13.2% for bosutinib | Not reached; hazard ratio for disease progression or death: 0.29 (95% CI: 0.12–0.69) | 12-month OS: 98.4% for asciminib vs. 94.7% for bosutinib | Most common (≥20%): thrombocytopenia, neutropenia, anemia, headache, fatigue, nausea, diarrhea (50.6% vs 60.5%) DC (treatment discontinuation (5.8% vs 21.1%) | Blood. 2021 Nov 25;138(21):2031-2041 |
| **ASC4FIRST (NCT04971226)** Asciminib in Newly Diagnosed Chronic Myeloid Leukemia | 405 | Newly diagnosed Ph+ CML-CP | Phase III, head-to-head, open-label, randomized | MMR at 48 weeks: 68% for asciminib 40mg bid vs. 49% for standard-of-care TKIs | Data not yet mature | Data not yet mature | ADR (≥20%): thrombocytopenia, neutropenia, anemia , headache, Myalgia nausea , diarrhea ADR & DC asciminib (38.0% and 4.5%, ) vs imatinib (44.4% and 11.1%) and second-generation TKIs (54.9% and 9.8%). | NEJM 2024;391:885-898 |

Thank you for listening

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搜尋結果均以本站制定的格式編寫，提供專業人士及一般民眾更易閱讀的藥物資訊！

快速搜尋癌症藥物、用藥相關知識