New Drug Update: Hematologic & Solid Tumor Malignancies

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Disclosures

I have nothing to disclose. I will be discussing off-label indications.

Objectives

1. Review pharmacology of newly FDA-approved oncology medications for use in the management of hematologic or solid tumor malignancies
2. Discuss primary literature supporting the approval and use of these medications
3. Identify clinical pearls and place in therapy for these medications

Recently Approved Agents for Hematologic Malignancies

Medication Name	Approval Date	Indication
Zanubrutinib (Brukinsa)	9/1/21* 9/14/21*	Waldenstrom's macroglobinemia R/R marginal zone lymphoma
Ruxolitinib (Jakafi)	9/22/21*	Chronic GVHD
Asciminib (Scemblix)	10/29/21	Ph-positive chronic myeloid leukemia
Ropeginterferon alfa-2b (Besremi)	11/12/21	Polycythemia vera
Abatacept (Orencia)	12/15/21*	Prophylaxis of acute GVHD
Ciltacabtagene autoleucel (Carvykti)	2/28/22	R/R multiple myeloma
Pacritinib (Vonjo)	2/28/22	Primary or secondary myelofibrosis
Ibrutinib (Imbruvica)	8/24/22*	Pediatric patients with chronic GVHD
Pemigatinib (Pemazyre)	8/26/22*	R/R myeloid/lymphoid neoplasms with fibroblast growth factor receptor 1 rearrangement

*New Indication

FDA. Oncology (Cancer) /Hematologic Malignancies Approval Notifications. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

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Asciminib (Scemblix®)

Approved

- October 29, 2021

Indication

- Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase, in adults previously treated with 2+ tyrosine kinase inhibitors (TKI) or with the T315I mutation

Drug Class

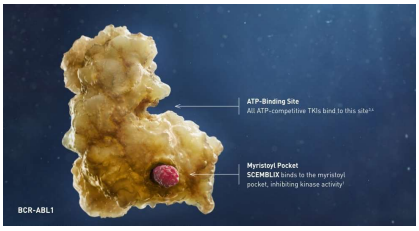
- STAMP inhibitor (specifically targeting the ABL myristoyl pocket)

Mechanism of Action

- Potent inhibition of ABL1 kinase activity of the BCR-ABL1 fusion protein via allosteric binding to the ABL myristoyl pocket, alternative binding site to traditional TKIs

Scemblix (Asciminib) tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; October 2021.

Asciminib MOA



Hughes TP et al. N Engl J Med. 2019; 381(24):2315-26
Novartis. Mechanism of Action | SCEMBLIX® (asciminib) Tablets for Ph+ CML . Available at https://www.hcp.novartis.com/products/scemblix/ph-cml/mechanism-of-action/

Dosing and Adjustments

DOSING

CML-chronic phase, resistant or intolerant to 2+ prior TKIs
- 80 mg by mouth daily
- 40 mg by mouth twice daily

CML-chronic phase, with T315I mutation
- 200 mg by mouth twice daily

ADJUSTMENTS

No renal or hepatic adjustments

Dose reduction levels for toxicity adjustments

Reduction	80mg daily	40 mg twice daily	200mg twice daily
First	40 mg daily	20 mg twice daily	160 mg twice daily
Subsequent	Permanently discontinue		

Scemblix [Asciminib] tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; October 2021.

ASCEMBL

- Open-label, randomized, phase 3 trial (n=233)
- Evaluated efficacy and safety of asciminib 40 mg twice daily vs. bosutinib 500 mg daily
- Included adult patients with CML in chronic phase that are resistant/intolerant to ≥ 2 prior TKIs
- Excluded T315I & V299L mutations

Rea D et al. Blood. 2021; 138(21): 2031-2014.

ASCEMBL – Efficacy Endpoints

Efficacy Endpoint	Asciminib (n=157)	Bosutinib (n=76)	Risk difference (95 % CI)
MMR at 24 weeks, % (BCR-ABL1^{IS} ≤ 0.1%)	25.5	13.2	12.2% (2.19-22.30) 2-sided p = 0.029
CCyR at 24 weeks, %	40.8	24.2	17.3% (3.62-30.99)
EMR at 12 weeks, % (BCR-ABL1^{IS} ≤ 10%)	63.1	43.4	--
DMR at 24 weeks, % MR^{4} (BCR-ABL1^{IS} ≤ 0.01%) MR$^{4.5}$ (BCR-ABL1^{IS} ≤ 0.0032%)	10.8 5.3	8.9 1.3	--

MMR at 24-weeks was greater with asciminib regardless of line of therapy and in patients with prior lack of efficacy to another TKI

Rea D et al. Blood. 2021; 138(21): 2031-2014.

MMR – MAJOR MOLECULAR RESPONSE EMR – EARLY MOLECULAR RESPONSE
CCYR – COMPLETE CYTOGENETIC RESPONSE DMR – DEEP MOLECULAR RESPONSE

CABL-001X2101

- Phase I, dose escalation study (n=150)
- Primary objective – to determine maximum tolerated or recommended dose of asciminib (10-200mg once or twice daily)
- Adult patients with chronic (n=141) and accelerated (n=9) phase CML that are resistant/intolerant to ≥ 2 prior TKIs
- T315I not excluded if one prior TKI received (n=33)

Hughes TP. N Engl J Med. 2019;381(24):2315-2326.

CABL-001X2101

Patients with T315I mutation (n=33)
- 15 of 28 patients (54%) with CP-CML had prior ponatinib exposure
- 2 of 5 patients (40%) with AP-CML had prior ponatinib exposure

Most patients with T315I mutation achieving a response with asciminib received doses of more than 150 mg twice daily

Efficacy in chronic phase CML without T315I mutation:
- 92% with a hematologic relapse had a hematologic response
- 54% without a complete cytogenetic response at baseline had a complete cytogenetic response
- 37% achieved or maintained at major molecular response by 6 months and 48% by 12 months

Hughes TP. N Engl J Med. 2019;381(24):2315-2326.

