New Molecular Entities

Jaypirca™ (*pirtobrutinib*) – Loxo/Lilly Oncology received approval for its novel BTK inhibitor as treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy (including treatment with another BTK inhibitor). The approval was based on response rates observed among 120 MCL patients who were treated with Jaypirca™ after having previously received a different BTK inhibitor. Among those patients 60 (50 percent) had either a "complete" or "partial response" (15 and 45 patients, respectively). The median duration of response was 8.3 months. While Jaypirca™ joins an increasingly crowded field of small molecules targeting BTK, it is the first non-covalent ("reversible") inhibitor of the protein implicated in B-cell proliferation and, as such, can reestablish inhibition in some MCL patients previously treated with covalent BTK inhibitors (*ibrutinib, acalabrutinib, or zanubrutinib*).

Orserdu™ (*elacestrant*) -- Stemline Therapeutics, a subsidiary of one of the oldest pharma companies in the world, was granted approval to market the first oral therapy that targets a genetic mutation that often arises in breast cancer patients treated with aromatase inhibitors. The approval is for use of the new "selective estrogen receptor downregulatory" as treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy. Support for the approval comes from a randomized trial that enrolled 478 postmenopausal women and men with ER+/HER2- advanced or metastatic breast cancer of which 228 patients had *ESR1* mutations, Within the mutation-positive cohort, 46 percent of the 115 patients randomized to treatment with Orserdu™ were event free by the reporting date (with a median progression-free survival of 3.8 months) while that was true for only 31 percent of the patients randomized to treatment with either *fulvestrant* or an aromatase inhibitor (who had a median PFS of 1.9 months). However, the statistically significant difference in PFS observed in the ESR1 mutation-positive patients did not hold for the broader population of patients that were enrolled in the trial. An exploratory analysis in the 250 patients without *ESR1* mutations showed no significant

advantage in PFS conferred by treatment with Orserdu™ (hence the approval being limited to use in mutation-positive patients). An announcement of the approval of a companion diagnostic that identifies ESR1 mutation-positive patients---the Guardant360 CDx assay—accompanied FDA's press release on Orsertu™

Changes in Labeled Indications

Brukinsa® (*zanubrutinib*) **–** Beigene BTK inhibitor—which first came to market in 2019 indicated for use in mantle cell lymphoma and was subsequently approved in Waldenstrom's macroglobulinemia and relapsed/refractory marginal zone lymphoma--is now also approved for treating adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL). Evidence in support of the new indication comes from one randomized study (SEQUOIA) that recruited previously untreated CLL/SLL patients and from a second (ALPINE) that evaluated effectiveness in patients with previously treated relapsed/refractory disease. Most of the patients in the SEQUOIA trial were randomized to treatment with either Brukinsa® (n=241) or a combination of *bendamustine* and *rituximab* (n=238). Efficacy was assessed based on progression free survival (PFS), which was significantly better in the Brukinsa® arm (85 percent without progression or death and median PFS not yet reached) than in the *bendamustine+rituxan* arm (70 percent without progression or death and a median PFS of 33.7 months). Patients recruited to the trial whose disease had a 17p deletion (n=110) were not randomized—rather, all were treated with Brukinsa® and evaluated based on response to therapy (achieved by 88 percent of them). Response to therapy also served as the principal efficacy measure in the ALPINE trial (n=652), which randomized previously treated patients to receive either Brukinsa® or *ibrutinib*. Whereas 80 percent of patients in the Brukinsa® arm responded to therapy, the same was true for 73 percent of patients treated with *ibrutinib*. Median duration of response had not yet been reached in either patient cohort after a median follow-up of 14.1 months

Keytruda® (*pembrolizumab*) – Merck's checkpoint inhibitor had its role in NSCLC expanded to now include use in the adjuvant setting, specifically as adjuvant therapy following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥4 cm), II, or IIIA disease. Evidence supporting the new use comes from a Phase III trial (n=1,177) in which NSCLC patients randomized to receive Keytruda post-resection demonstrated significantly superior disease-free survival (DFS) to that of patients randomized to receive placebo. The magnitude of the improvement is somewhat unclear because the detailed results included in new label are only for the 1,010 patients who also received chemotherapy. Within that group, 65 percent of patients in the Keytruda group remained disease free at study's end (with a median disease-free interval of 58.7 months) while the same was true for 54 percent of patients in the placebo arm (median disease-free interval of 34.9 months). In a

subgroup analysis of the 167 trial patients that did not receive chemotherapy, there was no difference seen in DFS between patients randomized to placebo or Keytruda.

