2022–2023 Drug Updates in Solid Tumors

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Presenter's disclosures of conflicts of interest are found at the end of this article.

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Abstract

At JADPRO Live 2023 in Orlando, Lisa M. Holle, PharmD, BCOP, FHOPA, FISOPP, briefed advanced practitioners on key US Food and Drug Administration approvals from late 2022 to late 2023. Dr. Holle described indications, mechanisms of action, and monitoring and management of side effects of new therapies in solid malignancies.

At the popular New Drug Updates session at JADPRO Live 2023, Lisa M. Holle, PharmD, BCOP, FHOPA, FISOPP, clinical professor at UConn School of Pharmacy and UConn School of Medicine, and oncology pharmacist at UConn Health Neag Comprehensive Cancer Center, reviewed new US Food and Drug Administration (FDA) approvals in solid malignancies.

FUTIBATINIB FOR CHOLANGIOCARCINOMA

Futibatinib is a novel, selective, pan-FGFR inhibitor indicated for previously treated patients with unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma with *FGFR2* gene fusions. FGFR inhibitors bind to the receptor and the tyrosine kinase, which has downstream effects on multiple pathways that are involved in cell production (e.g., JAK-STAT pathway, the PI3K pathway, the Ras-Raf-MEK pathway).

"Unlike the other two drugs that are approved for intrahepatic cholangiocarcinoma, futibatinib is an irreversible, highly selective inhibitor. This helps prevent some of the resistance that can develop to these types of drugs, as it binds more selectively and has a longer duration of effect," commented Dr. Holle.

Approval was based on the FOENIX-CCA2 study, which was a multinational phase III trial. About 80% of patients had an *FGFR* gene fusion. Forty percent of patients had an objective response, with the majority being partial responses. The duration of response was approximately 9.7 months.

Dosing, Monitoring, and Adverse Event Management

Patients take five 4-mg tablets for a total of 20 mg once daily with or without food. There are no black box warnings, but there are warnings for ocular toxicity, hyperphosphatemia, and embryo-fetal toxicity. P-

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glycoprotein and CYP3A4 inhibitors and inducers should be avoided in this population. Futibatinib can increase the exposure of P-glycoprotein and BCRP substrates. In terms of grade 3 or 4 adverse effects, hyperphosphatemia occurred in 40%, hypophosphatemia in 20%, and hyponatremia in 15% of patients.

It is important to monitor the phosphate levels of patients on FGFR inhibitors.

"I would recommend that you monitor the phosphate level weekly, especially in the beginning until you're sure how the patient reacts to the medication," said Dr. Holle.

Clinicians should ensure that the patient is not on any phosphate-increasing drugs, such as vitamin D, antacids, or phosphate supplements. In addition, they should be on a low-phosphate diet, which includes avoiding processed foods, animal products, whole grains, and beans.

Ocular toxicity is another key toxicity. An ophthalmologic exam is needed at baseline every 2 months for the first 6 months and every 3 months thereafter. Collaborating closely with an ophthalmologist is important in order to have patients evaluated immediately if symptoms occur. The drug should also be stopped until the symptoms resolve.

Additional laboratory values that should be monitored include coagulation studies at baseline, liver function tests, and renal function, along with phosphate levels, serum glucose, and electrolytes at each cycle. As futibatinib is an inhibitor of fibroblast growth factor receptor, there can be toxicities related to dryness of the mucous membranes and skin. These include skin toxicity, hand-foot syndrome, and fingernail and toenail disfiguration, as well as constipation, mucositis, and xerostomia.

TREMELIMUMAB FOR HCC AND NSCLC

Tremelimumab is a new CTLA-4 inhibitor, similar to ipilimumab, the other CTLA-4 inhibitor on the market. Checkpoint inhibitors are responsible for helping T-cell regulation, binding the CTLA-4 immunoglobulin on T cells in order to stop the checkpoint from happening and allowing T cells to target the destruction of tumor cells. It is approved in combination with durvalumab for two different indications: One is for unresectable hepatocellular carcinoma in the metastatic setting and the other with platinum-based chemotherapy for metastatic non–small cell lung cancer (NSCLC) without *EGFR* or *ALK* aberrations.