Adverse Events

COMMON	SERIOUS
Myelosuppression	Pancreatitis
Hypertension	Cardiovascular toxicity (hypertension, ischemia, thrombosis, heart failure, and arrhythmia)
Hypersensitivity (rash, edema)	
Fatigue, arthralgia	

Rea D et al. Blood. 2021; 138(21): 2031-2014.
Scemblix (Asciminib) tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; October 2021.

Monitoring and Pearls

MONITORING	CLINICAL PEARLS
Complete blood count	Should be taken without food, 2 hours after or 1 hour before a meal
Serum lipase & amylase	Do not crush or chew
Pregnancy status	Available as 20mg & 40mg tablets
Adherence	Emetic risk: Minimal/Low (< 30%)
	No issues with acid suppressants

Scemblix (Asciminib) tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; October 2021.

Place in Therapy

Chronic phase CML with resistance or intolerance to 2+ prior TKIs

T315I mutation with failure of or desire to avoid ponatinib
- Data for asciminib prior to ponatinib in this setting is limited

NCCN. Chronic Myeloid Leukemia. V 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

Future Directions

Clinical trials that are currently active:

- Front-line CML
  - In combination with other TKI or as monotherapy (NCT03906292)
  - As monotherapy compared to other TKIs (NCT04971226)
- Second-line CML as monotherapy (NCT05384587)
- Pediatric CML as monotherapy (NCT04925479)

- Ph+ B-ALL or CML in lymphoid blast crisis, in combination with dasatinib & prednisone (NCT03595917)

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/results?cond=&term=asciminib&cntry=&state=&city=&dist=

Ciltacabtagene autoleucel (Carvykti™)

Approved
- February 28, 2022

Indication
- Relapsed/refractory multiple myeloma in adult patients after ≥ 4 lines of therapy including a proteosome inhibitor (PI), immunomodulator (IMiD), and anti-CD38 monoclonal antibody

Drug Class
- B-cell maturation antigen (BCMA)-directed genetically modified autologous chimeric antigen receptor (CAR) T-cell therapy

Mechanism of Action
- Patient's T-cells are genetically modified to express a CAR that targets BCMA within 2 distinct binding domains. After infusion back into the patient, these anti-BCMA CAR-T cells recognize and eliminate BCMA-expressing target cells. BCMA is over-expressed on multiple myeloma B-cells

Carvykti (ciltacabtagene autoleucel) [Prescribing Information]. Horsham, PA: Janssen Biotech Inc; March 2022.

Dosing and Adjustments

LYMPHODEPLETING CHEMOTHERAPY

Cyclophosphamide 300 mg/m^2 & Fludarabine 30 mg/m^2 x3 days

Cilta-cel is infused 5-7 days after start of lymphodepletion

Consider repeating lymphodepleting chemotherapy if cilta-cel is delayed > 14 days and patient has recovered from initial course

CILTA-CEL DOSING

Target dose: 0.5-1.0 x 10^6 CAR-positive viable T-cells per kg

Maximum dose: 1 x 10^8 CAR-positive viable T-cells per kg

Pre-medication (30-60 minutes prior):
- Acetaminophen 650mg – 1000mg PO
- Diphenhydramine 25mg – 50mg IV

Carvykti (ciltacabtagene autoleucel) [Prescribing Information]. Horsham, PA: Janssen Biotech Inc; March 2022.

CARTITUDE-1

- Single-arm, open-label, phase 1b/2 study at 16 U.S. centers (n=113, with 97 patients receiving cilta-cel)
- Primary objective – to characterize safety and establish target dose, as well as evaluate overall response rate
- Study included fit adult patients with the following treatment history
  - exposure to ≥ 3 prior lines of therapy or double refractory to a PI and IMiD
  - have received a PI, IMiD, and anti-CD38 antibody
- Excluded patients with prior CAR T-cell targeted or BCMA-targeted therapy

Berdeja et al. Lancet 2021;398(10297):314-324.

CARTITUDE-1 – Efficacy Endpoints

Efficacy Endpoint	Cilta-Cel (n=97)	95% CI
Overall response rate, n (%) Stringent complete response, n (%)	94 (97) 65 (67)	91.2 – 99.4
Median time to CR or better, months (IQR)	1.9 (1-6.5)	--
Median duration of response, months	NR	15.9 – NE
12-month progression free survival, n (%)	74 (77)	66.0 – 84.3
12-month overall survival, n (%)	86 (89)	80.2 – 93.5
MRD negativity rate at 10^{-5}	53/57 (93)	

At 2-year follow-up (median 27.7 months), 82.5% of patients achieved a stringent CR

27-month PFS rate was 54.9% (95% CI 44.0-64.6) and OS rate was 70.4% (95% CI 60.1-78.6)

Berdeja et al. Lancet 2021;398(10297):314-324.
Martin T et al. J Clin Oncol. 2022; 00:1-10. Available at: ascopubs. org

CR: complete response, IQR: interquartile range, MRD: minimal residual disease; PFS: progression free survival, OS: overall survival

CARTITUDE-1 – Safety Endpoints

Safety Endpoint	All-Grade	Grade 3-4
Hematologic Neutropenia Anemia Thrombocytopenia	97 (100) 93 (96) 79 (81) 77 (79)	96 (99) 92 (95) 66 (68) 58 (60)
Infection	56 (58)	19 (20)
Cytokine Release Syndrome	92 (95)	4 (4)
Neurotoxicity ICANS Other neurotoxicity	20 (21) 16 (17) 12 (12)	9 (9) 2 (2) 8 (8)
Secondary primary malignancies	9 (9)	--

CRS and neurotoxicity were primarily grade 1-2.

