Clarion Perspectives from the

ASH Annual Meeting 2019

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Multiple Myeloma: A Time of Transformation

BCMA-targeted regimens are poised to transform treatment of late-line MM

CAR-T has excellent efficacy in heavily pretreated patients; bispecifics may be similarly strong.

Therapy	Company	Modality	Trial	Median (range) prior lines	Efficacy (≥VGPR = very good partial response or better)
JNJ-68284528/ LCAR-B38M	**Janssen/ Nanjing Legend**	CAR-T (auto)	CARTITUDE-1	5 (3–18)	≥VGPR **86%**, CR 69% (n=29)[1,2]
			LEGEND-2 (China)	3 (1–9)	≥VGPR **77%**, CR 74% (n=57), mPFS=19.9 mo[3]
bb21217	**Celgene/bluebird**	CAR-T (auto)	CRB-402	6 (3–17)	≥VGPR **52%**, CR 15% (n=33)[4]
CT103A	**IASO Biotherapeutics**	CAR-T (auto)	ChiCTR1800018137 (China)	4 (3–6)	≥VGPR **88%**, CR 71% (n=17)[5]
CC-93269	**BMS/Celgene**	bispecific (xCD3)	CC-93269-MM-001	5 (3–13)	≥VGPR **30%**, CR 17% total (n=30) ≥VGPR **78%**, CR 44% at highest dose (n=9)[6]
Belantamab mafodotin	**GSK**	ADC	DREAMM-2, 2.5 mg/kg	7 (3–21)	≥VGPR **19%** (n=97)[7]
			DREAMM-2, 3.4 mg/kg	6 (3–21)	≥VGPR **20%** (n=99)[7]

- The impressive efficacy of BCMA CAR-T can be achieved with <10% rates of grade 3+ CRS and neurotoxicity[1-4], though the turnaround times and high cost of CAR-T manufacturing make bispecifics a compelling alternative. Other BCMA bi-specifics include **REGN5458 [Regeneron]**[8] and **PF-06863135 [Pfizer]**[9]
- Dual-antigen CAR-Ts include CD38xBCMA CAR-T [Cellyan][10] and CD19 CAR-T/BCMA CAR-T combination [Unicar][11]

Anti-CD38 daratumumab (Darzalex) [Janssen] combinations continue to raise the bar in NDMM

- In newly diagnosed MM (NDMM) eligible for transplant, dara + bortezomib + thalidomide + dexamethasone is approved for use with HSCT[12]. The GRIFFIN study of dara + **lenalidomide (Revlimid) [BMS/Celgene]** + **bortezomib (Velcade) [Takeda]** + dex (**D-RVd**) and HSCT showed 90.9% ≥VGPR, 51.5% CR post-consolidation (n=99), and responses continued to deepen over time[13]. The MASTER study of dara + **carfilzomib (Kyprolis) [Amgen/Onyx]** + len + dex (**Dara-KRd**) and HSCT was even more compelling: 100% ≥VGPR, 95% stringent CR post-consolidation (n=42)[14]. A similar regimen (w-KRd-D) produced 97% ≥VGPR in the absence of transplant (n=35 evaluable)[15]
- In NDMM ineligible for transplant, dara + bortezomib + melphalan + prednisone (**D-VMP**) was approved based on the ALCYONE trial[12]. An update of ALCYONE showed mPFS ~36 mo. and 42-mo. OS ~75%[16]
- Other dara frontline combinations with powerful efficacy include the IMiD-free Dara + cyclophosphamide + bortezomib + dex (**Dara + CyBorD**)[17] and Dara + **ixazomib (Ninlaro) [Takeda]** + len + dex (**Dara-IRd**)[18]
- In r/r MM, dara is already approved in combinations with bortezomib + dex (**D-Vd**), **pomalidomide (Pomalyst) [BMS/Celgene]** + dex (**Dara + Pd**), and as monotherapy[12]. A new combination, dara + carfilzomib + dex (**KdD**), reported significant improvement over Kd alone: ORR 84.3% vs 74.7%, CR 28.5% vs 10.4%, PFS HR = 0.63[19]

