AML & MDS: A New Era of Targeted Therapy & Immunotherapy

1L AML: Building on the wave of FDA-approvals for targeted therapy
- For 1L AML patients “unfit” for intensive therapy, data presented for newly FDA-approved agents include:
  - For BCL2 inhibitor venetoclax (Venclexta [Abbvie/Genentech]) + low-dose cytarabine (LDAC) or hypomethylating agents (HMAs), subgroup analyses show long survival for CR/CRI patients.\(^1\-^3\)
  - SMO inhibitor glasdegib (Daurismo [Pfizer]) + LDAC has comparable efficacy to venetoclax.\(^4\,^5\)
- For mutation-defined subsets of AML, FDA recently approved three targeted therapies:
  - IDH2 inhibitor enasidinib (Idhifa [Celgene/Agios]), IDH1 inhibitor ivosidenib (Tibsovo [Agios]), and FLT3/AXL inhibitor gilteritinib (Xospata [Astellas]), all approved for monotherapy use
- These agents can also be added to 7+3 for even better efficacy.\(^7\-^11\) However, the IDH inhibitors cause differentiation syndrome in up to 19% of patients, which may be life-threatening.\(^12\)
- For 1L AML patients “fit” for intensive chemo (7+3), promising novel agents include the following:
  - Anti-PD1 nivolumab (Opdivo [BMS]) +7+3 achieves 77% CR/CRI/CRp (n=44) and mOS 18.5 mo\(^14\)
  - IDO pathway inhibitor indoximod (NewLink) + high-dose cytarabine (HiDAC) achieves 77% CR/CRI (n=22).\(^14\)
  - E-selectin inhibitor uproleselan (Glycomimetics) +7+3 achieves 72% CR/CRI (n=25), mOS 12.5 mo\(^15\)
  - Aurora kinase A inhibitor alisertib (Takeda) +7+3 achieves 64% CR/CRI (n=39) and mOS 12.2 mo\(^16\)

Relapsed/refractory AML: A new wave of novel therapies
- New targeted therapies showing promising efficacy in r/r AML include:
  - Another FLT3 inhibitor, quizartinib (Daichi) with 48% CR/CRI/CRp (n=245) for FLT3-mutant AML.\(^17\)
  - Uproleselan (mentioned above for 1L) + salvage chemo (MEC) for 41% CR/CRI (n=54 at RP2D)\(^15\)
  - MDM2 inhibitor idasanutlin (Roche) combined with venetoclax for 33% CR/CRI/CRp (n=24)\(^18\)
- Immunotherapies are also emerging, though some are more advanced and promising than others:
  - Immune checkpoint inhibitors like nivo ± ipilimumab (Yervoy [BMS]) may sig. augment HMA efficacy.\(^19\)
  - Anti-CD33 bispecific (BiTE) AMG 330 (Amgen) and antibody-drug conjugate (ADC) IMGN779 (Immunogen) had single-agent CRs in early studies\(^20\,^21\), but it remains unclear whether they improve on standard of care
  - Anti-CD123 bispecific ( XmAb platform) XmAb14045 (Novartis/Kencor) and ADC IMGN632 (Immunogen) also had CRs but also have not yet shown differentiation.\(^22\,^23\). The CD123 bispecific (DART platform) flotetuzumab (MacroGenics) has only modest efficacy: 18.5% CR/CRI, 25.9% ORR, median DOR ~3 mo\(^24\)
  - CAR-T therapies are still in exploratory stages in AML. For example: CLL1-CD33 cCAR [iCell Gene Ther.]\(^25\), CYAD-01 [Celyad] targeting NKG2D\(^26\), and CAR-Ts targeting FLT3\(^27\) and CD123.\(^28\)

MDS: Making waves of its own
- Higher-risk MDS may soon be treated with novel agents, including mechanisms distinct from those in AML:
  - RAS inhibitor rigosertib (Onconova) + azacitidine, which achieves 77% CR or marrow CR (n=13) in HMA-naïve patients, and 38% CR/PR/mCR (n=24) in HMA-refractory patients.\(^29\)
  - XPO inhibitor selinexor (Karyopharm) monotherapy has 32% mCR (n=19) in HMA-refractory patients.\(^30\)
- Immune checkpoint inhibitors may also become options in higher-risk MDS. For example:
  - Nivo + aza achieved 65% CR/mCR (n=20) and mOS 11.8 mo in 1L (HMA-naïve) treatment.\(^31\)
  - Ipi monotherapy achieved 20% mCR (n=20) and mOS 8.5 mo in HMA-refractory patients.\(^31\)
  - Pembrolizumab (Keytruda [Merck]) + aza seems to have similar efficacy in a small study.\(^32\)
  - However, atezolizumab (Tecentriq [Roche]) + aza had little efficacy and increased mortality.\(^33\)
- Anemia in lower-risk MDS may also soon be treated with novel agents including:
  - TGFβ superfamily inhibitor luspatercept (Celgene/Acceleron) achieved ~38% RBC transfusion-independence lasting ≥8 weeks (n=153).\(^34\)
  - Pembrolizumab + reduced transfusion burden in β-thalassemia.\(^35\)
  - TERT inhibitor metelstat (Geron) had similar efficacy, ~37% RBC-TI ≥8 wks, but in an early study (n=38).\(^36\)
Multiple Myeloma: Expansion and Innovation

