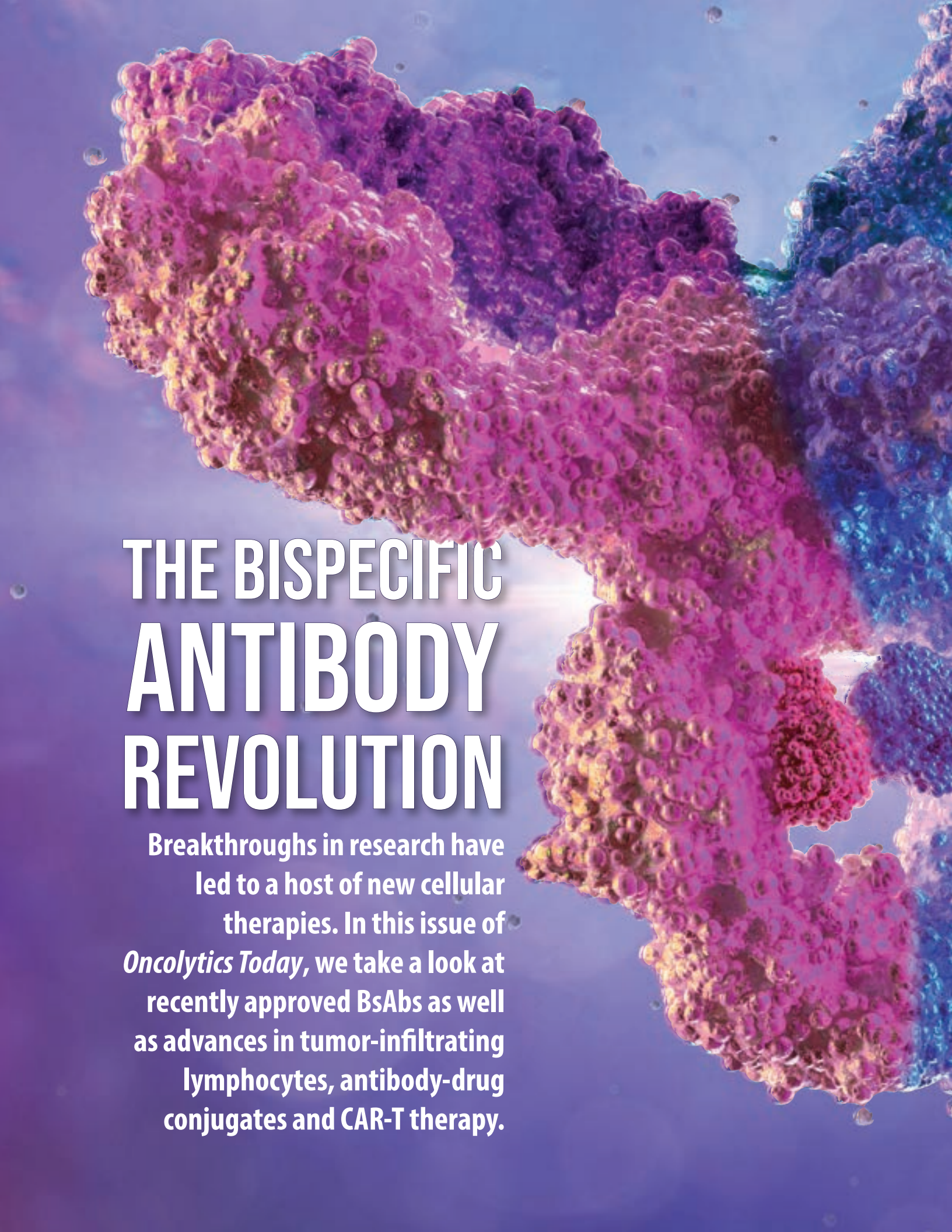

# THE BISPECIFIC ANTIBODY REVOLUTION

**Breakthroughs in research have led to a host of new cellular therapies. In this issue of *Oncolytics Today*, we take a look at recently approved BsAbs as well as advances in tumor-infiltrating lymphocytes, antibody-drug conjugates and CAR-T therapy.**

## TABLE 1: BsABs IN LYMPHOMA (AS OF AUGUST 15, 2024)

| Drug | Mosunetuzumab-axgb (LUNSUMIO™)[1,2] | Epcoritamab-bysp (EPKINLY®)[3,4] | Glofitamab-gxbm (COLUMVI™)[5,6] |
|---|---|---|---|
| **Manufacturer** | Genentech, Inc. | Genmab US, Inc. | Genentech, Inc. |
| **Target** | CD3xCD20 | CD3xCD20 | CD3xCD20 |
| **Indication** | R/R follicular lymphoma following 2 or more lines of therapy | 1. R/R diffuse large B-cell lymphoma following 2 or more lines of therapy<br>2. R/R follicular lymphoma following 2 or more lines of therapy | R/R diffuse large B-cell lymphoma following 2 or more lines of therapy |
| **Route of administration** | IV | SC | IV |
| **Dosing schedule** | C1: Days 1, 8, 15<br>C2+: Day 1, every 21 days, for up to 8 cycles in CR or up to 17 cycles for PR or SD | C1-3: Days 1, 8, 15, and 22<br>C4-9: Days 1 and 15<br>C10+: Day 1, every 28 days until progression | C1: obinutuzumab, Day 1; glofitamab-gxbm Days 8 and 15<br>C2-12: day 1, every 21 d |
| **CRS mitigation** | | | |
| **Step-up dosing** | C1D1: 1mg<br>C1D8: 2mg<br>C1D15: 60mg<br>C2D1: 60mg<br>C3+D1: 30mg | R/R DLBCL<br>C1D1: 0.16mg<br>C1D8: 0.8mg<br>C1D15: 48mg<br>C1D22: 48mg<br>C2D1+: 48mg<br><br>R/R FL<br>C1D1: 0.16mg<br>C1D8: 0.8mg<br>C1D15: 3mg<br>C1D22: 48mg<br>C2D1+: 48mg | C1D1: obinutuzumab 1,000mg<br>C1D8: 2.5mg (first glofitamab-gxbm dose)<br>C1D15: 10mg<br>C2D1+: 30mg |
| **Premedications** | 1. A/P 500-1,000mg, 30 minutes prior, for C1 and C2<br>2. Diphenhydramine 50-100mg (or equivalent), 30 minutes prior, for C1 and C2<br>3. Dexamethasone 20mg or methylprednisolone 80mg, 1 hour prior, for C1 and C2. Continue all premedications if CRS with prior dose. | 1. A/P 650-1,000mg, 30-120 minutes before C1 treatments<br>2. Diphenhydramine 50mg (or equivalent), 30-120 minutes before C1 treatments<br>3. Dexamethasone 15mg or prednisolone 100mg (or equivalent), 30-120 minutes before C1 treatments and for three consecutive days after. Continue dexamethasone thereafter if G2 or G3 CRS with prior dose. | 1. A/P 500-1,000mg, 30 minutes before all treatments<br>(2) Diphenhydramine 50mg (or equivalent), 30 minutes before all infusions<br>3. Dexamethasone 20mg (or equivalent), 1 hour before treatment on C1D8, C1D15, C2D1, and C3D1. Continue if CRS with prior dose. |