Selinexor combinations may also have a role to play

- XPO1 inhibitor **selinexor (Xpovio) [Karyopharm]** was recently approved in combination with dex in late-line MM[20] and shows activity in various combinations including pom + dex[21] , carfilzomib + dex[22], and len + dex[23]. Although its efficacy is not as dramatic as BCMA therapies or dara, it is active post-dara[20] and post-CAR-T[24]

MM therapies are expanding to related malignancies

- **High-risk smoldering myeloma**: ixazomib + len + dex has PFS of 100% (n=48) with median 15-mo follow-up[25]
- **Systemic AL amyloidosis**: ixazomib + dex had mPFS of 18.0-20.1 mo. vs 11.0-16.7 mo. for the physician's choice control (dex, IMiD+dex, or chemo+dex) in the ph 3 TOURMALINE study[26]
- **Primary plasma cell leukemia**: carfilzomib + len + dex produced VGPR or better in 80% of patients[27]

1) ASH 2019 #577; 2) #928; 3) #579; 4) #927, data pooled across all 3 dose levels; 5) #582; 6) #143; 7) Lonial 2019 Lancet Oncol https://doi.org/10.1016/S1470-2045(19)30788-0; 8) #3176; 9) #1869; 10) #930; 11) #578; 12) Darzalex product label; 13) #691; 14) #860; 15) #862; 16) #859; 17) #863; 18) #864; 19) #LBA-6; 20) Xpovio product label; 21) #141; 22) #3157; 23) #3165; 24) #1854; 25) #580; 26) #139; 27) #693

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AML & MDS: Expansion and Innovation

Venetoclax is poised to enter new settings

- BCL-2 inhibitor **venetoclax (Venclexta) [Abbvie/Genentech]** is already approved in combination with hypomethylating agents (HMAs) azacitidine or decitabine, or with low-dose cytarabine for 1L AML ineligible ("unfit") for intensive chemotherapy[1] and is looking to expand into new AML/MDS indications:
  - **1L "fit" AML**: Venetoclax + intensive chemo (e.g. 7+3, FLAG-IDA, Hi-DAC +IDA) demonstrated CR/CRi ~70-90% with manageable tolerability[2,3,4]
  - **1L high-risk (HR) MDS**: Venetoclax + AZA results in CR/mCR = 77% (n=57) with a manageable safety profile at 400mg venetoclax dosing[5]
- However, there remains room for improvement even in venetoclax's original indication of 1L unfit AML: FLT3 and TP53 mutations are associated with poorer outcomes[6,7], and post-VEN, the mOS is only 2.4 months[8]

Agents targeting leukemic stem cells (LSCs) stir excitement

- Anti-CD70 **cusatuzumab [argenx/Janssen]** + AZA achieved CR/CRi = 84% (n=12) 1L unfit AML, while eliminating CD70-expressing LSCs in patient samples[9]
- Anti-CD47 **magrolimab [FortySeven]** + AZA achieved CR/CRi=55% (n=22) in 1L unfit AML (with notable efficacy in TP53-mut pts), and CR= 50% (n=24) in HR-MDS; eliminated putative LSCs in 40% of responding pts[10]
- Although TIM3 is best known as a T cell immune checkpoint, it may also play a role in LSC self-renewal and activation. Anti-TIM3 **MBG453 [Novartis]** + HMA achieved CR/CRi =29% (n=22) in 1L unfit AML and CR/mCR = 47% (n=19) in HR-MDS[11]. A separate study suggests TIM3+ LSC level may predict relapse after allo-SCT in AML[12]

FLT3 and IDH mutation-targeted therapies continue to emerge and move earlier

- FLT3 inhibitor **crenolanib [Arog]** + chemo achieved CR =85% (n=27) in younger patients with 1L AML, mOS not reached at 29 mo median follow up[13]
- IDH2 inhibitor **enasidenib (IDHIFA [Agios/Celgene])** + AZA achieved CR=53% (n=68) vs. 12% with AZA alone in 1L unfit AML[14]
- IDH1 inhibitor **olutasidenib [Forma]**+ AZA demonstrated CR = 54% (n=46) in 1L unfit and R/R AML[15], and CR= 55% (n=17) in HR-MDS patients[16]