Tukysa®(*tucatinib*) -- Seagen's kinase inhibitor, which came to market approved for use in HER2+ breast cancer, was approved for use in colorectal cancer (CRC) as well, specifically for treating adult patients with RAS wild-type HER2-positive unresectable or metastatic CRC that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The approval was based on evidence of response seen in 32 of 84 patients recruited to a single-arm study in which patients with metastatic or unresectable CRC received the HER2 inhibitor in combination with *trastuzumab*. The median duration of response was 12.4 months and about one third of responders (38 percent) had a response that lasted 12 months or longer. HER2 overexpression is estimated to occur in about 3- 5 percent of metastatic CRC.

Accelerated Approvals Reconsidered

- **None**

New Generics and Biosimilars

Full approvals were granted for:

- *Abiraterone acetate* from Teva Pharmaceuticals
- *Cabazitaxel* from Sandoz, and
- *Nelarabine* from Kindos

Tentative approval was granted for:

- *Acalabrutinib* from Alembic Pharmaceuticals

Safety-related Changes

Jakafi® (*ruxolitinib*) -- A new subsection titled "Monitoring to Assess Safety" was added to the Dosage and Administration portion of the prescribing information for Incyte's kinase inhibitor. The new subsection instructs clinicians to perform a complete blood count (CBC) and inquire about past infections (including tuberculosis, herpes simplex, herpes zoster, and hepatitis B) prior to administering Jakafi and—during treatment--to perform a CBC every 2-4 weeks until doses are stabilized, as well as a lipid parameter assessment every 8-12 weeks. In addition, new language has been added to the warnings section of the label clarifying that *herpes zoster infection* has been reported with use of Jakafi®, that patients should be

monitored for both reactivation and possible transmission, and that physicians should consider treatment interruption if evidence of disease or dissemination occurs.

Marinol® (*dronabinol*) – The guidance in the prescribing information, which had advised female patients with infants and small children not to breastfeed while being treated with the antiemetic and for 9 days after the last dose, has been revised. Citing the beneficial effects of breastfeeding, the new guidance only recommends that "Weight should be monitored in breastfed infants of mothers with nausea and vomiting associated with cancer chemotherapy in whom breastfeeding is appropriate."

Taxotere® (*docetaxel*) -- Revisions were made in the recommended timeframes for contraceptive use by both male and female's patients being treated with the antineoplastic agent. The period for recommended use of contraception post-therapy for females was shortened from 6 to 2 months, while the period for males was extended from 3 to 4 months post-therapy.

Changes in Dosing/Administration

Lumakras® (*sotorasib*) -- Amgen received approval for the introduction of a 320 mg strength tablet of its KRAS inhibitor. The NSCLC drug had previously been available only as a 120mg tablet.

New Data

Darzalex® (*daratumumab*) -- The Clinical Studies section of the prescribing information for Janssen's CD38-directed antibody for multiple myeloma was updated to include a) overall survival results from two studies (MMY3003 and MMY3004) examining Darzalex® use for relapsed/refractory disease, and b) progression-free survival results from a trial evaluating the benefits of adding Darzalex® to a regimen of *lenalidomide* and *low-dose dexamethasone* for newly diagnosed patients (MMY3008). The newly added results show that the advantages in response rates that supported approval of Darzalex® have, with longer study follow-up, translated into advantages in both overall survival (in the two trials conducted in relapsed/refractory patients) and in progression-free survival (in the study of Darzalex® as part of a front-line regimen for newly diagnosed patients).