CRS – median time to onset of 7 days (IQR 5-8), median duration 4 days (IQR 3-6)

Neurotoxicity – median time to onset of 8 days (IQR 6-9), median duration 4 days (IQR 3-6.5)

Berdeja et al. Lancet 2021;398(10297):314-324.

ICANS: immune effector cell-associated neurotoxicity syndrome

Adverse Events

COMMON

Cytokine Release Syndrome (CRS)

Myelosuppression

Hypersensitivity

SERIOUS

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Hemophagocytic lymphohistiocytosis / macrophage activation syndrome (HLH/MAS)

Infection

Secondary malignancy (MDS & AML)

Berdeja et al. Lancet 2021;398(10297):314-324.
Carvykti [ciltacabtagene autoleucel] [Prescribing Information]. Horsham, PA: Janssen Biotech Inc; March 2022.

Monitoring and Pearls

MONITORING

Daily monitoring for 10 days following infusion for signs/symptoms of CRS or neurotoxicity

Complete blood counts & organ function

Blood pressure, oxygenation, temperature

Headache, mental status changes, discoordination, handwriting

CLINICAL PEARLS

Only available through Carvykti REMS Program

Manufacturer targets a 25-day turnaround time for manufacturing

Confirm that 2 doses of tocilizumab are in stock prior to administration

Patient must remain within proximity of certified healthcare facility for at least 4 weeks

Avoid prophylactic or other systemic steroids

Carvykti [ciltacabtagene autoleucel] [Prescribing Information]. Horsham, PA: Janssen Biotech Inc; March 2022.

Place in Therapy

Therapies for patients with Late Relapses (>3 prior therapies)
• *After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD* ▸ **Belantamab mafodotin-blmf** ▸ **Idecabtagene vicleucel** ▸ **Ciltacabtagene autoleucel**
• *After least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody* ▸ **Selinexor/dexamethasone**

No head-to-head studies comparing BCMA-targeted therapies

A meta-analysis of indirect treatment comparisons demonstrated advantages of cilta-cel over physician's choice therapy

- Reduced risk of progression by 80% (HR: 0.20 [95% CI: 0.06, 0.70])
- Reduced risk of death by 76% (HR: 0.24 [95% CI: 0.22, 0.26])

NCCN. Multiple Myeloma. V5.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
Costa et al. Curr Med Res Opin. 2022:1-9.

Future Directions

CARTITUDE-2 (NCT04133636)
- Multi-cohort study evaluating single-arm cilta-cel as an earlier line of therapy

CARTITUDE-4 (NCT04181827)
- Study comparing cilta-cel to PVd or DPd in patients with relapsed/refractory multiple myeloma

Both are investigating outpatient use due to low incidence of grade 3+ CRS seen in CARTITUDE-1

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/results?term=ciltacabtagene

Audience Response Question #1

Which of the following is true regarding ciltacabtagene autoleucel use?

A. Patients should be premedicated with acetaminophen, diphenhydramine, and dexamethasone
B. Many patients experienced grade 3-4 cytokine release syndrome and require inpatient monitoring for 4 weeks
C. Patients should receive lymphodepleting chemotherapy with cyclophosphamide and fludarabine starting 5-7 days prior to ciltacabtagene autoleucel cell infusion
D. Ciltacabtagene autoleucel is the preferred anti-BCMA therapy for relapsed/refractory myeloma

Pacritinib (Vonjo®)

Approved
- February 28, 2022

Indication
- Intermediate- or high-risk primary or secondary myelofibrosis (MF) with platelet count $\leq$ 50,000/mm^3

Drug Class
- Janus associated kinase 2 (JAK2)-targeted tyrosine kinase inhibitor

Mechanism of Action
- Kinase inhibitor with activity against wild-type JAK2 and mutated JAK2$^{(V617F)}$, JAK1-sparing. Also suppresses interleukin-1 directed inflammation through IL-1 receptor associated kinase 1 (IRAK1) inhibition, leading to reduction in splenomegaly, myelosuppression, cytokine production, and fibrosis.

Vonjo (pacritinib) [Prescribing information]. Seattle, WA: CTI Biopharma Corp; February 2022.

Dosing and Adjustments

DOSING

200 mg by mouth twice daily

Taper or discontinue other kinase inhibitors prior to initiation

ADJUSTMENTS

Avoid use in patients with:

- eGFR < 30 ml/min
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment

Dose reduction levels for toxicity adjustments:

Initial Dose	200 mg twice daily
First reduction	100 mg twice daily
Second reduction	100 mg once daily
Discontinue if unable to tolerate 100 mg once daily	

Vonjo (pacritinib) [Prescribing Information]. Seattle, WA: CTI Biopharma Corp; February 2022.

PERSIST-2

- Phase 3, randomized, international study (n=311)
- Primary objective – to compare efficacy of pacritinib versus best available therapy (BAT) in patients with MF and thrombocytopenia
- Included intermediate-to-high risk primary or secondary MF with platelets ≤ 100,000 and splenomegaly

Mascarenhas J et al. JAMA Oncol. 2018;4(5):652-659.

