Accelerated Approvals Reconsidered

On April 21, the FDA convened its Oncology Drug Advisory Committee (ODAC) to discuss the use of *PI3K inhibitors* for treating hematologic malignancies. The class of drugs under discussion target the phosphoinositide 3-kinase (PI3K) pathway, whose dysregulation has been implicated in assorted oncologic and autoimmune diseases. The meeting was occasioned by "concerning trends in overall survival (OS)" as well as mounting evidence of severe toxicities in post-approval studies of this class of drugs. The focus was on four products:

- **Aliqopa®** (*copanlisib*) – Bayer was granted an accelerated approval in 2017 as 4th line therapy for relapsed or refractory FL. However, subsequent trials (of Aliqopa® in combination with Rituxan) for indolent NHL found no difference in OS between treatment and control arms.
- **Copiktra®** (*duvelisib*) – Regular approval was granted to Secura in 2018 for use of Copiktra® for treating CLL and SLL based on a trial demonstrating superior progression-free survival. However, a final analysis of that trial found no difference in OS between treatment and control arms. The drug also received an accelerated approval for FL based on PFS, but a post-approval study demonstrating clinical benefit was never completed and the company voluntarily withdrew the approval for FL at the end of 2021.
- **Ukoniq®** (*umbralisib*) – Accelerated approval was granted last year for use in TG Therapeutics' drug for treating FL and marginal zone lymphoma. However, the company voluntarily withdrew the approvals for those indications prior to the ODAC meeting, effectively withdrawing the drug from the US market. That decision was largely based on interim results from a Phase III trial that TG Therapeutics had hoped would support expansion of the label to include use in CLL. However, those results showed increased mortality among patients in the treatment arm, was halted, and the application for label expansion voluntarily withdrawn.
- **Zydelig®** (*idelalisib*) – Gilead's drug was originally approved in 2014 for chronic lymphocytic leukemia (CLL) but 3 trials—in CLL or indolent NHL—were halted in 2016 due to increased deaths or toxicities in the treatment arms. The drug was also granted accelerated approval in 2014 for follicular lymphoma (FL) and small lymphocytic lymphoma (SLL) but Gilead voluntarily withdrew approval for those indications earlier this year.

Based on its review of these four drugs, the bases used for their approval, and results from post-approval studies, the ODAC voted unanimously that future approvals for this class of drugs be based on randomized controlled studies that included OS as an endpoint (rather than on single-arm studies that relied on response rates as principal efficacy endpoints).

Changes in Dosing/Administration

- **Zepzelca™** (*lurbinectedin*) – Additional details on how to administer Zepzelca™ have been incorporated into Section 2.4 of the alkylating agent's label. Whereas the sole recommendation on how to administer the small cell lung cancer therapy had been to inspect the vial for impurities (as one should for all parenteral drugs), the newly added instructions now specify that:
    - The drug can be administered with or without an in-line filter but if infusion lines containing in-line filters are utilized, polyethersulfone in-line filters with pore sizes of 0.22 micron are recommended.
    - Not to use in-line nylon membrane filters when the reconstituted solution is diluted using 0.9% Sodium Chloride Injection, USP.
    - Compatibility with other intravenous administration materials has been demonstrated
        - in polyolefin containers,
        - with polyvinyl chloride (non-DEHP-containing), polyurethane and polyolefin infusion sets, and
        - with implantable venous access systems with titanium and plastic resin ports and with polyurethane or silicone intravenous catheters.
    - Not to co-administer with other IV drugs concurrently within the same line.

Changes in Labeled Indications

- **Lupron Depot®** (*leuprolide acetate*) – AbbVie was informed that it could remove the word "palliative" from the indication for use of its hormonal therapy for advanced prostate cancer. It is not clear whether that removal implied an expanded role for the product (i.e., use for treatment and not just palliation of advanced prostate cancer) or an editorial decision reflecting little distinction between "palliation" and "treatment" for what is currently an incurable condition.

New Biosimilars and Generics

- **Alymsys®** *(bevacizumab-maly)* – Amneal Pharma was granted approval for its VEGF inhibitor, thereby joining Pfizer and Amgen with marketed biosimilars of Avastin®.
- FDA granted a tentative approval to *bendamustine hydrochloride* from Apotex Inc.

In addition, full approvals were granted for:

- *Decitabine* from Jiangsu Hansoh Pharmaceutical Group; and

- *Sunitinib malate* from Dr. Reddy's.

New Data

- **Gilotrif®** (*afatinib dimaleate*) – The results of a study of *afatinib* in pediatric tumors, which was initiated in 2015 to assess the safety and efficacy of Boehringer's kinase inhibitor in children, were incorporated into the prescribing information for the NSCLC therapy. The study included 37 patients between the ages of 2 and 17 who had recurrent or refractory solid tumors with known ErB pathway dysregulation. Although the results were not sufficient to establish safety and efficacy in children, "(n)o new safety signals were observed in pediatric patients in this trial" and the pharmacokinetic parameters that were observed in the study "were within range of values in adults."

New Molecular Entities

- **Vijoice®** (*alpelisib*) – Novartis was granted accelerated approval to market a newly branded version of its breast cancer drug (Piqray®) as treatment for PIK3CA-Related Overgrowth Spectrum (PROS), a group of conditions that share a mutation in the PI3K gene, which in turn leads to uncontrolled growth. Clinical features of PROS include congenital or childhood onset, sporadic and mosaic overgrowth, and progressive disease. While not a "cancer" therapy (or a "new molecular entity") the approval of Vijoice® is included because of the volume of cancer-related regulatory activity this month focused on PI3K inhibitors (see discussion below regarding the April ODAC meeting).