| **Hospitalization** | Not required | C1D15: 24-h admission (DLBCL only), not required for FL | C1D8: 24-h admission |
| **CRS occurrence** | G1: 26%; G2: 17%; G3: 1%; G4: 1%; G5: 0%<br>Time course for CRS onset<br>C1D1: 23.3%<br>C1D8: 5.6%<br>C1D15: 36.4%<br>C2D1: 10.3%<br>C3+D1: 2.4%<br>Median time (hours) to CRS onset<br>C1D1: 5<br>C1D8: 20<br>C1D15: 27<br>C2D1: 38 | G1: 34%; G2: 15%; G3: 3%; G4: 0%; G5: 0%<br>Time course for CRS onset<br>C1D1 DLBCL 9% FL 14%<br>C1D8 DLBCL 16% FL 7%<br>C1D15 DLBCL 61% FL 17%<br>C1D22 DLBCL 6% FL 49%<br>Median time (hours) to CRS onset<br>All doses: DLBCL 24, FL 59<br>First full dose: DLBCL 20, FL 61 | G1: 47%; G2: 12%; G3: 3%; G4: 1%; G5: 0%<br>Time course for CRS onset<br>C1D8: 42.8%<br>C1D15: 25.2%<br>C2: 26%<br>C3+: 0.9%<br>Median time (hours) to CRS onset<br>C1D8: 13.5<br>(range: 6-52) |
| **Median duration of CRS** | Three days (range: 1-29 days) | Two days (range: 1-27 days) | 30.5 hours (range: 0.5-317 hours) |
| **ICANS** | G1-2: 3%; G3: 0%; G4: 0%; G5: 0% | G1: 4.5%; G2: 1.3%; G3: 0%; G4: 0%; G5: 0.6% | G1-2: 5%; G3-4: 3%; G5: 0% |
| **Any Grade Adverse Events (with >25% incidence)** | Lymphopenia (100%), decreased phosphate (78%), anemia (68%), WBC decreased (60%), neutropenia (58%), thrombocytopenia (46%), cytokine release syndrome (44%), fatigue (42%), glucose increase (42%), rash (39%), AST increased (39%), decreased magnesium (34%), hypokalemia (33%), ALT increased (32%), headache (32%), pyrexia (29%), musculoskeletal pain (28%) | Lymphopenia (87%), anemia (62%), hyponatremia (56%), decreased phosphate (56%), decreased WBC (53%), cytokine release syndrome (51%), neutropenia (50%), thrombocytopenia (48%), AST increased (48%), ALT increased (45%), decreased potassium (34%), decreased magnesium (31%), fatigue (29%), musculoskeletal pain (28%), injection site reactions (27%) | Lymphopenia (90%), decreased fibrinogen (84%), anemia (72%), cytokine release syndrome (70%), decreased phosphate (69%), neutropenia (56%), thrombocytopenia (56%), hyponatremia (49%), hypocalcemia (49%), infection (35%), hypokalemia (32%) |
| **Grade 3 or > Adverse Events (with >25% incidence)** | Lymphopenia (98%), decreased phosphate (46%), increased glucose (42%), neutropenia (40%) | Lymphopenia (77%), neutropenia (32%) | Lymphopenia (83%), neutropenia (26%), decreased phosphate (28%) |
| **REMS Program** | No | No | No |
| **Drug Approval** | December 2022 | May 2023 (DLBCL), June 2024 (FL) | June 2023 |
| **Pivotal Trial** | GO29781 | EPCORE NHL-1 | NP30179 |