PERSIST-2 – Efficacy Endpoints

Patients were randomized 1:1:1 to pacritinib 400mg daily, 200mg twice daily, or BAT (any treatment for MF, symptom-directed treatment, or watch-and-wait)

Endpoint	Pacritinib 400 mg daily (n=104)	Pacritinib 200 mg twice daily (n=107)	All Pacritinib (n=211)	Best available therapy (n=100)
Splenic volume reduction (SVR) of 35% or more, n (%)	11 (15) p=0.02	16 (22) p=0.001	27 (18) p=0.001	2 (3) --
Reduction in total symptom score (TSS) of 50% or more, n (%)	13 (17) p=0.65	24 (32) p=0.01	37 (25) p=0.08	10 (14) --
Overall survival events, n (%) HR (95% CI)	15 (14) 1.18 (0.57-2.44)	10 (9) 0.68 (0.3-1.53)	25 (12) --	14 (14) --

Significant improvement in SVR seen in both pacritinib arms, with symptom score improvement in twice daily arm

Trend toward improved survival in twice daily pacritinib group, though did not achieve statistical significance.

Mascarenhas J et al. JAMA Oncol. 2018;4(5):652-659.

Adverse Events

COMMON	SERIOUS
Diarrhea	Cardiac events (including grade 3-4)
Fatigue, dizziness	Bleeding (including grade 3-4)
Thrombocytopenia	Withdrawal syndrome
Peripheral edema	

Improved side effect profile with twice-daily pacritinib vs once-daily pacritinib

Full clinical hold placed on pacritinib by the FDA due to bleeding and cardiovascular concerns, now overturned

Mascarenhas J et al. JAMA Oncol. 2018;4(5):652-659.
Vonjo (pacritinib) [Prescribing Information]. Seattle, WA: CTI Biopharma Corp; February 2022.

Monitoring and Pearls

MONITORING	CLINICAL PEARLS
Complete blood count	Administer with or without food
Coagulation parameters (PT, PTT, INR)	Minimal-low emetic risk
Baseline EKG, and as necessary	Major CYP3A4 substrate – contraindicated with strong inducers or inhibitors
Signs/symptoms of bleeding	Withhold 7 days prior to elective surgery or invasive procedures, and resume once hemostasis achieved
Diarrhea	Available as 100 mg capsules
Signs of infection	
Adherence	

Vonjo (pacritinib) [Prescribing Information]. Seattle, WA: CTI Biopharma Corp; February 2022.

Place in Therapy

Higher-risk myelofibrosis patients
- With platelets < 50,000/mm^3 and not a transplant candidate
- Consider with platelets ≥ 50,000/mm^3 and not a transplant candidate after one prior JAK inhibitor

Can also consider Pacritinib for symptomatic, lower-risk myelofibrosis patients with no response or loss of response to prior therapy, if platelets < 50,000/mm^3

NCCN. Myeloproliferative Neoplasms. V3.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf

Recently Approved Agents for Solid Tumor Malignancies

Medication Name	Approval Date	Indication
Mobocertinib (Exkivity)	9/15/21	Advanced or metastatic NSCLC with EGFR exon 20 insertion mutations
Cabozantinib (Cabometyx)	9/17/21*	Advanced/metastatic differentiated thyroid cancer
Tisotumab vedotin-tftv (Tivdak)	9/20/21	Recurrent or metastatic cervical cancer
Abemaciclib (Verzenio)	10/12/21*	Adjuvant treatment in HR+, HER2-, node positive, early breast cancer
Pafolacianine (Cytalux)	11/29/21	Optical imaging agent for interoperative identification of malignant ovarian lesions
Tebentafusp-tebn (Kimmtrak)	1/25/22	HLA-A*01:01-positive unresectable or metastatic uveal melanoma
Nivolumab and relatlimab-rmbw (Opdualag)	3/18/22	Unresectable or metastatic melanoma
Lutetium Lu 177 vipivotide tetraxetan (Pluvicto)	3/23/22	PSMA-positive metastatic castration-resistant prostate cancer
Fam-trastuzumab deruxtecan-nxki (Enhertu)	8/5/22* 8/11/22*	HER2-low breast cancer HER-2 mutant non-small cell lung cancer
Durvalumab (Imfinzi)	9/2/22*	Locally advanced or metastatic biliary tract cancer in combination with gemcitabine and cisplatin

*New Indication

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Mobocertinib (Exkivity)	9/15/21	Advanced or metastatic NSCLC with EGFR exon 20 insertion mutations
Cabozantinib (Cabometyx)	9/17/21*	Advanced/metastatic differentiated thyroid cancer
Tisotumab vedotin-tftv (Tivdak)	9/20/21	Recurrent or metastatic cervical cancer
Abemaciclib (Verzenio)	10/12/21*	Adjuvant treatment in HR+, HER2-, node positive, early breast cancer
Pafolacianine (Cytalux)	11/29/21	Optical imaging agent for interoperative identification of malignant ovarian lesions
Tebentafusp-tebn (Kimmtrak)	1/25/22	HLA-A*01:01-positive unresectable or metastatic uveal melanoma
Nivolumab and relatlimab-rmbw (Opdualag)	3/18/22	Unresectable or metastatic melanoma
Lutetium Lu 177 vipivotide tetraxetan (Pluvicto)	3/23/22	PSMA-positive metastatic castration-resistant prostate cancer
Fam-trastuzumab deruxtecan-nxki (Enhertu)	8/5/22* 8/11/22*	HER2-low breast cancer HER-2 mutant non-small cell lung cancer
Durvalumab (Imfinzi)	9/2/22*	Locally advanced or metastatic biliary tract cancer in combination with gemcitabine and cisplatin

*New Indication

FDA. Oncology (Cancer) /Hematologic Malignancies Approval Notifications. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications.