Safety-Related Changes

- **Balversa®** (*erdafitinib*) – The warning (n Section 5.2) regarding hyperphosphatemia in patients treated with Janssen's targeted therapy for locally advanced or metastatic urothelial carcinoma was expanded. The new section ("Hyperphosphatemia and Soft Tissue Mineralization") urges physicians to monitor patients throughout treatment, to restrict phosphate intake in all patients to 600-800 mg daily, and, if serum phosphate is above 7.0 mg/dL, to consider adding an oral phosphate binder until levels return for 5.5 mg/dL or less. In addition, new subsections—8.6 on treating patients with renal impairment and 8.7 on treating patients with hepatic impairment—were added to Section 8 of the prescribing information (Use in Specific Populations). The recommendations remain that no dose adjustments are needed with mild to moderate impairment of either type and that either "no data" or only "limited data" are available for treating patients with severe renal or severe hepatic impairment, respectively.

- **Beleodaq®** (*belinostat*) – The Highlights section of the prescribing information for Acro Pharma's histone deacetylase inhibitor for relapsed or refractory peripheral T-cell lymphoma was updated to include *gastrointestinal toxicity* (which seems to have been inadvertently left out of previous versions).

- **Idamycin®** (*idarubicin*) and **Idamycin PFS®** (*idarubicin*) **--** The Pregnancy subsection of Warnings and Precautions (for both formulations of Pfizer's antileukemic anthracycline) were updated with the addition of a statement for both men and women to seek advice for fertility preservation before treatment and/or seek genetic counselling after treatment. The expansion also includes advice to nursing women on the washout period for the commencement of breastfeeding after the last dose.

- **Ninlaro®** (*ixazomib citrate*) – A new "limitations of use" statement has been added to the Indications and Usage section of the prescribing information for Takeda's proteasome inhibitor. The statement—that "Ninlaro® is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma (MM) in combination with lenalidomide and dexamethasone outside of controlled clinical trials"—was added based on the findings from three randomized studies which showed 1) that patients randomized to receive Ninlaro® in the maintenance setting actually had increased mortality compared patients randomized to placebo, and 2) the addition of Ninalro® to a regimen of lenalidomide and dexamethasone as first-line therapy for MM did not lead to improved outcomes.

- **Zepzelca™** (*lurbinectedin*) – Two new subsections—one on *Extravasation Resulting in Tissue Necrosis* and one on *Rhabdomyolysis*—were added to the Warnings and Precautions section of the prescribing information for the novel alkylating agent that Jazz Pharmaceuticals brought to market in 2020. The new language urges physicians to consider use of a central venous catheter to reduce the risk of extravasation, to monitor patients for signs and symptoms of extravasation during infusions, to discontinue the infusion should extravasation occur and, in that event, to monitor for signs and symptoms of tissue necrosis. With respect to *rhabdomyolysis,* the recommendations are to monitor CPK prior to initiating therapy--and periodically during treatment—and to withhold, reduce the dose, or permanently discontinue treatment based on severity of the condition (with recommendations for dose modification newly included in Table 2 of the label).

Other Changes

None

CLINICAL TRIALS INFORMATION

Current Trials MUSC - Hollings Cancer Center
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DLBCL/Aggressive NHL

A Phase 1b Open-Label Study to Evaluate the Safety and Anti-cancer Activity of Loncastuximab Tesirine in Combination with Other Anti-cancer Therapies Agents 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. This trial is currently going through a major amendment to only include the combination of ADCT-402 with Polatuzumab. Anticipate that it opens for enrollment later this month.

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, Placebo-Controlled, Phase 3 Study of Brentuximab Vedotin or Placebo in Combination with Lenalidomide in Subjects with Relapsed or Refractory DLBCL

Patient Population/Notes: Likely to be very effective in certain subsets of patients with DLBCL including those relapsing after CAR-T cell as well.

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.

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. Have enrolled a lot of patients on this trial - thanks for referring!

Multiple Part Clinical Trial of Brentuximab Vedotin in Classical Hodgkin Lymphoma Subjects

Patient Population/Notes: Very exciting trial that combines Brentuximab and Nivolumab with cytotoxic chemotherapy (Adriamycin and Dacarbazine) in the frontline setting. We are excited about this trial because there will be no vinblastine given with BV so hopefully less neuropathy and improvement in efficacy as BV+Nivo alone looks to have very promising efficacy in frontline/relapsed setting. Results of AD+BV in this setting already promising so this is likely to be a very effective treatment option! Great trial for early stage non-bulky patients which is a big % of newly dx cHL!

Mantle Cell Lymphoma

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. Anticipate that it opens for enrollment later this month.

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. Trial will be activated at the beginning of June.

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. Anticipate that it opens for enrollment later this month.

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 Ibrutinib plus Obinutuzumab versus Ibrutinib plus Venetoclax plus Obinutuzumab in Untreated Older Patients (>/=70 years of age) with CLL

Patient Population/Notes: Cooperative group trial for patients >/= 70. Patients are excluded if they have SLL, but can have 17p or TP53 mutation.

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 who 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. 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 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.

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. Set to open for enrollment later this month.

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