**ABBREVIATIONS: A/P:** Acetaminophen; **ALL:** Acute Lymphoblastic Leukemia; **ALT:** Alanine Aminotransferase; **AST:** Aspartate Aminotransferase; **BCMA:** B-Cell Maturation Antigen; **BCP:** B-cell Precursor; **CRS:** Cytokine Release Syndrome; **C:** Cycle; **CD**: Cluster of Differentiation; **D:** Day; **DLBCL:** Diffuse Large B Cell Lymphoma; **DLL3:** Delta-like ligand 3; **ES-SCLC:** Extensive Stage Small Cell Lung Cancer; **FL:** Follicular Lymphoma; **G1:** Grade 1; **G2:** Grade 2; **G3:** Grade 3; **G4:** Grade 4; **G5:** Grade 5; **GPRC5D:** G-protein-coupled receptor, class C, group 5, member D; **HLA:** Human Leukocyte Antigen; **ICANS:** Immune Effector Cell-Associated Neurotoxicity Syndrome; **IV:** Intravenous; **MRD:** Minimal Residual Disease; **NR:** Not Reported; **NS:** Normal Saline; **PR:** Partial Response; **R/R:** Relapsed/Refractory; **SC:** Subcutaneous; **WBC:** White Blood Cell

## TABLE 2: BsABs IN MULTIPLE MYELOMA (AS OF AUGUST 15, 2024)

| Drug | Teclistamab-cqyv (TECVAYLI®)[7,8] | Talquetamab-tgvs (TALVEY™)[9,10] | Elranatamab-bcmm (ELREXFIO™)[11,12] |
|---|---|---|---|
| **Manufacturer** | Janssen Biotech, Inc. | Janssen Biotech, Inc. | Pfizer |
| **Target** | CD3xBCMA | CD3xGPRC5D | CD3xBCMA |
| **Indication** | RRMM following four or more lines of therapy | RRMM following four or more lines of therapy | RRMM following four or more lines of therapy |
| **Route of administration** | SC | SC | SC |
| **Dosing schedule** | C1: days 1, 3, 5<br>C2+: weekly until progression<br>For patients who have achieved and maintained a CR or better for >6 months, consider biweekly dosing | Weekly<br>C1: days 1, 4, 7<br>C2+ weekly until progression<br><br>Biweekly<br>C1: days 1, 4, 7, 10<br>C2+: every two weeks until progression | C1: days 1, 4, 8<br>C2+: once weekly through week 24<br>Week 25+: biweekly |
| **CRS mitigation**<br>Step-up dosing | C1D1: 0.06mg/kg<br>C1D3 (within two to four days after dose1): 0.3mg/kg<br>C1D5 (within two to four days after dose 2): 1.5 mg/kg<br>C2D1 (one week after first treatment dose): 1.5mg/kg weekly | Weekly dosing<br>C1D1: 0.01 mg/kg<br>C1D4 (between 2-4 days of previous dose): 0.06mg/kg<br>C1D7 (between 2-4 days of previous dose): 0.4mg/kg<br>C2D1 (one week after first treatment dose): 0.4mg/kg once weekly<br><br>Biweekly dosing<br>C1D1: 0.01mg/kg<br>C1D4 (between 2-4 days of previous dose): 0.06mg/kg<br>C1D7 (between 2-4 days of previous dose): 0.4 mg/kg<br>C1D10 (between 2-7 days after dose 3): 0.8mg/kg<br>C2D1: 0.8 mg/kg every two weeks | C1D1: 12mg<br>C1D4 (min of two days between dose 1 and 2): 32mg<br>C1D8 (min. of three days between dose 2 and 3): 76mg<br>C2D1 (one week after first treatment dose; min. of six days between treatment doses): 76mg |