Mobocertinib (Exkivity)

Approved

- September 14, 2021

Indication

- Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutation, with progression on/after platinum-based chemotherapy

Drug Class

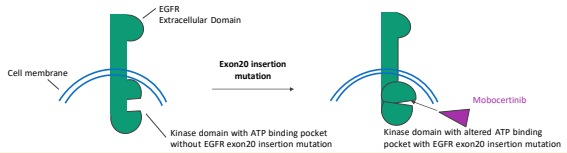
- Irreversible EGFR-targeted tyrosine kinase inhibitor

Exkivity (mobocertinib) [Prescribing Information]. Lexington, MA: Takeda Pharmaceuticals America Inc; September 2021.

Mechanism of Action

Mechanism of Action

- Mobocertinib binds and irreversibly inhibits the *EGFR* Exon20 insertion (*EGFR*ex20ins) mutation to reduce proliferation and survival of tumor cells



Exkivity (mobocertinib) [Prescribing Information]. Lexington, MA: Takeda Pharmaceuticals America Inc; September 2021.
Figure adapted: About Exkivity. Available at: https://www.exkivityhcp.com/about

Dosing and Adjustments

DOSING

160 mg by mouth once daily until disease progression or unacceptable toxicity

Consider prophylactic antiemetics

ADJUSTMENTS

No renal or hepatic adjustments
- Not studied in severe impairment

Dose reduction levels for toxicity

Initial Dose	160 mg once daily
First reduction	120 mg once daily
Second reduction	80 mg once daily
Discontinue if unable to tolerate 80 mg once daily	

Exkivity (mobocertinib) [Prescribing Information]. Lexington, MA: Takeda Pharmaceuticals America Inc; September 2021.

Clinical Trial

- 3-part, phase 1/2 , open-label trial (n=124)
- Primary objective – to evaluate ORR of mobocertinib in patients with previously-treated, EGFRex20ins-mutated NSCLC
- Included two cohorts: platinum pre-treated patients (PPP, n=114) and a single-arm extension (EXCLAIM)
- Outcomes reported for platinum-pretreated patients

Zhou et al. JAMA Oncol. 2021;7(12)e214761.

Endpoints

114 patients were enrolled in the PPP cohort, including 86 patients from the EXCLAIM cohort & 28 patients from the dose-escalation and expansion phase

- 10 patients in the EXCLAIM cohort were not pre-treated with platinum agents

Endpoint	PPP Cohort (n=114)	EXCLAIM cohort (n=96)
Objective response rate[IRC-assessed], n (%) [95% CI]	32 (28) [20-37]	24 (25) [17-35]
Median duration of response[IRC-assessed], months (95% CI)	17.5 (7.4-20.3)	NR (5.6-NR)
Median progression free survival[IRC-assessed], months (95% CI)	7.3 (5.5-9.2)	7.3 (5.5-9.1)
Median overall survival[IRC-assessed], months (95% CI)	24.0 (14.6-28.8)	NR (13.1-NR)

Results between cohorts were similar, with 28% ORR and median DOR of 17.5 months in the platinum-pretreated patients.

Response rates and duration of response were improved with mobocertinib compared to historical standards and similar to amivantamab

IRC – independent review committee

Zhou et al. JAMA Oncol. 2021;7(12)e214761.

Adverse Events

COMMON

- Diarrhea
- Rash
- Nausea/vomiting
- Stomatitis
- Fatigue

SERIOUS

- Cardiac toxicity
  - Reduced ejection fraction, cardiomyopathy, heart failure, QTc prolongation
- Pulmonary toxicity
  - Interstitial lung disease, pneumonitis
- Diarrhea (grade 3-4 events reported)

Zhou et al. JAMA Oncol. 2021;7(12)e214761.
Exkivity (mobocertinib) [Prescribing Information]. Lexington, MA: Takeda Pharmaceuticals America Inc; September 2021

Monitoring and Pearls

MONITORING

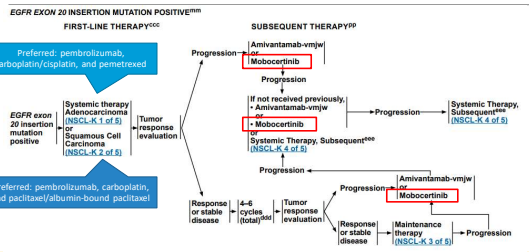
- EGFR exon 20 insertion mutation status
- Cardiac function, baseline ECHO & EKG then as clinically indicated
- Diarrhea
- Electrolytes
- Pregnancy status
- Pulmonary symptoms

CLINICAL PEARLS

- Moderate-to-high emetic potential
- Administer with food to reduce nausea
- Available as 40 mg capsule
- Assess for drug interactions
  - Major substrate of CYP3A4, may require dose reductions
  - Avoid concomitant QTc-prolonging agents

Exkivity (mobocertinib) [Prescribing Information]. Lexington, MA: Takeda Pharmaceuticals America Inc; September 2021.

Place in Therapy



NCCN. Non-Small Cell Lung Cancer. V. 4.2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Audience Response Question #2

Which of the following recently approved oral agents may require antiemetic premedication due to moderate-high emetic risk?

A. Asciminib
B. Pacritinib
C. Mobocertinib
D. Zanubrutinib

Tisotumab vedotin-tftv (Tivdak)

Approved

- September 20, 2021

Indication

- Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy

Drug Class

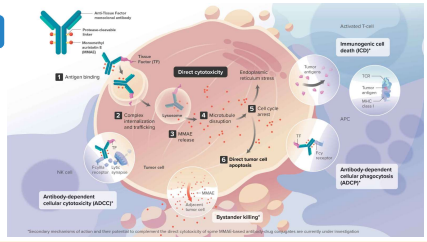
- Tissue factor (TF)-directed antibody drug conjugate

Tivdak (tisotumab vedotin) [Prescribing Information]. Bothell, WA; Seagen Inc; March 2022.