The HIMALAYA trial was a global, open-label, phase III, multicenter study of 1,171 patients with unresectable hepatocellular carcinoma. Patients were randomly assigned to receive tremelimumab (300 mg IV) plus durvalumab (1,500 mg IV every 4 weeks; called STRIDE), durvalumab (1,500 mg IV every 4 weeks), or sorafenib (400 mg orally twice daily). STRIDE dosing used tremelimumab as a primer to "shut down" the immune system, and was then followed by durvalumab every 4 weeks. The median overall survival (OS) comparing STRIDE dosing vs. sorafenib increased by about 3.5 months with the STRIDE dosing, which was statistically significant.

The POSEIDON study was a global, open-label, phase III study of 1,013 patients with *EGFR/ALK* wild-type metastatic NSCLC randomized to receive durvalumab and chemotherapy, chemotherapy, or the combination of tremelimumab, durvalumab, and chemotherapy for four cycles, followed by maintenance durvalumab therapy every 4 weeks and a one-time dose of tremelimumab at week 16. Progression-free survival (PFS) increased by about 0.7 months in the tremelimumab arm, and there was a trend for improved OS, although the data were not completely mature at the time of the study publication. The dual therapy of durvalumab and chemotherapy also improved PFS, but OS was not improved.

Dosing, Monitoring, and Adverse Event Management

The dosing depends upon the indication. There are no dose adjustments as with all immunotherapies. There were also no unexpected adverse events outside of the typical immune-related adverse events.

As with other checkpoint inhibitors, patients should be monitored and assessed for immune-related adverse events. There are no specific premedications indicated with tremelimumab to prevent infusion-related reactions.

MIRVETUXIMAB SORAVTANSINE FOR OVARIAN CANCER

Mirvetuximab soravtansine is an antibody-drug conjugate (ADC) formed by an immunoglobulin G1

antibody that is linked to a cytotoxic agent DM4 with a disulfide linker. It attaches to folate receptor alpha, a receptor overexpressed on the surface of epithelial tumor cells, characteristic of ovarian, endometrial, triple-negative breast, and non–small cell lung cancers. After an ADC/receptor complex is formed, mirvetuximab soravtansine-gynx is internalized, and DM4 is released inside the cell. DM4 leads to cell-cycle arrest and apoptosis and is also able to diffuse into neighboring cells and induce further cell death. Mirvetuximab soravtansine is indicated for the treatment of adults with folate receptor alpha–positive, platinum-resistant epithelial, ovarian, fallopian tube, and primary peritoneal cancer in the setting of having received at least one to three systemic therapies.

The SORAYA study was a phase II study. It used a specific assay to assess for folate receptor alpha positivity. The primary endpoint was overall response rate (ORR), which was approximately 30% for this patient population that has few options for treatment. Most were partial responses, and the median duration of response was 7 months.

Dosing, Monitoring, and Adverse Event Management

"There are two key things to know about this drug. In the trial, it was dosed on ideal body weight. The package insert uses adjusted ideal body weight. This is different because we typically use actual body weight for most of our anticancer medications," noted Dr. Holle. "It also has a significant amount of potential ophthalmologic toxicity. We give lubricating eye drops and corticosteroid eye drops to the patient starting on day 0 through a day 8 of each cycle."

Mirvetuximab soravtansine is given intravenously at 6 mg/kg adjusted ideal body weight administered every 3 weeks.

Nausea and ophthalmologic toxicity were frequently reported side effects. Typical premedications such as a steroid, diphenhydramine, acetaminophen, and an antiemetic are used for infusion-related reactions and nausea. Lubricating eye drops are given four times a day and as needed throughout the treatment period. The patient must wait 10 minutes before they use the steroid eye drops. It is used six times a day for the first 4 days, and then four times a day after that through the eighth day. There is a black box warning for ocular toxicity. Closely working and collaborating with an ophthalmologist is important.

The ophthalmologic exam includes a visual acuity and slit-lamp exam at baseline for every other cycle for eight cycles, and as needed. It is recommended to hold off on writing a prescription for steroid eye drops until that exam has been done, because if it is not normal, steroid eye drops should not be administered. With any onset of symptoms, patients should immediately be referred to an ophthalmologist and the dose held or adjusted. The patient should be counseled on good eyelid margin hygiene, such as keeping it clean, using warm compresses, wearing sunglasses, avoiding contacts, and reducing screen time. Ten percent of patients had interstitial lung disease, and peripheral neuropathy can also occur.

