SUCCESSFUL TREATMENT OF CD19+ MIXED PHENOTYPE ACUTE LEUKEMIA WITH BREXUCABTAGENE AUTOLEUCEL (BREXU-CEL) PLUS TYROSINE KINASE INHIBITOR

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INTRODUCTION

- Mixed phenotype acute leukemia (MPAL) represents a rare subtype of acute leukemia characterized by either two distinct blast populations of different lineages (bilineal) or a single blast population with immunophenotypic features of both myeloid and lymphoid lineages (biphenotypic).[1-3]
- Due to its rarity and phenotypic heterogeneity, there is no standard approach to MPAL treatment, and outcomes are generally poor, with allogeneic stem cell transplant being the only curative option.

CASE

- A 72-year-old female patient presented with Philadelphia chromosome positive (Ph+) bilineal MPAL in whom both leukemic lineages were CD19-positive by flow cytometry. Unfortunately, she was ineligible for allogeneic stem cell transplant due to chronic kidney disease (CKD; creatinine ~2.5 mg/dL).
- She underwent induction therapy with a tyrosine kinase inhibitor (TKI), cyclophosphamide, vincristine, and dexamethasone for two cycles as well as intrathecal methotrexate and cytarabine, resulting in complete remission (CR) with detectable BCR::ABL1 transcripts by qPCR (0.02%) in bone marrow (BM). In an effort to eliminate minimal residual disease, the patient received two cycles of blinatumomab with a TKI, which was complicated by grade 1 cytokine release syndrome (CRS) without improvement in BCR::ABL1 (post-treatment BM qPCR 0.06%).
- Due to ineligibility for allogeneic stem cell transplant and CD19 positivity of both leukemic lineages, she was treated with Brexucabtagene autolucel (Tecartus), a commercial CD19-directed CAR T-cell therapy. Tyrosine kinase inhibitor therapy was held from lymphodepletion to day +90. Neutrophil engraftment occurred on day +13 and platelets never dropped below 88 × 10^9/L. Treatment was complicated by grade 1 ICANS immune effector cell-associated neurotoxicity syndrome (handwriting) treated with dexamethasone and grade 2 CRS (fever and hypotension) treated with tocilizumab.
- At day +30, the patient remained in complete remission with a BCR::ABL1 in BM of 0.01%. Latest disease reassessment at day +180 showed BCR::ABL1 in BM of 0.02%. She remains on maintenance therapy with asciminib 200 mg daily.
- ***This represents first reported use of anti-CD19 CAR T-cell therapy for MPAL and supports its feasibility in CD19-positive MPAL patients who may not be candidates for allogeneic stem cell transplant.***

PATIENT DATA & CLINICAL COURSE

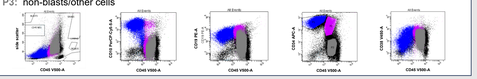
MPAL Diagnosis

CBC: WBC 32K, Hgb 7.1, plt 232, 30% circulating blasts

Bone marrow biopsy: > 95% cellular, 72% blasts
- *BCR::ABL1 qPCR:* p190 (43.55%), p210 negative
- *Myeloid NGS:* negative
- *FISH:* positive for gain of RUNX1T1 and deletion 16q22
- *Microarray:* loss of chromosome 7 (40% of cells)

Population	#Events	%Parent	%Total
All Events	100,000	#####	100.0
LYMPHS	0	0.0	0.0
CD45 NEG	29	0.0	0.0
MONOS	1	0.0	0.0
GRANS	10	0.0	0.0
BLASTS	0	0.0	0.0
P1	25,976	26.0	26.0
P2	13,099	13.1	13.1
P3	38,574	38.6	38.6

Flow cytometry (bone marrow):
- **P1 (28% blasts with B lineage):** CD34+CD10+CD13+**CD19+**CD22+TDT+MPO-
- **P2 (13% blasts with myeloid lineage):** CD34+CD13+CD33+CD117+**CD19+**CD22-CD10-TDT-MPO+
- P3: non-blasts/other cells



Blinatumomab Consolidation

- Blinatumomab is a bispecific T cell engager (BiTE) that binds to CD19 on B cells and CD3 on T cells
- Blinatumomab is approved for CD19+ B-ALL with positive minimal residual disease, often as a bridge to stem cell transplant (SCT)
- Case reports describe successful MRD elimination with blinatumomab in CD19+ B/myeloid and CD19+ B/T-type MPAL[5,6,7]