Mechanism of Action

Mechanism of Action

- Anti-TF IgG1-kappa antibody conjugated to microtubule-disrupting agent monomethyl auristatin E (MMAE), binds to TF-expressing cancer cells leading to internalization of ADC-TF complex and release of MMAE. MMAE disrupts polymerization of microtubules and leads to cell cycle arrest. Also demonstrates antibody-dependent cytotoxicity and cellular phagocytosis.



Tivdak (tisotumab vedotin) [Prescribing Information]. Bothell, WA; Seagen Inc; March 2022.
Seagen: Tisotumab vedotin. Available at: https://www.seagen.com/science/pipeline/tisotumab-vedotin.

Dosing and Adjustments

DOSING

2 mg/kg (max 200 mg) IV once every 3 weeks until progression or unacceptable toxicity

- Administered over 30 minutes

Ophthalmic care and premedication

- Topical corticosteroid drops: prior to infusion and 3x/day for 72 hours after each infusion
- Topical vasoconstrictor eye drops: 3 drops per eye prior to each infusion
- Cooling eye packs: prior to and during each infusion (total 60 minutes)
- Topical lubricating eye drops: during treatment and for 30 days after last dose

ADJUSTMENTS

No renal adjustments

Avoid use in moderate-severe hepatic impairment (total bilirubin > 1.5x ULN)

Dose reduction levels for toxicity adjustments:

Initial Dose	2 mg/kg
First reduction	1.3 mg/kg
Second reduction	0.9 mg/kg
Discontinue if unable to tolerate 0.9 mg/kg dose	

Tivdak (tisotumab vedotin) [Prescribing Information]. Bothell, WA; Seagen Inc; March 2022.
Prepping for Tivdak required eye care. Available at:https://www.tivdakhcp.com/eye-care/.

innovaTV 204 / GOG-3023 / ENGOT-cx6

- Single-arm, open-label, phase 2, multicenter study across the U.S. and Europe (n=101)
- Primary objective – to evaluate objective response rate of tisotumab vedotin
- Included women with recurrent or metastatic cervical cancer after progression on or after 2 or fewer lines, including doublet chemotherapy + bevacizumab
- Included squamous cell, adenocarcinoma, and adenosquamous histologies

Coleman RL et al. Lancet Oncol. 2021;22(5):609-619.

innovaTV 204 / GOG-3023 / ENGOT-cx6

Endpoint	Tisotumab vedotin (n=101)	95% CI
Objective response rate, %	24 (24)	16-33
Median duration of response, months	8.3	4.2-NR
Median time to response, months	1.4	--
Median progression free survival, months	4.2	3.0-4.4
Median overall survival, months	12.1	9.6-13.9
6-month overall survival rate, %	79	69-86
12-month overall survival rate, %	51	41-61

Responses were similar across pre-specified subgroups (histology, number of prior lines, exposure to prior bevacizumab)

Response rates and duration of response improved compared to historical rates seen with single-agent chemotherapy (RR ~5-15%; DOR 2-6 months)

Coleman RL et al. Lancet Oncol. 2021;22(5):609-619.

Adverse Events

COMMON

- Dry eye, conjunctivitis
- Nausea
- Alopecia
- Fatigue

SERIOUS

- Hemorrhage
- **Ocular toxicity**
  - Ulcerative keratitis, visual acuity changes
- Peripheral neuropathy
- Pulmonary toxicity

Coleman RL et al. Lancet Oncol. 2021;22(5):609-619.
Tivdak (tisotumab vedotin) [Prescribing Information]. Bothell, WA; Seagen Inc; March 2022.

Monitoring and Pearls

MONITORING

- Signs of ocular toxicity
- Hemorrhage
- Neuropathy (paresthesia, weakness)
- Pulmonary symptoms (hypoxia, cough, pneumonia)
- Pregnancy status

CLINICAL PEARLS

- Ophthalmic exams required at baseline, prior to each dose, and as clinically indicated
- Avoid use of contact lenses
- Low emetic potential
  - If nausea occurs, add a prophylactic antiemetic
- Available as 40 mg vial

Tivdak (tisotumab vedotin) [Prescribing Information]. Bothell, WA; Seagen Inc; March 2022.

Place in Therapy

- Second-line or subsequent therapy for recurrent or metastatic cervical cancer
- Category 2A in NCCN guideline recommendations
- Most other recommended regimens in this setting are category 2B, but pembrolizumab or nivolumab are preferred for PD-L1 positive tumors, with pembrolizumab also preferred for MSI-H/dMMR tumors

NCCN. V1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.

Future Directions

Monotherapy in other solid tumors
- Ovarian (NCT03657043), lung/colorectal/pancreatic/head and neck (NCT03485209)

In combination with PD-1 inhibitor, carboplatin, or bevacizumab in recurrent/metastatic cervical cancer (NCT03786081)

Phase 3, randomized study comparing to investigator's choice of chemotherapy in recurrent/metastatic cervical cancer (NCT04697628)

ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/results?term=tisotumab&Search=Search

Audience Response Question #3

Which of the following outpatient referrals should be made for all patients initiating tisotumab vedotin-tftv?

A. Neurology
B. Ophthalmology
C. Cardiology
D. Endocrinology

Tebentafusp-tebn (Kimmtrak)

Approved

- January 26, 2022

Indication

- Unresectable or metastatic, HLA-A*02:01-positive uveal melanoma in adults

Drug Class

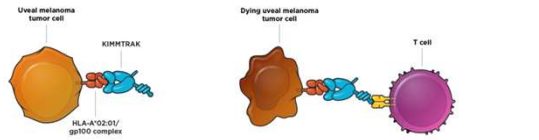
- Bi-specific T-cell engager; immune mobilizing monoclonal T-cell receptors against cancer (ImmTAC)

Kimmtrak (tebentafusp) [Prescribing Information]. Conshohoken, PA: Immunicore Commercial LLC; February 2022.

