Accelerated Approvals Reconsidered

None

Changes in Dosing/Administration

Turalio® (*pexidartinib*) – Along with the warning regarding fat intake, comes a change in dosage recommendations for Turalio® as well as the introduction of a new strength capsule. Whereas the recommended dosage had been 400 mg twice daily, taken at least an hour before or two hours after meals, the new recommendations are for 250 mg twice daily, taken together with low-fat meals. In accordance with the new recommended dosage, Daiichi Sankyo has received approval to market a 125 mg strength capsule (intended to replace the 200 mg capsules that were available until now).

Changes in Labeled Indications

Cotellic® (*cobimetinib fumarate*) – Genentech's MEK inhibitor, first approved in 2015 for use in combination with the company's BRAF inhibitor (Zelboraf®) for melanoma, was approved for use as a single agent for treating adult patients with histiocytic neoplasms—a diverse set of rare diseases that often have quite poor prognoses. Approval for the new indication was supported by evidence from a small Phase II single-arm study (n=26) that used "response" (measured by both PET and RECIST) as the primary efficacy endpoint. Enrolled patients, 21 of whom had already failed prior systemic therapy, had multi-system disease, recurrent or refractory disease, or single-system disease that was unlikely to benefit from conventional therapies. After a median follow-up of almost a year, 16 of the 24 patients evaluable by PET demonstrated a complete response, with a median time to response of 2 months.

Imfinzi® (*durvalumab*) – The list of indications approved for AZ's immunotherapy was expanded to include use in combination with Imjudo® for *hepatocellular carcinoma* (described above). The approval comes one month after the PD-L1 inhibitor was approved for use, in combination with gemcitabine and cisplatin, as treatment for adult patients with locally advanced or metastatic biliary tract cancer.

New Biosimilars and Generics

Full approvals were granted for:

- *Bortezomib* from both Mylan Labs and Waverley Pharma;
- *Clofarabine* from Eugia Pharma;
- *Cyclophosphamide* from Xellia Pharms APS;
- *Doxorubicin hydrochloride* from Celerity Pharms;
- *Leuprolide acetate* from Amneal; and
- *Paclitaxel* from Alembic Pharms Ltd.

Tentative Approvals granted for:

- *Bendamustine hydrochloride* from Breckenridge Pharmaceuticals; and
- Teva Pharmaceuticals received a tentative "Type-2" approval ("new active ingredient") for Alvaiz, a branded formulation of *eltrombopag choline.*

New Data

Kisqali® (*ribociclib succinate*) – Data on overall survival for post-menopausal women with HR-positive, HER2-negative, advanced or metastatic breast cancer enrolled in a randomized study comparing Kisqali® + *letrozole to letrozole* + placebo were added to the prescribing information for Novartis' kinase inhibitor. Those data show that after a median follow-up of 80 months, survival for the Kisqali-treated group remained significantly higher than that for the *letrozole* only cohort of patients ((median of 63.9 and 51.4 months, respectively), resulting in an estimated 24 percent reduction in the risk of death.

Scemblix® (*asciminib*) – Novartis reported longer term follow-up data from the randomized trial that served as the basis for last year's initial approval of its kinase inhibitor for treating Philadelphia-positive CML. That approval was supported by the significantly superior response to therapy (in terms of both "complete cytogenic response" and "major molecular response") observed in Scemblix® patients after a 24-week observation period compared to that seen in patients randomized to be treated with *bosutinib*. The updated data show that the superior response continues after a 96 week follow up, thereby confirming the long-term efficacy and safety of Scemblix® and demonstrating its clinical benefit.

Tagrisso® (*osimertinib*) – The pharmacokinetics section for AstraZeneca's kinase inhibitor was updated with results of a study examining the drug's ability to enter the brain. The study relied on PET brain imaging studies in both healthy volunteers and in NSCLC patients with brain metastases and showed that following intravenous injection of a micro dose of 11C-labeled Osimertinib, the drug is in fact distributed to the brain.