Daratumumab extends its reach in front-line standard of care for frail, elderly patients
Supported by a phase 3 trial of anti-CD38 daratumumab (Darzalex [Janssen]) + lenalidomide (Revlimid [Celgene]) + dexamethasone vs len + dex for newly diagnosed MM patients ineligible for high-dose chemo or transplant:
- With a median follow-up of 28 months, dara + len + dex achieved 3-fold higher MRD negativity (24% vs 7%) and substantially improved PFS (71% vs 56% at 30 months) compared to len + dex alone
- These results likely support label expansion to include the len + dex combination; daratumumab was previously approved for 1L transplant-ineligible patients in combination with bortezomib + melphalan + prednisone (VMP), though VMP is primarily a regimen used in Europe

A flurry of CAR-Ts readouts, though clear differentiation and signs of lasting durability still awaited
Supported by phase 1 or 1/2 trials, several players reported the latest BCMA-targeted CAR-T data in r/r MM:
- Across several anti-BCMA CAR-T programs, late-line multiple myeloma patients have high response rates (ORR ~82-100%; ≥VGPR ~50-80%)3-10. The key question is durability, however, and follow-up is still early
- Some of the CAR-T programs in China3-6 have reported mPFS ranges from ~10 mo. (CAR-T [Huzhong U])3 to ~15 mo. (CAR-T [HRAIN Biotech]; LCAR-B38M [Nanjing Legend, J&J])4,5. These reports show that the current generation of CAR-T improves survival in late-line MM, but does not cure the majority of patients
- For some agents being studied in the US (P-BCMA-101 [Poseida]; JCARH125 [Juno, Celgene], bb21217 [bluebird bio])7,8,10,11, the focus is on construct and process optimization, to maximize the level of T-central memory cells to improve durability. For example, Juno attempts to do this by using a fixed 1:1 ratio of CD4+:CD8+ cells10, while bluebird is treating its CAR-T cells ex vivo with a PI3K inhibitor, bb007

Non-cell therapy approaches also compete in R/R multiple myeloma
- The anti-BCMA BiTE AMG 420 [Amgen] is promising in 3L+ multiple myeloma with 70% ORR,12 though the requirement for continuous infusion presents a significant logistical hurdle
- The oral XPO1 inhibitor selinexor [Karyopharm] + dexamethasone looks promising in very late-line patients with good efficacy (26% ORR, penta-exposed and triple class refractory)13 and potential ease of use

Non-Hodgkin Lymphomas: Durability Through Novel Immunotherapy

In refractory B-NHL, CD19-targeted CAR-T therapy shows lasting durability among responders
Supported by the 2-year assessment of the ZUMA-1 trial of Axicabtagene ciloleucel (Yescarta) [Kite/Gilead]:
- Previously reported trial data showed 83% ORR, with a drop off in efficacy leading to only 5.9 mo mPFS1
- However, among the ~40% of patients still showing a response at 12 mo., nearly all of these (93%) continued to respond at 24 mo.2,3
- OS has not yet been reached, and survival curves show a striking plateau after the 2-year mark2,3

ADCs and bispecifics also compete in the CAR-T space, with good efficacy and likely lower price
ADCs and bispecifics aim to find their place in B-cell lymphoma, supported by phase 1/2 data for polatuzumab vedotin [Roche] and phase 1 data for competing anti-CD20 x anti-CD3 bispecific antibodies – REGN1979 [Regeneron] and mosunetuzumab [Roche]:
- The CD79b-targeted ADC polatuzumab vedotin + bendamustine + rituximab (Rituxan) shows 41% ORR in R/R DLBCL; although mPFS is only 5.4 mo, responders have a median duration of response of 28.4 mo4
- As monotherapy, the bispecific REGN1979 looks especially promising in r/r follicular lymphoma (100% ORR in n=10 patients), albeit less efficacious in DLBCL (42% ORR in n=19 patients)5
- Compared to REGN1979, mosunetuzumab showed lower ORR (40% overall, 61% in follicular lymphoma), though noted durable remissions in some responders lasting >2 years6
CLL: Treatment Grows More Powerful and Sophisticated