Additionally, complete blood count should be monitored for myelosuppression, renal hepatic dysfunction, and electrolytes due to the cytotoxic component.

ADAGRASIB FOR NSCLC

Adagrasib is a *KRAS* inhibitor indicated for adults with *KRAS* G12C–mutated locally advanced or metastatic non–small cell lung cancer who have received at least one prior therapy. Adagrasib binds to KRAS at the switch-II pocket and maintains it in the guanosine diphosphate phase as opposed to a triphosphatase phase, which is necessary for downstream signaling induction. By having it in the diphosphate phase, it inhibits downstream signaling, prevents cell proliferation, and causes cell death.

The KRYSTAL-1 study was a phase II expansion cohort study with patients who have *KRAS* G12C mutations previously treated with platinum-based therapy and a checkpoint inhibitor. They received adagrasib at 600 mg twice daily. Most responses were partial responses. The overall objective response rate was 43%. However, over 80% of patients had a measurable change in disease burden.

Dosing, Monitoring, and Adverse Event Management

Adagrasib is given as three 200-mg tablets twice daily. Although it does not need to be taken with

food, it is recommended in order to minimize potential gastrointestinal toxicities.

Common adverse events are diarrhea, nausea, fatigue, and vomiting. There are warnings and precautions surrounding gastrointestinal toxicity, such as nausea, vomiting, and diarrhea, as well as obstruction, colitis, or ileus. QTc prolongation has also been observed. Hepatotoxicity and pneumonitis were seen, although not as frequently as with mirvetuximab soravtansine. Grade 3 or 4 adverse events included lymphopenia, pneumonia, hepatotoxicity, and dyspnea.

QTc interval–prolonging medications should be avoided in patients taking adagrasib. Adagrasib should be withheld if there is a greater than 60-ms increase from baseline or a one-time increase of a QTc interval greater than 500 ms.

Liver function tests should be evaluated at baseline, monthly for the first 3 months, and then as needed. It is recommended to avoid hepatotoxic drugs in these patients. It is a moderately to highly emetogenic drug, so patients may need prophylactic antiemetics.

In addition, a complete blood count with a differential at baseline and periodically, lipase at baseline and periodically, and renal function, liver function, and electrolyte monitoring is recommended. Interstitial pneumonitis occurred in approximately 4% of patients, which was not as high as it was with mirvetuximab soravtansine, but it can occur. Therefore, patients should be monitored for those signs and symptoms. Neuropathy, peripheral edema, and arthralgias have also been reported.

NADOFARAGENE FIRADENOVEC FOR BLADDER CANCER

Nadofaragene firadenovec is a viral gene-based therapy for high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors. It is the first gene therapy FDA approved in bladder cancer.

This drug is a nonreplicating adenoviral vector-based gene therapy designed to deliver a copy of a gene encoding a human interferon alfa-2b (IFNα2b) to the bladder urothelium. The virus is instilled into the bladder and the adenovirus releases that interferon alfa, which will then irritate the bladder cells and cause apoptosis (Figure 1).

CS-OO3 was a phase II study in patients with high-risk BCG-unresponsive non-muscle invasive bladder cancer (carcinoma in situ, with or without papillary tumors). There were 98 evaluable patients, and 51% of those had a complete response at 12 months.

"The duration of response was about 10 months, but interestingly, more than 40% of patients had a response that lasted more than a year. At this point, 95% of patients did not go on to have muscle-invasive bladder cancer, which is important because that's what we're trying to prevent. About 75% of those patients didn't need to have a cystectomy," commented Dr. Holle.

Dosing, Monitoring, and Adverse Event Management

Nadofaragene firadenovec is instilled through a catheter into the bladder every 3 months for four doses (at 0, 3, 6, 9 months) and is left in the bladder for an hour. Patients may be given an anticholinergic premedication to prevent bladder spasms.