Turalio® (*pexidartinib*) – When the kinase inhibitor was first approved for use (in 2019) it was because, after a 25-week long observation period, patients with symptomatic tenosynovial giant

cell tumor (TGCT) randomized to receive Turalio® exhibited superior outcomes (reductions in tumor volume and improvements in range of motion) to those seen in TGCT patients randomized to placebo. Data from the open-label extension part of that study are now reported in the prescribing information and show that the overall response rate after 96 weeks in the 61 patients originally randomized to the Turalio® arm was 61 percent (95% CI: 48%, 72%) and that the median duration of response had not yet been reached in the 37 responders."

New Molecular Entities

Imjudo® (*tremelimumab-actl*) – AstraZeneca was granted marketing approval for its novel CTLA-4 blocking antibody for use, in combination with Imfinzi® (*durvalumab*), for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). Support for the approval comes from a large (N=1,171) trial in which uHCC patients (who had not yet received any systemic therapy) were randomized to receive either the two checkpoint inhibitors in combination, *durvalumab* alone, or *sorafenib* as a single agent. Results showed that the median overall survival among patients receiving both immunotherapies was 16.4 months (95% CI 14.16–19.58), significantly better than the median of 13.8 months seen for patients in the sorafenib group. Additionally, the results supported the non-inferiority of *durvalumab* to *sorafenib* as single agent therapy. The median duration of response for the three patient cohorts (combined IO agents, *durvalumab* alone, and sorafenib) was 22.3, 16.8, and 18.43 months, respectively. The potential of combined use of AZ's two checkpoint inhibitors is currently being explored in Phase III trials for a range of other malignancies, including lung (both small and non-small cell), bladder, and urothelial cancers.

Pedmark® (*sodium thiosulfate*) – Fennec Pharmaceuticals, a late-stage biotech company with a single product, received its first FDA marketing approval late last month (which was not reported in September's newsletter). The approval is for use of Pedmark® to reduce the risk of ototoxicity associated with cisplatin use in pediatric patients 1 month of age and older being treated for localized, non-metastatic solid tumors. Approval was based on results from two randomized, open label studies, one with 114 pediatric patients being treated with cisplatin-based chemotherapy for standard-risk hepatoblastoma and the second with 125 pediatric patients treated with a chemotherapy regimen that included a cumulative cisplatin dose of 200 mg/m2 or higher. The frequency of ototoxicity in patients treated with Pedmark was lower than among patients in the control groups in both studies (39 versus 68 percent and 44 versus 58 percent, respectively) although that difference was only statistically significant in the first study. FDA's approval comes with the limitation that "the safety and efficacy of Pedmark® have not been established when administered following cisplatin infusions longer than 6 hours" because irreversible ototoxicity may have already occurred during longer infusions.

Tecvayli™ (*teclistamab-cqyv*) – Janssen was granted an accelerated approval for use of its novel bi-specific T cell engager as treatment for adult multiple myeloma (MM) patients with relapsed or refractory disease who have received at least four lines of prior therapy (to include a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody). Efficacy of the new molecule—which relies on distinct antibody fragments to simultaneously bind to the CD3 receptor found on T-cells and a protein (BCMA) found on MM cells—was demonstrated by an overall response rate of 61.8 percent a single-arm study that included 110 heavily pretreated MM

patients. Almost half (45.5 percent) of the responders in that study had a complete response. With a median follow-up of 7.4 months, more than 90 percent of initial responders continued to respond at 6 months and two-thirds continued at 9 months. Median duration of response had not yet been reached at the time the study was reported.

Safety-Related Changes

Elzonris® (*tagraxofusp-erzs)* – Information on timing for two of the adverse events observed in the pre-approval clinical trial of Stemline Therapeutics' treatment for blastic plasmacytoid dendritic cell neoplasm—*capillary leak syndrome* and *hepatoxicity*—was added to sections 5.1 and 5.3 of the prescribing information for the CD123-directed cytotoxin. The additions clarify that all but 5 of the 55 patients experiencing CLS in the pre-approval trial did so during the first cycle of therapy, that the incidence of *elevated liver enzymes* (seen in a majority of study patients) also occurred during the first cycle of therapy, and that the elevation of liver enzymes was reversible following dose interruption.