Allogeneic SCT Evaluation

- *Comorbidities:* age > 40, diabetes, anxiety, CKD (baseline Cr ~1.5, Cr at presentation 2.3, Cr thereafter ~2-3; eGFR ~15-25)
- eGFR < 45 is independently associated with increased NRM, decreased OS, and increased renal failure after allo SCT[9]
- *Kidney biopsy:* severe interstitial fibrosis and glomerulosclerosis in global and segmental pattern, diffuse acute tubular injury

Brexu-cel for Ph+ B-ALL

- Brexucabtagene autoleucel is a CD19-directed chimeric antigen receptor T cell therapy with a response rate > 70% in adults with relapsed/refractory B-ALL (including BCR::ABL positive disease)[4]
- CART therapy was offered as an alternative to allo SCT due to lower risk of renal toxicity (less intensive conditioning regimen, no calcineurin inhibitor, less mucositis, no GVHD)

TKI Maintenance

- The optimal TKI choice and duration following CART therapy for BCR::ABL positive B-ALL is unknown
- Dasatinib was discontinued for symptomatic pleural and pericardial effusions
- Ponatinib was held for AKI, then later resumed and discontinued for a symptomatic, ichthyotic rash
- Asciminib dose was increased from 80 mg/day to 200 mg/day in response to uptrending BCR::ABL

12/2024: A 72 year old woman with history of type 2 diabetes mellitus, hypertension, anxiety, and chronic kidney disease (**baseline Cr ~1.5**) presented with weakness and AKI on CKD (**Cr 2.3**). Based on bone marrow histopathology and flow cytometry, she was diagnosed with bilineal MPAL in which **both blast populations were CD19 positive**.

12/2024: Cytoreduced with hydroxyurea + TKI followed by 1 cycle of induction chemotherapy with **modified hyper-CVAD + TKI:**
- Cyclophosphamide 150 mg/m^2 daily on days 1-3
- Vincristine 2 mg on days 1, 8
- Intrathecal (IT) methotrexate (12 mg x1), cytarabine (100 mg x1)
- TKI*

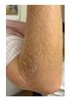
*Started on ponatinib 30 mg daily, transitioned to dasatinib 20 mg daily due to concern for nephrotoxicity

2/2025-5/2025: 3 cycles of consolidation chemotherapy with **Blinatumomab + TKI:**
- Blinatumomab 28mcg daily continuous IV infusion x28 days of a 48-day cycle x3 cycles
- IT methotrexate (12 mg x4)
- IT cytarabine (50 mg x3)
- TKI**

** Dasatinib held for pleural and pericardial effusions after dose increased from 20 mg daily to 40 mg daily

6/2025-9/2025: Ponatinib 30 mg daily resumed, then held for ichthyotic rash which remained symptomatic despite aggressive supportive care

Skin Biopsy:
- Occasional corps ronds with a superficial lymphocytic infiltrate with moderate eosinophils
- Consistent with drug eruption, viral exanthem, or Grover's Disease



Left upper extremity

9/2025: Lymphocyte collection
10/2025: Lymphodepletion, Brexu-cel

Complications:
- CRS grade 2 (culture-negative fever, hypotension) managed with antibiotics, supportive care, and tocilizumab x3 doses
- ICANS grade 1 (handwriting and counting backwards), managed with dexamethasone tapered over 1 week

12/2025 (T +44):
Asciminib 80 mg daily resumed

3/2026 (T +150):
Asciminib increased to 200 mg daily for uptrending BCR::ABL (peak 0.16%)

Considerations for indefinite TKI treatment:
- What is the optimal duration of maintenance therapy?
- What is the ideal disease monitoring strategy and frequency?
- What is the likelihood of CD19-negative and/or BCR::ABL negative relapse? Does continued maintenance therapy increase the likelihood of resistance mutation(s)?

SUMMARY

- **Significance:** Anti-CD19 CART therapy is a potential therapeutic strategy for transplant-ineligible patients with CD19-positive MPAL, a rare leukemia with historically poor outcomes.
- **Limitations** of this report include single case experience, limited number of MPAL cases with uniform CD19 positivity, and relatively short follow-up (180 days post-CART).
- **Future studies** are needed to determine the optimal timing of CART therapy within the multiphase treatment of MPAL.

CONTACT

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