Immunotherapy development continues in r/r AML

- CD123xCD3 bispecific (DART platform) **flotetuzumab [Macrogenics]** achieved CR/CRi = 20% (n=30) in primary refractory AML[17]. Anti-CD123 ADC **IMGN632 [Immunogen]** achieved similar efficacy, CR/CRi =16% (n=66) in R/R AML, but easier dosing and safety (no CRS/neurotox) may offer an advantage over the bispecific approach[18]
- NKG2D CAR-T **CYAD-01 [Celyad]** with preconditioning chemo reported ORR=0% (n=9) in r/r AML and MDS[19] which surprisingly is much worse than a previous study of CYAD-01 without the preconditioning[20]

Oral HMAs poised to join or displace the standard IV agents

- 1L Fit AML: Oral azacitidine **CC-486 [BMS/Celgene]** likely to emerge as post-chemo maintenance SoC after reporting mOS = 22.9 mo (n=238) vs. 16 mo on placebo in older AML patients[21]
- Oral cedazuridine and decitabine fixed-dose combination **ASTX727 [Otsuka/Astex]** proved pharmacokinetic equivalence to IV decitabine in HR-MDS patients, though clinical responses from phase 3 are still pending. Astex plans to file an NDA by year-end 2019[22,23]

Addressing unmet needs across MDS risk categories

- Mutant p53 reactivating compound **APR-46 [Aprea]** reported CR=61% (n=33) in TP53-mut HR-MDS[24]
- NEDD8 inhibitor **pevonedistat [Takeda Oncology]** + AZA achieved CR/CRi = 23.8%(n=23) in HMA-failed MDS[25]
- Lower-risk MDS patients could soon achieve RBC transfusion independence with agents like HIF stabilizer **roxadustat [Astellas/FibroGen]**[26], TGFβ superfamily inhibitor **luspatercept [BMS/Celgene/Acceleron]**[27,28], and telomerase inhibitor **imetelstat [Geron]**[29]

1) Venclexta product label; 2) ASH 2019 #3908; 3) #176; 4) #178; 5) #568; 6) #462; 7) #546; 8) 738; 9) #234; 10) #569; 11) #570; 12) #2702; 13) #1326; 14) #643; 15) #231; 16) #674; 17) #733; 18) #734; 19) #3844; 20) ASH 2018 #902; 21) ASH 2019 #LBA-3; 22) #846; 23) Astex website accessed Dec 18, 2019; 24) #676; 25) #4236; 26) #843; 27) #4243; 28) #841; 29) #4248

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NHL & ALL: New Data and New Challengers for CD19 CAR-T

Autologous CD19 CAR-T therapies continue to show curative efficacy in subsets of DLBCL and ALL

- **Axicabtagene ciloleucel (Yescarta) [Gilead/Kite]** may have a survival plateau for DLBCL patients in the ZUMA-1 trial: 3-year OS = 47%[1,2]
- Real-world data for axi-cel in DLBCL and **tisagenlecleucel (Kymriah) [Novartis]** in DLBCL and ALL thus far match their clinical trial efficacy; tisa-cel real-world safety seems much better, reflecting better AE management[3,4,5,6]
- Latecomer **lisocabtagene maraleucel [BMS/Celgene/Juno]** shows DLBCL efficacy similar to Yescarta/Kymriah—ORR= 73%, and a possible OS plateau at ~45% (median follow-up ~18 mo)—with only 2% CRS which may increase outpatient use[7,8,9]
- Another latecomer, **AUTO1 [Autolus]** shows high MRD-negative response rates for both pediatric and adult r/r ALL with virtually no grade 3+ CRS, though durability remains to be proven[10,11]

Antibody-based challengers to CAR-T show compelling response rates

While cures have not yet been shown, off-the-shelf delivery and likely lower cost make these important competitors