Other

Balversa® (*erdafitinib*) -- The term *onycholysis* was changed to *nail disorder* in the listing of adverse events associated with use of Janssen's kinase inhibitor.

Ixempra ® (*ixabepilone*) – The first bulleted Indication in the Highlights section of the prescribing information was revised to match verbatim the first indication listed in the full prescribing information

Clinical Trial Information

DLBCL/Aggressive NHL

1. A Phase Ib Trial of Zanubrutinib in Combination with R CHOP (ZaRCHOP) for Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

- Patient population/notes: Open to all patients with newly diagnosed DLBCL. Please consider sending patients with newly diagnosed DLBCL patients, especially if non-GCB subtype. Once Pola is approved with R-CHP (likely 4/2023) there may be an amendment to this protocol and will keep you all posted! This trial should be opening this month after upcoming amendment

2 (a). A Phase 1b Open-Label Study to Evaluate the Safety and Anti-cancer Activity of Loncastuximab Tesirine in Combination with Polatuzumab Vedotin in Patients with Relapsed or Refractory B-cell Non-Hodgkin Lymphoma

- Patient population/notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that received FDA approval in 2021 for R/R DLBCL. This Trial is investigating the combination of ADCT-402 with Polatuzumab Vedotin and will enroll R/R patients with DLBCL, FL, MCL, MZL, and BL and is open for enrollment.

3. A Phase 3 Randomized Study of Loncastuximab Tesirine Combined with Rituximab Versus Immunochemotherapy in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) (LOTIS-5)

- Patient population/notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that received FDA approval in 2021. This trial is open to DLBCL patients relapsing after $\geq$ 1 therapy. This would be a good option for patients who

have progressed on R-CHOP/R-EPOCH, and either are not good candidates for CAR-T/Auto SCT or not interested in either.

4. A Randomized Double-Blind Phase III Study of Ibrutinib During and Following Autologous Stem Cell Transplantation Versus Placebo in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma of the Activated B-cell Subtype

- Patient population/notes: Cooperative group trial for DLBCL patients being referred for Auto SCT. Please consider sending patients early on after relapse so they can be considered for this trial as they will need to have tissue sent off for confirmation of ABC (MUSC team can take care of tissue request, etc.)

5. A Phase II/III Randomized Study of R-Mini-CHOP With or Without CC-486 (Oral Azacitidine) in Patients Aged 75 Years or Older with Newly Diagnosed Diffuse Large B Cell Lymphoma, Grade IIIB Follicular Lymphoma, Transformed Lymphoma, and High-Grade B-Cell Lymphomas with MYC and BCL2 and/or BCL6 Rearrangements

- Patient population/notes: Cooperative group trial for newly diagnosed elderly DLBCL patients. These patients typically do not well and are not candidates for clinical trials, so we are very happy to offer this trial here at Hollings!

6(a). Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase 1/2a Dose Escalation Trial with Dose Expansion Cohorts

- Patient population/notes: Phase 1 study utilizing bispecific monoclonal antibody targeting CD37 (antigen widely expressed on B-cells). This is a phase 1 so open to multiple R/R subtypes of NHL.

7(a). A Phase 1/2, Open-Label, Dose- Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma

- Patient population/notes: GEN3013 (Epcoritamab) is a Bi-specific T-cell engager (binds CD3 on T-cells and CD20 on lymphoma B-cells) - GEN3013 with recent press release showing very promising results in aggressive NHL. Study now opened an

extra cohort in aggressive LCL for a limited time as they will only enroll ~ 80 patients to this arm.