Mechanism of Action

Mechanism of Action

- Consists of a soluble HLA-A*02:01-restricted T-cell receptor specific to glycoprotein 100 (gp100) peptide, fused to anti-CD3 fragment. Once bound, ImmTAC molecule recruits and activates polyclonal T-cells to release inflammatory cytokines & cytolytic proteins to lyse uveal melanoma cells



Kimmtrak (tebentafusp) [Prescribing Information]. Conshohoken, PA: Immunicore Commercial LLC; February 2022.
How Kimmtrak works. Available at: https://www.kimmtrak.com/#howkimmtrakworks.

Dosing and Adjustments

DOSING

Day 1: 20 mcg IV over 15-20 minutes

Day 8: 30 mcg IV

Day 15 and beyond: 68 mcg once weekly until disease progression or unacceptable toxicity

Monitor for at least 16 hours after completion of first 3 infusions. If tolerated, subsequent infusions may be given outpatient with 30 minutes of observation

ADJUSTMENTS

No renal or hepatic adjustments
- Not studied in severe impairment

Discontinuation or pauses in dose escalation due to toxicities may occur

Kimmtrak (tebentafusp) [Prescribing Information]. Conshohoken, PA: Immunicore Commercial LLC; February 2022.
How Kimmtrak works. Available at: https://www.kimmtrak.com/#howkimmtrakworks.

IMCgp100-202

- Open label, phase 3, randomized (2:1) trial (n=378)
- Primary objective – to evaluate overall survival in patients treated with tebentafusp compared to standard of care control arm (pembrolizumab, ipilimumab, or dacarbazine)
- Included fit adult patients with HLA-A*02:01-positive, untreated metastatic uveal melanoma

Nathan P et al. N Engl J Med. 2021;385(13):1196-1206.

IMCgp100-202 – Endpoints

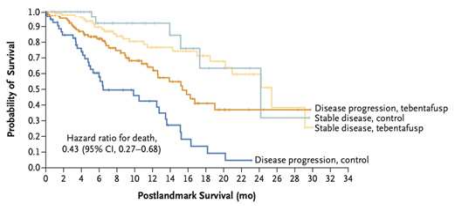
Patients were randomized 2:1 to tebentafusp (n=252) or control arm (n=126)
- Control arm: pembrolizumab (103 patients, 82%), ipilimumab (16 patients, 13%), and dacarbazine (7 patients, 6%)

	Tebentafusp (n=252)	Control Arm (n=126)	HR (95% CI)
Overall survival at 1-year, % (95% CI)	73 (66-79)	59 (48-67)	0.51 (0.37-0.71)
Median OS, months (95% CI)	21.7 (18.6-28.6)	16.0 (9.7-18.4)	
Median OS (rash within 1 week), months (95% CI)	27.4 (20.2-NR)	--	--
PFS at 6-months, %	31	19	0.73 (0.58-0.94)
Median PFS, months (95% CI)	3.3 (3-5)	2.9 (2.8-3.0)	

Although numerically longer survival, rash was not found to be an independent predictor of survival benefit based on multivariate analysis

Nathan P et al. N Engl J Med. 2021;385(13):1196-1206.

IMCgp100-202 – Endpoints



Tebentafusp recipients demonstrated an overall survival benefit, which was also seen in those patients with no tumor shrinkage and with tumor growth as their best response on treatment

Nathan P et al. N Engl J Med. 2021;385(13):1196-1206.

Adverse Events

COMMON

Cytokine release syndrome (fever, hypotension)

Rash, pruritis

Nausea, vomiting, diarrhea

Fatigue, arthralgia

SERIOUS

Rash

Hepatic toxicity

Cytokine release syndrome

Nathan P et al. N Engl J Med. 2021;385(13):1196-1206.
Kimmtrak (tebentafusp) [Prescribing Information]. Conshohoken, PA: Immunicore Commercial LLC; February 2022.

Monitoring and Pearls

MONITORING

AST, ALT, total bilirubin

Fluid status, vital signs, oxygenation

Skin reactions

Pregnancy status

CLINICAL PEARLS

Ensure patients are euvolemic prior to initiation

First 3 infusions should be administered under close observation. If no grade 2+ hypotension, subsequent doses can be given outpatient.

Patients must undergo genotype testing to identify HLA-A*02:01 expression

Kimmtrak (tebentafusp) [Prescribing Information]. Conshohoken, PA: Immunicore Commercial LLC; February 2022.

Place in Therapy

SYSTEMIC THERAPY FOR DISTANT METASTATIC DISEASE[a]

Preferred Regimens
- When available and clinically appropriate, enrollment in a clinical trial is recommended.
- Tebentafusp-tebn in patients who are HLA A*02:01-positive (category 1)

Other Recommended Regimens[a]
- Consider one or more of the following options:
  - Immunotherapy[b]
    - Anti PD-1 monotherapy
      - Pembrolizumab
      - Nivolumab
    - Nivolumab/ipilimumab
    - Ipilimumab
  - Cytotoxic Regimens
    - Dacarbazine
    - Temozolomide
    - Paclitaxel
    - Albumin-bound paclitaxel
    - Carboplatin/paclitaxel
  - Targeted Therapy[c,d]
    - Trametinib

NCCN. Melanoma: Uveal. V2.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf.

Nivolumab and relatlimab-rmbw (Opdualag)

Approved
- March 18, 2022

Indication
- Unresectable or metastatic melanoma in adult and pediatric patients ≥ 12 years of age

Drug Class
- Immune checkpoint inhibitor
- Anti-lymphocyte-activation gene 3 (LAG-3) & anti-programmed death 1 (PD-1) monoclonal antibodies

Opdualag (nivolumab/relatlimab) [Prescribing Information Princeton, NJ; Bristol-Myers Squibb Company; March 2022.