Common adverse drug reactions are related to instilling something into the bladder, such as discharge, bladder spasm, and fatigue. Urinary tract infections are possible. Hyperglycemia occurred in 6% of patients. It was otherwise well tolerated. As the drug is a virus, it should not be administered in patients who are immunocompromised or immunodeficient. In addition, caretakers who are immunocompromised or immunodeficient need to take caution to not be infected with the adenovirus. It is contraindicated if there is hypersensitivity to interferon.

Monitoring includes infections and laboratory values such as a complete blood count with differential, triglycerides, and serum glucose during treatment.

ELACESTRANT FOR BREAST CANCER

Elacestrant, like fulvestrant, is a selective estrogen receptor degrader (SERD), but unlike fulvestrant, it is orally administered. Elacestrant inhibits the estrogen receptor, allowing estrogen receptor degradation so it is not able to be incorporated. It does not have any agonist properties as selective estrogen receptor modulators do. This is

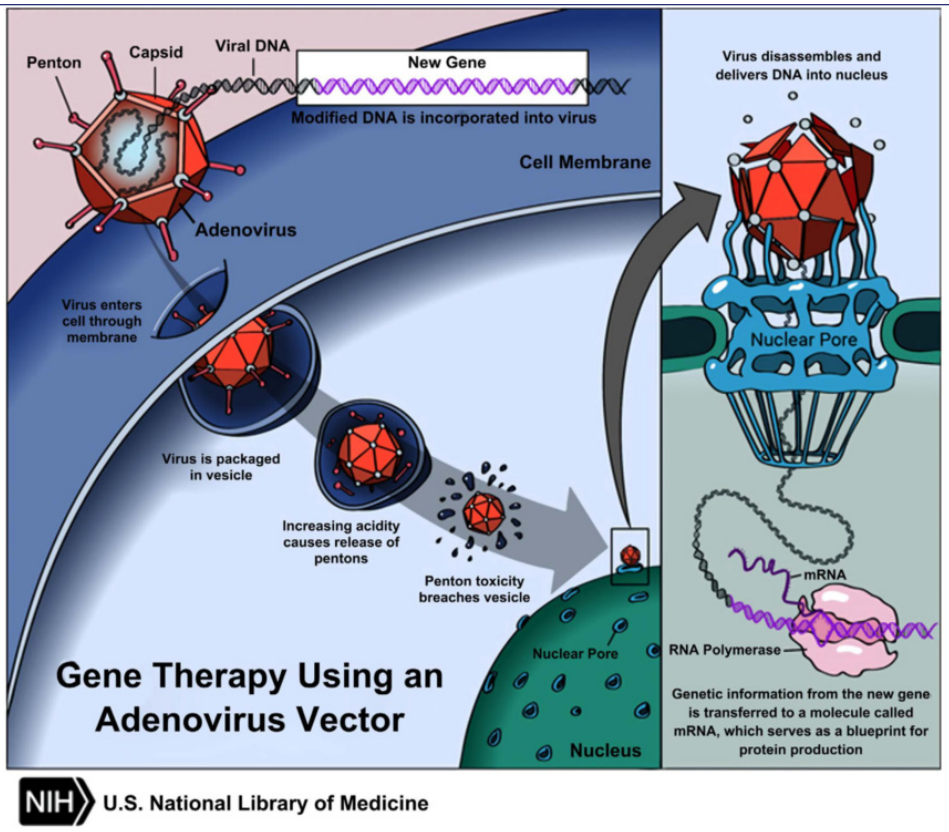

Figure 1. Schematic representing use of viral vectors in carrying certain genetic information to recipient cells. Reproduced from the U.S. National Library of Medicine.

even more effective in patients who have an *ESR1* mutation, which occurs in about 40% of patients who have hormone-positive breast cancer. It is indicated for postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer who have already progressed after at least one line of endocrine therapy.

The EMERALD study was a global, open-label phase III study. It included 477 patients with ER-positive, HER2-negative advanced breast cancer who had previously received one or two lines of endocrine therapy and a CDK4/6 inhibitor, and one or more chemotherapy regimens. Patients were randomized to receive either standard of care with a SERD like fulvestrant or an aromatase inhibitor. The overall 12-month PFS for all patients was 22.3% vs. 9.4%, which was statistically significant. For patients with an *ESR1* mutation, the 12-month PFS was also good, at 27% compared with 8%, which was also statistically significant.