| Premedications | (1) A/P 650-1,000mg (or equivalent), one to three hours prior, for C1 treatments<br>(2) Diphenhydramine 50mg (or equivalent), one to three hours prior, for C1 treatments<br>(3) Dexamethasone 16mg, one to three hours prior, for C1 treatments | (1) A/P 650-1,000mg (or equivalent), one to three hours prior, for C1 treatments<br>(2) Diphenhydramine 50mg (or equivalent), one to three hours prior, for C1 treatments<br>(3) Dexamethasone 16mg (or equivalent), one to three hours prior, for C1 treatments | (1) A/P 650mg (or equivalent), ~1 hour prior, for C1 treatments<br>(2) Diphenhydramine 25mg (or equivalent), ~1 hour prior, for C1 treatments<br>(3) Dexamethasone 20mg (or equivalent), ~1 hour prior, for C1 treatments |
| Hospitalization | For 48 hours after administration of step-up doses | For 48 hours after administration of step-up doses | For 48 hours after administration of first step-up dose, and for 24 hours after administration of second step-up dose |
| **CRS occurrence** | G1: 50%; G2: 21%; G3: 0.6%; G4: 0%; G5: 0% | G1: 57%; G2: 17%; G3: 1.5%; G4: 0%; G5: 0% | G1: 44%; G2: 14%; G3: 0.5%; G4: 0%; G5: 0% |
| | Time course for CRS onset<br>C1D1: 42%<br>C1D3: 35%<br>C1D5: 24%<br>Subsequent doses: 3% | Median time (h) to CRS onset<br><br>All doses: 48 | Time course for CRS onset<br>Weekly dosing<br>C1D1: 29%<br>C1D4: 44%<br>C1D7: 30%<br><br>Biweekly dosing<br>C1D7: 33%<br>C1D10: 12% | Median time (h) to CRS onset<br><br>All dose: 27 (range 0.1-167) | Time course for CRS onset<br>C1D1: 43%<br>C1D4: 19%<br>C1D8: 7%<br>C1D1: 1.6% | Median time (d) to CRS onset<br><br>All doses: 2 (range: 1-9) |
| **Median duration of CRS** | Two days | 17 hours (range 0-622 hours) | Two days (range: one to 19 days) |
| **ICANS** | Any grade: 6% | Any grade: 9% | Any grade: 3.3% |
| **Any Grade Adverse Events (with >25% incidence)** | Cytokine release syndrome (72.1%), neutropenia (70.9%), anemia (52.1%), thrombocytopenia (40%), lymphopenia (34.5%), diarrhea (28.5%), fatigue (27.9%), nausea (27.3%), pyrexia (27.3%), injection-site reaction (26.1%) | Lymphopenia (90%), pyrexia (83%), cytokine release syndrome (76%), WBC decreased (73%), dysgeusia (70%), anemia (67%), neutropenia (64%), thrombocytopenia (62%), albumin decreased (66%), nail disorder (50%), Alk phos increased (49%), phosphate decreased (44%), musculoskeletal pain (43%), skin disorder (41%), rash (38%), ALT increased (33%), AST increased (31%), hypokalemia (31%), hyponatremia (31%), weight loss (35%), dry mouth (34%), xerosis (30%), fatigue (37%) | Lymphopenia (91%), WBC decreased (69%), anemia (68%), neutropenia (62%), thrombocytopenia (61%), cytokine release syndrome (58%), decreased albumin (55%), fatigue (43%), increased AST (40%), increased creatinine (38%), injection site reaction (37%), hypokalemia (36%), diarrhea (36%), rash (35%), upper respiratory tract infection (34%), musculoskeletal pain (34%), Alk phos increased (34%), diarrhea (32%), decreased CrCl (32%) |
| **Grade 3 or > Adverse Events (with >25% incidence)** | Neutropenia (64.2%), anemia (37%), lymphopenia (32.7%) | Lymphopenia (80%), WBC decreased (35%), neutropenia (35%), anemia (30%) | Lymphopenia (84%), neutropenia (51%), anemia (43%), decreased WBC (40%), thrombocytopenia (32%) |
| **REMS Program** | Yes | Yes | Yes |
| **Drug Approval** | October 2022 | August 2023 | August 2023 |
| **Pivotal Trial** | MajesTEC-1 | MonumenTAL-1 | MagnetisMM-3 |

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**TABLE 3: BsABs IN OTHER INDICATIONS** (AS OF AUGUST 15, 2024)

| Drug | Blinatumomab (BLINCYTO®)[13-16] | Tebentafusp-tebn (KIMMTRAK®)[17,18] | Tarlatamab-dlle (IMDELLTRA™)[19,20] |
|---|---|---|---|
| **Manufacturer** | Amgen, Inc. | Immunocore Commercial LLC | Amgen, Inc. |
| **Target** | CD3xCD19 | CD3xgp100peptide-HLA | CD3xDLL3 |
| **Indication** | (1) MRD+ BCP-ALL<br>(2) R/R BCP-ALL<br>(3) BCP-ALL in the consolidation phase | HLA-A*02:01-positive unresectable or metastatic uveal melanoma | ES-SCLC following progression on platinum-based chemotherapy |
| **Route of administration** | IV | IV | IV |
| **Dosing schedule** | MRD+ BCP-ALL and BCP-ALL in consolidation phase<br>Induction Cycle 1: days 1-28 then 14 days off<br>Consolidation Cycles 2-4: days 1-28 then 14 days off<br><br>R/R BCP-ALL<br>Induction C1 and C2: days 1-28 then 14 days off<br>Consolidation C3-5: days 1-28 then 14 days off<br>Continued Therapy C 6-9: days 1-28 then 56 days off | Once weekly until progression | C1: days 1, 8 ,15<br>C2+: days 1 and 15; every 28 days until progression |
| **CRS mitigation** | | | |
| Step-up dosing | R/R BCP-ALL, Induction Cycle 1:<br>Days 1-7: 9mcg/day<br>Days 8-28: 28mcg/day<br>Note: see PI for dosing for patients under 45kg | C1D1: 20mcg<br>C1D8: 30mcg<br>C1D15: 68mcg<br>C2D1+: 68mcg once weekly | C1D1: 1mg<br>C1D8+: 10mg<br>C1D15: 10mg<br>C2D1+: 10mg every two weeks |