- Anti-CD19 Ab **MOR208 (tafasitamab) [Morphosys]** + lenalidomide has ORR = 60% in r/r DLBCL patients with 12-mo OS = 87% for 2L patients[12]
- Anti-CD19 BiTE **blinatumomab (Blincyto) [Amgen]** has 2-yr PFS of 59% and 2-yr OS of 79% (n=105) in 2L ALL[13]. Blina combined with TKI **dasatinib (Sprycel) [BMS]** produced ~14-mo DFS of 90% in 1L adult Ph+ ALL[14]
- CD20xCD3 bispecific **mosunetuzumab [Roche]** has ~19% CR in aggressive NHL (n=124) and ~43% CR in indolent NHL (n=67); CRS and neurotox rates were comparable to current CAR-T therapies[15]. Other CD20 bispecifics with promising early data include **RG6026 [Roche]**[16], **REGN1979 [Regeneron]**[17,18] and **GEN3013 [Genmab]**[19]
- Anti-CD22 ADC **inotuzumab ozogamicin (Besponsa) [Pfizer]** + chemo regimen CVP produced 61% CR/CRi in CD22+ r/r ALL[20]
- Anti-CD79 ADC **Polivy [Genentech]** + bendamustine + rituximab (BR) had confirmed ORR = 47.5%, mOS = 12.4 mo. in transplant ineligible r/r DLBCL (n=40)[21]; Polivy + obinutuzumab + len induced ORR=76% in r/r FL[22]

Allogeneic CAR cell therapies continue to make progress

- Donor-derived CD19 CAR-T produced CR in 12 of 13 r/r ALL patients; 6/13 were disease-free at median 11 mo. follow-up in a UCL study[23]
- Donor-derived CD19 CAR-CIK (cytokine-induced killer) cell therapy produced CR/CRi in 8 of 13 r/r ALL patients[24]
- CAR-NK cell therapy **FT596 [Fate]** + rituximab induced deeper responses and prevented antigen escape compared to CAR-T in preclinical lymphoma cell lines; in-human trials are slated to begin Q1 2020[25]

CLL: The BTK battle

BTK inhibitor grows increasingly competitive

- Real world data shows both the dominance of **ibrutinib (Imbruvica) [Janssen/Abbvie/Pharmacyclics]** and the remaining need: 86% of CLL patients receive BTK inhibitor in first line, but ~40% do not respond[1]
- 2nd generation BTK inhibitor **acalabrutinib (Calquence) [AstraZeneca]** ± obinutuzumab demonstrated superiority to obinutuzumab + chlorambucil in treatment-naïve CLL (ORR 94% vs. 79%) in treatment-naïve CLL[2,3], supporting FDA approval for this indication[4]
- BTK inhibitor **zanubrutinib (Brukinsa) [BeiGene]** achieved ORR = 100% (n=22) and 24-mo PFS =95% in treatment-naïve CLL, and ORR=95% (n=101) and 24-mo PFS = 91% in R/R CLL[5]
- Earlier-stage competitors include reversible BTK inhibitors potentially less sensitive to resistance mechanisms: **ARQ531 [ArQule/Merck]** (ORR=89% in R/R CLL C481S-mut; n=9)[6] and **LOXO-305 [Eli Lilly]** (ORR=50% in R/R CLL C481S-mut; n=2)[7]. A BTK degrader **NRX0492 [Nurix]** shows promising preclinical data[8]
- Beyond BTK, other approaches continue to be explored in CLL, such as the combination of anti-CD20 **ublituximab** + PI3Kδ/CK1ε inhibitor **umbralisib [TG Therapeutics]** + venetoclax, which achieved ORR=100% (n=13) in R/R CLL[9]

1) ASH 2019 #203; 2) #243; 3) 764; 4) #1599; 5) #766; 6) #2619; 7) #593; 8) #241; 9) #2868; 10) #225; 11) #226; 12) #1582; 13) #LBA-1; 14) #740; 15) #006; 16) #1584; 17) #762; 18) #4007; 19) #758; 20) #741; 21) #4081; 22) #126; 23) #776; 24) #200; 25) #301

1) ASH 2019 #1756; 2) #031; 3) #032; 4) press release Nov 21, 2019; 5) #500; 6) # 4298; 7) #501; 8) #174; 9) #360

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Genetic Blood Disorders: Start of a New Era

Sickle cell disease and β-thalassemia receive new treatment options

*History was made in 2019 with the approval of two novel therapies for SCD—anti-P-selectin antibody **crizanlizumab (Adakveo) [Novartis]** and hemoglobin S polymerization inhibitor **voxelotor (Oxbryta) [Global Blood Therapeutics]**[1]—as well as a novel therapy for transfusion-dependent β-thalassemia, a TGF superfamily inhibitor, **luspatercept (Reblozyl) [BMS/Celgene/Acceleron]**. However, the emergence of new treatments for hemoglobinopathies has only just begun. Other drugs in the pipeline with clinical data include:*