Dosing, Monitoring, and Adverse Event Management

Elacestrant is a 345-mg tablet taken once a day with food. There is an 84-mg tablet available for dose reductions. A dose reduction is necessary if a patient has Child-Pugh score B.

The warnings for elacestrant are for dyslipidemia and embryo-fetal toxicity. There are interactions with CYP3A4 inhibitors and inducers, and it is recommended to reduce the dose of a P-glycoprotein or a BCRP substrate since elacestrant is an inhibitor of these two substrates. It is well tolerated. The only reported grade 3 or 4 adverse event was anemia, which occurred in 2% of patients.

In terms of monitoring, a lipid profile needs to be performed, including triglycerides, both at baseline and periodically.

"I was having a discussion with my colleagues on what it means to 'periodically monitor for lab values.' It depends on a host of factors, such as how often or soon a side effect is going to be seen, and how critical that side effect might be," said Dr. Holle.

"For example, hypertriglyceridemia is something that we don't want to have happen for a long period of time, but it's not something that needs to be addressed immediately and will take time to manage. Therefore, it probably doesn't need to be done with every cycle. It will also depend on what your workflow is for monitoring patients."

A complete blood count with differential and liver function test is recommended at baseline and periodically. There should also be a metabolic panel. Increases in creatinine may be observed, but it does not signify that there is a change in kidney function. Hyponatremia can occur, although it is not clinically significant. Myalgias and arthralgias can also occur, so clinicians should monitor and treat symptomatically as with other estrogen- or hormone-receptor drugs.

RETIFANLIMAB FOR MCC

Retifanlimab is another monoclonal antibody directed at PD-1, and therefore binds PD-1 in order to allow that checkpoint to be turned off and the T cells to be able to recognize foreign cells and cause cell death. Its indication is for patients with metastatic or recurrent locally advanced Merkel cell carcinoma.

The PODIUM-201 study was an open-label, phase II global study including patients with metastatic recurrent unresectable local regional Merkel cell carcinoma. The ORR in chemotherapy-naive patients was 52%. The majority of responses were partial responses, although upwards of 20% of patients had a complete response. The median duration of response was not reached at the time of the FDA approval.

Dosing, Monitoring, and Adverse Event Management

Retifanlimab is intravenously administered every 4 weeks, and like other checkpoint inhibitors, typically given for up to 2 years.

As with other checkpoint inhibitors, immune-mediated adverse events can occur. There is also the potential for infusion-related reactions. There are no required premedications for retifanlimab; therefore, clinicians should monitor patients and administer them if a reaction occurs. There is a unique warning for allogeneic hematopoietic stem cell transplant–related complications.

NIRAPARIB AND ABIRATERONE ACETATE FOR CRPC

The following drugs have already gained approval but have been reformulated. The first is a combination product of niraparib, a PARP inhibitor, and abiraterone acetate, an androgen receptor inhibitor. This combination product is used with prednisone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated metastatic castration-resistant prostate cancer.

"Androgen receptor inhibitors like abiraterone can be synergistic with PARP inhibitors in the setting where there are gene mutations that are responsible for DNA repair, such as *BRCA*, as well as other homologous recombinant gene functions," explained Dr. Holle.

The MAGNITUDE study was a phase III placebo-controlled trial in metastatic castration-resistant prostate cancer patients. There were two cohorts, those with homologous recombinant deficiency mutations such as *BRCA* or *ATM*, and those without any detectable alterations. The primary endpoint was radiographic PFS, which is common as a primary endpoint in prostate cancer trials. In the *BRCA1/2* mutation subgroup, the radiographic PFS time was improved from 10.9 months to 16.6 months. Within the homologous recombinant repair deficiency group, radiographic PFS was improved from 13.7 months to 16.5 months.

Dosing, Monitoring, and Adverse Event Management

The tablet is made up of 200 mg of niraparib and 1,000 mg of abiraterone. Because of the abiraterone component, it must be taken on an empty stomach. The tablet is given in combination with prednisone.

There are many drug interactions that are associated with this combination product. One in particular is to radium-223, which can increase the risk of fracture. It is recommended to wait 5 days after the last dose of radium-223 before starting abiraterone. In addition, severe hypoglycemia can occur with thiazolidinediones such as pioglitazone or repaglinide, which is thought to be due to the interaction with abiraterone. Grade 3 or 4 adverse events, such as hypertension, hypokalemia, and musculoskeletal adverse events, are most commonly associated with the abiraterone component.