Lynparza® (*olaparib*) – AN explicit statement that some of the thromboembolic events observed in patients enrolled in clinical trials for AZ's PARP inhibitor were "severe or fatal pulmonary embolisms" was added to Subsection 5.4 of the prescribing information. In addition, a recommendation that male patients with female partners of reproductive potential use effective contraception during treatment "and for three months afterward" was modified to now recommend contraception only during active treatment.

Padcev® (*enfortumab vedotin*) – The recommendation for dosage modification in the event of adverse *skin reactions* in patients treated with Astellas Pharmaceuticals' antibody-drug conjugate was modified. Whereas Subsection 2.2 of the prescribing information had previously included recommendations only for more serious reactions (Grade 3 and above), newly inserted language suggests that clinicians "consider withholding" the urothelial cancer therapy even for Grade 2 reactions.

Turalio® (*pexidartinib*) – A warning that Daiichi Sankyo's treatment for symptomatic tenosynovial giant cell tumor should not be taken with a high-fat meal (one that has more than 55 grams of total fat) was added to its prescribing information. The warning, prominently displayed in the Warnings and Precautions highlights, was added because of evidence that fat intake may increase both the incidence and severity of adverse reactions, including hepatoxicity, associated with use of the kinase inhibitor.

Other Changes

Sandostatin® (*octreotide acetate*) – A recommendation to discontinue Sandostatin® injection at least 24 hours before each injection of *lutetium Lu 177 dotatate* when using the radioactive targeted therapy for treating GEP-NET patients was added to the drug interactions section. The addition was made so that guidance is consistent with that currently included (as of March 2021) in the labeling for Sandostatin® LAR depot.

CLINICAL TRIALS INFORMATION

Current Trials MUSC - Hollings Cancer Center

Contact: Shanta Salzer, CCRP - **salzers@musc.edu**

DLBCL/Aggressive NHL

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 - likely to open up in later in August or in September. Please consider sending patients with newly diagnosed DLBCL patients, especially if non-GCB subtype. Once Pola is approved with R-CHP there may be an amendment to this protocol and will keep you all posted! This trial is waiting on a local amendment and will likely open at MUSC mid-November.

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.

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 recently received FDA approval. This trial is open to DLBCL patients after only 1 line of 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.

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.).

A Phase II/III Randomized Study of R-MiniCHOP with or Without CC-486 (Oral Azacitidine) in Patients Age 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 do well and are not candidates for clinical trials, so we are very happy to offer this trial here at Hollings!

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.

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

Hodgkin Lymphoma

Phase III Trial of Nivolumab Plus AVD vs. Brentuximab Vedotin Plus AVD in Patients with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma

Patient Population/Notes: Cooperative group study for advanced stage HL patients - please consider emailing or texting right away if you think you may have a patient who is a candidate for this study. We are one of the highest enrolling centers in the country thus far - thanks for referring!

Mantle Cell Lymphoma

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 contact Brian Greenwell if you have a patient.

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.

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 currently going thru a major amendment to only include 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.

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.

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 2020 and recent ASCO meeting. Open for enrollment in both mantle cell lymphoma and indolent NHL (follicular, marginal zone, SLL) as well as certain subsets of aggressive

NHL (double hit, PMBCL, FL3B). Will be a great option for patients who progress after CD19 CAR-T or not a candidate for CD19 CAR-T.

Indolent NHL

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!

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 a radioimmunoconjugate. We are happy to work with our nuclear medicine colleagues to offer this trial to WM patients throughout SC.

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 currently going thru a major amendment to only include 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.

Safety and Efficacy of GEN3009 (Duo HexaBody®-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.

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 2020 and recent ASCO meeting. 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

A 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 ¡Ã 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!

Safety and Efficacy of GEN3009 (Duo HexaBody®-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.

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 2020 and recent ASCO meeting. 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.

T-cell NHL

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 contact Brian Greenwell if you think you have a patient!

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 "pre-screen" patients for KIR3DL2 expression from their initial diagnostic sample.

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.

Do you have clinical trial information to share? Please contact **Christy Levine** at clevine@accc-cancer.org.