Mantle Cell Lymphoma

8. A Randomized 3-Arm Phase II Study Comparing 1.) Bendamustine, Rituximab and High Dose Cytarabine (BR/CR) 2.) Bendamustine, Rituximab, High Dose Cytarabine and Acalabrutinib (BR/CR-A), and 3.) Bendamustine, Rituximab and Acalabrutinib (BR-A) in patients </= 70 Years Old with Untreated Mantle Cell Lymphoma

- Patient population/notes: cooperative group study for frontline therapy in newly diagnosed MCL patients ≤ 70. Please call Brian Greenwell if you have a patient

9. A Randomized Phase III Trial of Consolidation with Autologous Hematopoietic Cell Transplantation Followed by Maintenance Rituximab vs Maintenance Rituximab Alone for Patients with Mantle Cell Lymphoma in Minimal Residual Disease Negative First Complete Remission

- Patient population/notes: Cooperative group study where patients will be randomized to auto SCT + maintenance rituximab vs maintenance rituximab alone. If you have any patients currently receiving induction for MCL please consider sending them here during induction for initial visit and we can plan on screening them once induction is completed.

2(b). A Phase 1b Open-Label Study to Evaluate the Safety and Anti-cancer Activity of Loncastuximab Tesirine in Combination with Polatuzumab Vedotin in Patients with Relapsed or Refractory B-cell Non-Hodgkin

- Patient population/notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that received FDA approval in 2021 for R/R DLBCL. This Trial is investigating the combination of ADCT-402 with Polatuzumab Vedotin and will enroll R/R patients with DLBCL, FL, MCL, MZL, and BL and is open for enrollment.

6(b). Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase 1/2a Dose Escalation Trial with Dose Expansion Cohort

- Patient population/notes: Phase 1 study utilizing bispecific monoclonal antibody targeting CD37 (antigen widely expressed on B-cells). This is a phase 1 so open to multiple R/R subtypes of NHL.

7(b). A Phase 1/2, Open-Label, Dose- Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma

- Patient population/notes: GEN3013 is a Bi-specific T-cell engager (binds CD3 on T-cells and CD20 on lymphoma B-cells) - GEN3013 with recent press release showing very promising results in aggressive NHL. Open for enrollment in both Mantle cell lymphoma and indolent NHL (follicular, marginal zone, SLL). Will be a great option for patients who progress after CD19 CAR-T or not a candidate for CD19 CAR-T.

Indolent NHL

10. Randomized Phase II Trial in Early Relapsing or Refractory Follicular lymphoma (Enrollment on hold)

- Patient population/notes: Cooperative group trial open to follicular lymphoma patients who have progressed within 2 years of completion of front-line therapy. There are three arms: obinutuzumab + revlimid, obinutuzumab + PI3K inhibitor, and chemo-immunotherapy. Please call us if you think you have a potential patient, and we will send right away!

11. Multicenter, Phase 2 Study of CLR 131 in Patients with Relapsed or Refractory (R/R) Select B-Cell Malignancies (CLOVER-1) and Expansion Cohort in Patients with Waldenstrom Macroglobulinemia (CLOVER-WaM)

- Patient population/notes: This is an exciting trial specifically for R/R WM patients which is great because they are often excluded from clinical trials. This trial utilizes treatment with a radioimmunoconjugate. We are happy to work with our nuclear medicine colleagues to offer this trial to WM patients throughout SC.

2(c). A Phase 1b Open-Label Study to Evaluate the Safety and Anti-cancer Activity of Loncastuximab Tesirine in Combination with Polatuzumab Vedotin in Patients with Relapsed or Refractory B-cell Non-Hodgkin

- Patient population/notes: Loncastuximab is a CD19 antibody drug conjugate (like BV but targets CD19) that received FDA approval in 2021 for R/R DLBCL. This Trial is investigating the combination of ADCT-402 with Polatuzumab Vedotin and will enroll R/R patients with DLBCL, FL, MCL, MZL, and BL and is open for enrollment.

6(b). Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase 1/2a Dose Escalation Trial with Dose Expansion Cohort

- Patient population/notes: Phase 1 study utilizing bispecific monoclonal antibody targeting CD37 (antigen widely expressed on B-cells). This is a phase 1 so open to multiple R/R subtypes of NHL.