- Anti-IL-1β (anti-inflammatory agent) **canakinumab (Ilaris) [Novartis]** outperformed placebo in improving several patient-reported metrics of vaso-occlusive crises (VOC) vs baseline, including daily pain, fatigue, and absences from school/work, as well as objective metrics such as hospitalization (median 0 vs 7.6 days/year)[2]
- Oral **arginine** also surpassed placebo, reducing analgesic use by ~half, accelerating pain resolution, and reducing average hospital stays by an average of 46 hours in a Nigerian study[3]
- Pyruvate kinase receptor (PKR) inhibitor **mitapivat (AG-348) [Agios]** produced a hemoglobin increase of ≥1.0 g/dL in 7 of 8 patients evaluable with β-thalassemia[4]. Mitapivat is also showing promise for PK deficiency[5].
- Other SCD therapies without clinical efficacy data yet include PKR inhibitor **FT-4202 [Forma]**[6] and endothelin receptor ET_A antagonist **ambrisentan (Letairis) [Gilead]**[7]
- Gene therapy is also in active development for SCD and β-thalassemia (reviewed by Breda et al.[8]), for example by silencing the *BCL11A* gene to induce fetal hemoglobin expression; this approach has shown preliminary efficacy in small numbers of patients[9,10]

Hemophilia: the gene therapy race continues

- Hemophilia B patients given recombinant human factor IX (hFIX) gene therapy **fidanacogene elaparvovec [Pfizer/Spark]** had a dramatically improved annualized bleeding rate (ABR) in the 52 weeks post-treatment vs pre-treatment: 0.4 vs 8.9 events/year (n=15)[11]. Chief rival **etranacogene dezaparvovec (AMT-061) [uniQure]**, which uses the more highly active Padua variant of hFIX reported similar results: 0 bleeding events in the 52 weeks post-treatment (n=3)[12]. Both therapies use AAV as the delivery vector, and both are in phase 3 trials; uniQure's trial HOPE-B is already fully enrolled[13,14].
- The key question for these gene therapies remains durability, given that both would likely require travel to specialist centers and very high price points; only a highly durable (potentially curative) therapy would be viable given other treatment options (e.g., factor IX replacement). Evidence is still emerging, but an older-generation therapy, **AMT-060 [uniQure]** reported stable hFIX expression for 10/10 patients treated with 4 years of follow-up[15]. Last year, another older generation therapy reported sustained hFIX expression after ~8 years of followup[16]
- Hemophilia A gene therapy is further behind, but long-term durability may be feasible: stable recombinant factor VIII expression has been shown for up to 10 years in a canine model of Hem A[17]

Lentiviral gene therapies show promise for other non-malignant blood disorders

- An ex vivo-engineered (lentiviral) hematopoietic stem cell therapy **[Orchard Therapeutics]** for Hurler disease, a lysosomal storage disorder (also known as mucopolysaccharidosis type 1). Preliminary data show amelioration of the metabolic and developmental defects of the disease[18]
- Another lentiviral gene therapy **RP-L102 [Rocket Pharmaceuticals]** for Fanconi anemia showed safety and early signs of efficacy in 2 patients: both showed stable or increased blood counts for at least 6 months[19]
- **MB-107 [Mustang Bio]** has shown promising early data for treating for X-SCID, a genetic immunodeficiency. All 9 infants treated with a follow-up of >3 months showed reconstitution of immune function[20]. Older children and young adult patients are more challenging to treat, but a modified vector may provide enhanced transduction[21]

1) FDA; 2) ASH 2019 #615; 3) #613; 4) #2249; 5) #3512; 6) #616; 7) #617; 8) Breda 2019 Mol Diagn Ther 23:173; 9) #LBA-5; 10) #974; 11) #3347; 12) #3348; 13) ClinicalTrials.gov; 14) uniQure press release Dec 9, 2019; 15) #2059; 16) ASH 2018 #491; 17) ASH 2019 #611; 18) #607; 19) #3350; 20) #2058; 21) #608

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