| Premedications | MRD+ BCP-ALL and BCP-ALL in consolidation phase<br>Corticosteroid (IV): Prednisone 100mg (or equivalent) prior to D1 dose in each cycle<br>For adults with R/R B-cell precursor ALL<br>Corticosteroid (IV): Dexamethasone 20mg prior to D1 dose in each cycle, prior to a step-up dose, and when restarting an infusion after interruption of ≥4 hours | None | (1) Dexamethasone 8mg IV (or equivalent), one hour before treatment on C1D1 and C1D8<br>(2) 1L NS IV over four to five hours immediately after infusion completion on C1D1, C1C8, and C1D15 |
| Hospitalization | MRD+ BCP-ALL and BCP-ALL in consolidation phase: C1 (3 d) and C2 (2 d)<br>R/R BCP-ALL: C1 (9 d), C2 (2 d) | Appropriate healthcare setting: Optional (monitor for 16 hours after infusion completion for first three doses; then as clinically indicated) | Appropriate healthcare setting: Optional (monitor for 22 to 24 hours from start of infusion on C1D1 and C1D8, 6-8 h post-infusion on C1D15, three to four hours post-infusion on C2D1 and C2D15, and two hours post-infusion on all subsequent infusions) |
| **CRS occurrence** | MRD+ BCP-ALL (any grade): 15%<br>R/R BCP-ALL (any grade): 7%<br>BCP-ALL in consolidation phase: 16% | G1: 12%; G2: 76%; G3: 0.8%; G4: 0%; G5: 0% | G1: 34%; G2: 19%; G3: 1.1%; G4: 0.5%; G5: 0% |
| | Time course for CRS onset: NR<br>Median time (d) to CRS onset: All doses: 2 | Time course for CRS onset<br>C1D1: ~85%<br>C1D8: ~75%<br>C1D15: ~60%<br>C2D1: ~30%<br>C2D8: ~10%<br>Median time to CRS onset: All doses: within the day of the infusion | Time course for CRS onset<br>C1D1: 39%<br>C1D8: 28%<br>C1D15: 6%<br>C1D1: 2%<br>Median time (h) to CRS onset: All doses: 13.5 (range: 1-268) |
| **Median duration of CRS** | Five days | Two days | Four days (IQR two to six days) |
| **ICANS** | Any grade: 7.5% | N/A | G1: 5.3%; G2 or greater: 3.7%; G5: 0% |
| **Any Grade Adverse Events (with >25% incidence)** | Pyrexia (91%), Infusion-related reactions (77%), headache (39%), infections-unspecified (39%), tremor (31%), neutropenia (31%), anemia (25%), chills (28%) | Cytokine release syndrome (89%), rash (83%), pyrexia (76%), pruritus (69%), chills (47%), nausea (43%), fatigue (41%), hypotension (38%), dry skin (29%), vomiting (26%) | Cytokine release syndrome (55%), fatigue (51%), pyrexia (36%), dysgeusia (36%), decreased appetite (34%), musculoskeletal pain (30%), constipation (30%), anemia (27%) |
| **Grade 3 or > Adverse Events (with >25% incidence)** | Neutropenia (28%) | N/A | Decreased lymphocytes (57%) |
| **REMS Program** | No | No | No |
| **Drug Approval** | December 2014 | January 2022 | May 2024 |
| **Pivotal Trial(s)** | BLAST, TOWER, ECOG-ACRIN E1910 | IMCgp100-202 | DeLLphi-301 |

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