7(c). A Phase 1/2, Open-Label, Dose- Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma

- Patient population/notes: GEN3013 (Epcortimab) is a Bi-specific T-cell engager (binds CD3 on T-cells and CD20 on lymphoma B-cells) - GEN3013 with recent press release showing very promising results in aggressive NHL. Open for enrollment in both Mantle cell lymphoma and indolent NHL (follicular, marginal zone, SLL). Will be a great option for patients who progress after CD19 CAR-T or not a candidate for CD19 CAR-T.

CLL/SLL

12. Randomized, Phase III Study of Early Intervention with Venetoclax and Obinutuzumab Versus Delayed Therapy with Venetoclax and Obinutuzumab in Newly Diagnosed Asymptomatic High-Risk Patients with Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma (CLL/SLL): EVOLVE CLL/SLL Study.

- Patient population/notes: This trial randomizes patients dx with CLL/SLL that do not currently have a treatment indication but have 'high risk' disease. High risk disease is defined as having a CLL-IPI score of ≥ 4 OR having complex cytogenetics (3+ chromosomal abnormalities). Patients can be enrolled up to 12 months from their

initial diagnosis and would be assigned to Ven+obinutuzumab at randomization or to 'delayed therapy' once they develop a traditional treatment indication. Whether patients are treated 'early' or 'delayed' they would have treatment paid for by study - Please call if any questions about patients or trial!

6(d). Safety and Efficacy of GEN3009 (DuoHexaBody®-CD37) in Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma - A First-in-Human, Open-label, Phase 1/2a Dose Escalation Trial with Dose Expansion Cohorts

- Patient population/notes: Phase 1 study utilizing bispecific monoclonal antibody targeting CD37 (antigen widely expressed on B-cells). This is a phase 1 so open to multiple R/R subtypes of NHL.

7(d). A Phase 1/2, Open-Label, Dose- Escalation Trial of GEN3013 in Patients with Relapsed, Progressive or Refractory B-Cell Lymphoma

- Patient population/notes: GEN3013 is a Bi-specific T-cell engager (binds CD3 on T-cells and CD20 on lymphoma B-cells) - this class of drug showed very exciting results at ASH in 2021 and recent ASCO meeting. Open for enrollment in both Mantle cell lymphoma and indolent NHL (follicular, marginal zone, SLL (not CLL)). Will be a great option for patients who progress after CD19 CAR-T or not a candidate for CD19 CAR-T.

T-cell NHL

13. A Randomized Phase II Study of CHO(E)P vs CC-486-CHO(E)P vs Duvelisib-CHO(E)P in Previously Untreated CD30 Negative Peripheral T-Cell Lymphomas

- Patient population/notes: Cooperative group study for frontline PTCL patients that are CD30 negative (standard for CD30+ patients frontline is CHP+BV). Duvelisib is a PI3K inhibitor and CC-486 is an oral hypomethylating agent. Patients would be eligible for auto SCT after trial. Please call Brian Greenwell if you think you have a patient!

14. A Multi-Center Phase Ib Trial Evaluating the Safety and Efficacy of Lacutamab in Patients with Relapse Peripheral T-Cell Lymphoma That Express KIR3DL2

- Patient population/notes: Lacutamab is a monoclonal antibody against KIR3DL2, which is expressed in ~50% of PTCL. Promising activity has already been seen in CTCL (MF/SS) and has been well tolerated. Enrolls patients with between 1 and 3 lines of therapy, but of note, they cannot have primary refractory disease. Brian G recommends referral of any T-cell lymphoma patients (even if currently in remission) who may be candidates in the future, as the company allows us to "prescreen" patients for KIR3DL2 expression from their initial diagnostic sample.

15. An Open-Label, Phase 2 Trial of Nanatinostat in Combination with Valganciclovir in Subjects With Epstein-Barr Virus-Positive (EBV+) Relapsed/Refractory Lymphomas (NAVAL-1)

- Patient population/notes: This trial will be open for multiple subtypes of EBV+ R/R NHL including PTCL, AITL, PTLD, or other EBV+ NHL. Great trial for many patients without clinical trial options otherwise.