Since PARP inhibitors can cause myelosuppression, a complete blood count with differential is recommended weekly for the first 4 weeks, then every 2 weeks for the next 8 weeks, and then monthly. Blood pressure should be monitored, as well as electrolytes and fluid retention weekly for the first 8 weeks and then monthly. Liver function tests should be ordered at baseline every 2 weeks for 12 weeks and then monthly, and glucose periodically. Adrenocortical insufficiency can occur, particularly when patients come off of prednisone.

"In most patients, this dose of prednisone will be enough to prevent that, but always keep that in the back of your mind if you have a patient who has significant fatigue or other signs of adrenocortical insufficiency," commented Dr. Holle.

MELPHALAN HEPATIC DELIVERY KIT FOR MELANOMA

The second reformulated drug is the melphalan hepatic delivery kit, which is indicated for adult patients with uveal melanoma with unresectable hepatic metastases that affect less than 50% of the liver, have no extrahepatic metastases or extrahepatic disease that is limited to bone, lymph nodes, subcutaneous tissue, or lung, and could be removed by surgery or radiated. Melphalan is an alkylating agent that inhibits DNA and RNA synthesis.

The approval was based on the phase III FOCUS trial, which randomized patients to this delivery system with melphalan or best alternative care, which could be transarterial chemoembolization, pembrolizumab, ipilimumab, or dacarbazine. The study had 91 patients, and the ORR was about 37%, with a duration of effect of approximately 14 months.

Dosing, Monitoring, and Adverse Event Management

The dosing is 3 mg/kg based on ideal body weight. It is an intra-arterial injection administered over 30 minutes, followed by a 30-minute washout period. It is given every 6 to 8 weeks. As there are many potential complications that can occur with this product, there is a Risk Evaluation and Mitigation Strategy program associated with it.

Hemorrhage is highly likely in this regimen. It should not be used in patients with uncorrected coagulopathy, and patients must wait 4 weeks after surgery or other liver procedures before this can be administered. All anticoagulation and antiplatelet agents should be discontinued prior to the patient undergoing a procedure. Platelets and coagulation parameters should be monitored routinely. Patients should also be screened for a history of bile duct surgeries.

"Hypotension is a real concern and is common in these patients, so you have to make sure they're euvolemic and discontinue medications such as angiotensin-converting enzyme inhibitors and calcium channel blockers," advised Dr. Holle.

With melphalan, myelosuppression is top of mind. Therefore, complete blood counts with differential should be monitored. It should not be administered if platelets are ≤ 100,000, hemoglobin < 10 g/dL, or absolute neutrophil count ≤ 2,000. These patients may need growth factor support. Hypersensitivities to keep in mind are an iodinated contrast allergy and a latex allergy to the catheter. Patients should be premedicated with steroids if they have a prior contrast allergy.

In addition, patients who have hypersecretory gastrointestinal conditions are more likely to have complications, so it is recommended to administer a proton pump inhibitor the day before and the morning of the procedure. Because melphalan is an alkylating agent, it has the potential for secondary malignancies, such as acute myelogenous leukemia or myelodysplastic syndrome. ●

Disclosure

The presenter has no relevant financial relationships to disclose.

References

Aboagye, E. O., Barwick, T. D., & Haberkorn, U. (2023). Radiotheranostics in oncology: Making precision medicine possible. *CA: A Cancer Journal for Clinicians*, *73*(3), 255–274. https://doi.org/10.3322/caac.21768

American Cancer Society. (2023). Key statistics for prostate cancer. https://www.cancer.org/cancer/types/prostate-cancer/about/key-statistics.html

Bayer. (2023). Nubeqa (darolutamide) package insert. https://www.nubeqa-us.com/pi

Tohi, Y., Kataoka, K., Miyai, Y., Kaku, Y., Dainichi, T., Haba, R., Tsunemori, H., & Sugimoto, M. (2021). Apalutamide-associated skin rash in patients with prostate cancer: Histological evaluation by skin biopsy. *IJU Case Reports, 4*(5), 299–302. https://doi.org/10.1002/iju5.12331