Clarion Perspectives from the

ASH 2018 Annual Meeting

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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[1–5]
  - SMO inhibitor **glasdegib (Daurismo [Pfizer])** + LDAC has comparable efficacy to venetoclax[1,6]
- For mutation-defined subsets of AML, FDA recently approved three targeted therapies:
  - IDH2 inhibitor **enasidenib (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[13]
  - 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 [Daiichi]** 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/Xencor]** 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=16) 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]. Luspatercept also reduced transfusion burden in β-thalassemia[35]
  - TERT inhibitor **imetelstat [Geron]** had similar efficacy, ~37% RBC-TI ≥8 wks, but in an early study (n=38)[36]

1) ASH-FDA Joint Session on New Approvals; 2) ASH 2018 #284; 3) #285; 4) #286; 5) #1424; 6) #1429; 7) #287; 8) #561; 9) #560; 10) #564; 11) #2736; 12) #288; 13) #905; 14) #332; 15) #331; 16) #766; 17) #563; 18) #767; 19) #906; 20) #25; 21) #26; 22) #763; 23) #27; 24) #764; 25) #901; 26) #902; 27) #903; 28) #964; 29) #230; 30) #233; 31) #465; 32) #464; 33) #466; 34) #1; 35) #163; 36) #463

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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[1]
- 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[2]

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 China[3–6] have reported mPFS ranges from ~10 mo. (**CAR-T [Huazhong 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 stem cells to improve durability. For example, Juno attempts to do this by using a fixed 1:1 ratio of $CD4^+$:$CD8^+$ cells[10], while bluebird is treating its CAR-T cells ex vivo with a PI3K inhibitor, bb007[11]

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

1) ASH 2018 #LBA-2; 2) OncLive 4 Dec '18, "Daratumumab Plus Rd New Frontline Standard in Transplant-Ineligible Myeloma"; 3) ASH 2018 #1013; 4) #956; 5) #955; 6) #960; 7) #1012; 8) #957; 9) #959; 10) #1011; 11) #488; 12) #1010; 13) #598

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 mPFS[1]
- 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 mark[2,3]

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]*** *monotherapy 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 mo[4]
- 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 years[6]

1) OncLive 4 Dec '18, "Axi-Cel Efficacy Persists at 2-Year Assessment for Large B-Cell Lymphoma"; 2) ASH 2018 #2967; 3) Locke FL, et al. [published online ahead of print, December 2, 2018]. Lancet Oncol http://dx.doi.org/10.1016/S1470-2045(18)30864-7; 4) ASH 2018 #1683; 5) ASH 2018 #1690; 6) ASH 2018 #399

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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 *IGHV*-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[1]
- **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[2]. The regimen was also active in r/r CLL[3], and adding obinutuzumab also had excellent efficacy[4]

Multiple strategies to minimize toxicities

- **Ibrutinib + rituximab (Rituxan [Genentech])** has better efficacy and safety/tolerability than fludarabine + cyclophosphamide + rituximab (FCR)[5], but **ibrutinib monotherapy** may be as efficacious and even better tolerated[6]. However, ibrutinib with a different anti-CD20, **obinutuzumab**, may produce deeper responses[7]
- **Acalabrutinib (Calquence [AstraZeneca])**: Although ibrutinib is less toxic than chemo, it does have AEs such as atrial fibrillation (AF)[8,9]. A newer BTKi acalabrutinib has improved safety/tolerability with little to no AF[10]
- **Limiting duration of treatment** on a fixed basis or based on MRD is viable for venetoclax + rituximab[11–13]

Diverse novel approaches for r/r CLL

- Promising examples include **lenalidomide** + rituximab[14], anti-PD1 **pembro** + anti-CD20 **ublituximab [TG Therapeutics]** + PI3Kδ inhib. **umbralisib [TG]**[15], and anti-CD19 CAR-T **CTL119 [Novartis]** + ibrutinib[16]

1) ASH 2018 #185; 2) #186; 3) #182; 4) #693; 5) #LBA-4; 6) #6; 7) #181; 8) #1869; 9) #3118; 10) #692; 11) #183; 12) #184; 13) #695; 14) #295; 15) #297; 16) #298

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[1]. It is now under FDA review
  - Anti-P-selectin **crizanlizumab [Novartis]** reduced vaso-occlusive crises (VOC) by more than half vs placebo[2]
- 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[3], 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[4]
  - **Long-term safety:** A patient treated 3 years ago has developed myelodysplasia[5]. It may be due to the chemo conditioning regimen rather than the lentivirus, but still suggests a need for process improvement[6]
- Whereas LentiGlobin directly targets the HbB gene, other gene therapies with promising early efficacy target fetal Hb (**RVT-1801 [Aruvant, a Roivant company]**)[7] or **BCL11A** (a fetal Hb regulator)[8,9]

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[10]. However, measurement of FIX-Padua may be highly assay-dependent, complicating comparisons[11]. Long-term durability remains unknown, but seems promising so far. Another gene therapy, **scAAV8-LP1-hFIXco** [UCL/KDHT/St Jude] can last >8 years[12]
- 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[13]. This may be a key limitation of the technology
- Gene therapies for β-thalassemia[14,15], Fanconi anemia[16], and Pearson syndrome[17] also show early promise

1) ASH 2018 #505; 2) #1082; 3) #1080; 4) #1026; 5); bluebird bio press release 2018/12/01; 6) Feuerstein, STAT News 2018/12/02; 7) #1021; 8) #1023; 9) Orkin & Bauer 2019 Annu Rev Med 70; 10) FierceBiotech 11/15/2018; 11) ASH 2018 #2198; 12) #491; 13) #487; 14) #167; 15) #1025; 16) #1024; 17) #1022

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