Combining multiple targeted agents may become the new standard for first-line treatment

- iFCG is the quadruple combination of BTK inhibitor ibrutinib (Imbruvica [AbbVie/Janssen]), chemo agents fludarabine and cyclophosphamide, and anti-CD20 obinutuzumab (Gazyva [Genentech]). For IGTV-mutant, 1L CLL, iFCG produced 100% ORR (n=44) and a CR/CRi rate that deepened to 81% after 12 mo. With 22 mo. median follow-up, no patients had CLL progression, though 1 patient died and 2 discontinued due to AEs.

- Ibrutinib + venetoclax in 1L high-risk CLL had 100% ORR, 96% CR/CRi by 18 mo. (n=26). With 14.8 mo. median follow-up, no patients had CLL progression, though 1 had Richter transformation, and 1 died due to an infection. The regimen was also active in r/r CLL, and adding obinutuzumab also had excellent efficacy.

Multiple strategies to minimize toxicities

- Ibrutinib + rituximab (Rituxan [Genentech]) has better efficacy and safety/tolerability than fludarabine + cyclophosphamide + rituximab (FCR), but ibrutinib monotherapy may be as efficacious and even better tolerated. However, ibrutinib with a different anti-CD20, obinutuzumab, may produce deeper responses.

- Acalabrutinib (Calquence [AstraZeneca]): Although ibrutinib is less toxic than chemo, it does have AEs such as atrial fibrillation (AF). A newer BTKi acalabrutinib has improved safety/tolerability with little to no AF.

- Limiting duration of treatment on a fixed basis or based on MRD is viable for venetoclax + rituximab.

Diverse novel approaches for r/r CLL

- Promising examples include lenalidomide + rituximab, anti-PD1 pembrol + anti-CD20 ubituximab [Targovax Therapeutics] + P3Kδ inhib. umbralisib [TG], and anti-CD19 CAR-T CTL119 [Novartis] + ibrutinib.

Non-malignant Hematology: Emergence of Disease-modifying Therapies

Sickle Cell Disease is entering a new era of targeted therapy and gene therapy

- New targeted therapies that may provide significant clinical benefit include the following:
  - Hemoglobin (Hb) stabilizer voxelotor [GBT] (± hydroxyurea) increased serum Hb levels in the majority of patients and improved symptom burden evaluated by patient diaries. It is now under FDA review.
  - Anti-P-selectin crizanlizumab [Novartis] reduced vaso-occlusive crises (VOC) by more than half vs placebo.
  - The leader in gene therapy in SCD, LentiGlobin [bluebird bio], wrestles with key issues of gene therapy:
    - Transgene expression sufficient for efficacy: Initial cohorts had low expression, but an improved manufacturing process now yields higher expression, eliminates VOC, and normalizes hemolysis markers.
    - Durability of response: The latest cohort shows benefits for >9 months, but longer follow-up is awaited.
    - Long-term safety: A patient treated 3 years ago has developed myelodysplasia. It may be due to the chemo conditioning regimen rather than the lentivirus, but still suggests a need for process improvement.
  - Whereas LentiGlobin directly targets the HbB gene, other gene therapies with promising early efficacy target fetal Hb (RVT-1801 [Arvant, a Roivant company]) or BCL11A (a fetal Hb regulator).

Gene therapy is progressing in hemophilia & other hematologic rare diseases

- Hem B gene therapies fidanacogene elaparvovec (aka PF-06838435 or SPK-9001) [Pfizer/Spark] and AMT-061 [UniQure] are the leaders; both use the high-expressing Padua allele of Factor IX (FIX), and both yield FIX levels >30% of normal, nearly eliminating bleeding events. However, measurement of FIX-Padua may be highly assay-dependent, complicating comparisons. Long-term durability remains unknown, but seems promising so far. Another gene therapy, scAAV8-LP1-hFIXcdn [UCL/KDHT/St Jude] can last >8 years.

- Hem A gene therapy SPK-8011 [Spark] had initial efficacy in 12/12 patients, but immune responses to the AAV vector eliminated transgene expression in 2 patients. This may be a key limitation of the technology.

- Gene therapies for β-thalassemia, Fanconi anemia, and Pearson syndrome also show early promise.