Nivolumab and relatlimab-rmbw (Opdualag)

Mechanism of Action
- Two monoclonal antibodies infused at the same time, one targeting the inhibitory immune checkpoint protein LAG-3 and the other targeting PD-1
- LAG-3 and PD-1 are expressed on T-cells and are upregulated in melanoma
- Relatlimab binds to and blocks LAG-3 and Nivolumab to PD-1, synergistically restoring effector function of exhausted T-cells to exert antitumor effects

Opdualag (nivolumab/relatlimab) [Prescribing Information Princeton, NJ; Bristol-Myers Squibb Company; March 2022.

Dosing and adjustments

DOSING

Nivolumab 480 mg & Relatlimab 160 mg IV as a single infusion once every 4 weeks until progression or unacceptable toxicity

Infused over 30 minutes

ADJUSTMENTS

No renal or hepatic adjustments

Hold and discontinuation parameters for immune-mediated adverse events

Opdualag (nivolumab/relatlimab) [Prescribing Information Princeton, NJ; Bristol-Myers Squibb Company; March 2022.

RELATIVITY-047

- Phase 2/3, international, double-blind, randomized (1:1) trial (n=714)
- Primary objective – to assess PFS of combination relatlimab & nivolumab compared to nivolumab-monotherapy in untreated metastatic or unresectable melanoma
- Stratified based on LAG-3 and PD-L1 expression (≥1% or < 1%), *BRAF* V600 mutation status, metastasis stage, and LDH levels
- Included patients that had received prior adjuvant or neoadjuvant immune checkpoint inhibitors, MEK inhibitors, BRAF inhibitors, or interferon

Tawbi HA et al. N Engl J Med. 2022;386(1):23-34.

RELATIVITY-047

Endpoint	Relatlimab-nivolumab (n=355)	Nivolumab (n=359)	HR (95% CI)
Median PFS, months (95% CI)	10.1 (6.4-15.7)	4.6 (3.4-5.6)	**0.75 (0.62-0.92)**
PD-L1 ≥ 1%	15.7 (10.1-25.8)	14.7 (5.1-NR)	0.95 (0.68-1.33)
PD-L1 < 1%	6.4 (4.6-11.8)	2.9 (2.8-4.5)	**0.66 (0.51-0.84)**
Mutated BRAF	10.1 (4.6-23.1)	4.6 (3.0-6.5)	0.74 (0.54-1.03)
Wild-type BRAF	10.1 (5.9-17.0)	4.6 (2.9-6.6)	**0.76 (0.59-0.98)**
LAG-3 ≥ 1%	12.58 (6.67-23.1)	4.76 (4.47-8.61)	**0.75 (0.59-0.95)**
LAG-3 < 1%	4.83 (2.86-10.05)	2.79 (2.79-4.63)	0.78 (0.54-1.15)
12-month PFS, % (95% CI)	47.7 (41.8-53.2)	36.0 (30.5-41.6)	--

Relatlimab-nivolumab had twice the median PFS and a 25% lower risk of disease progression or death compared to nivolumab monotherapy

Relatlimab-Nivolumab demonstrated significant improvement in PFS in patients with low expression of PD-L1, wild-type BRAF, and high expression of LAG-3 compared to nivolumab, though efficacy was seen across all pre-specified subgroups

Tawbi HA et al. N Engl J Med. 2022;386(1):23-34.

Adverse Events

COMMON	SERIOUS
Hypo/hyperthyroidism & thyroiditis	Hepatotoxicity (grade 3-4 ALT/AST elevation)
Rash/pruritis	Endocrinopathies (grade 3-4 elevated lipase)
Diarrhea/colitis	Pneumonitis
Hepatitis	Other immune-mediated adverse reactions
Fatigue/arthralgia	

Opdualag (nivolumab/relatlimab) [Prescribing Information Princeton, NJ: Bristol-Myers Squibb Company; March 2022.

Monitoring and Pearls

MONITORING

Immune mediated adverse events
- Diarrhea/colitis
- Rash
- Hepatic function (ALT, AST, bilirubin)
- Renal function
- Thyroid and endocrine function
- Myocarditis, pneumonitis
- Ocular toxicity

Pregnancy status

CLINICAL PEARLS

Not interchangeable with nivolumab (Opdivo)

Available as 240mg/80mg vial

Opdualag (nivolumab/relatlimab) [Prescribing Information Princeton, NJ; Bristol-Myers Squibb Company; March 2022.

Place in Therapy

First-line therapy for metastatic or unresectable melanoma:

Metastatic or unresectable disease →
- Preferred regimens
  - Anti PD-1 monotherapy[d,e]
    - Pembrolizumab (category 1)
    - Nivolumab (category 1)
  - Nivolumab/ipilimumab (category 1)[d,e,f]
  - Nivolumab and relatlimab-rmbw[d]
  - Combination targeted therapy if *BRAF* V600-activating mutation[g,h,i,j]
    - Dabrafenib/trametinib (category 1)
    - Vemurafenib/cobimetinib (category 1)
    - Encorafenib/binimetinib (category 1)
- Other recommended regimens
  - Pembrolizumab/low-dose ipilimumab[k] (category 2B)
  - Combination targeted therapy and immunotherapy if *BRAF* V600-activating mutation present[d,g,h]
    - Vemurafenib/cobimetinib + atezolizumab[l]

RELATIVITY-047 investigators advise that expression of LAG-3 and PD-L1 was not useful in predicting benefit and does not yet have a clear role in selecting treatment

Acknowledgements

Slides adapted from presentation by Sarah Burnette, PharmD, BCOP on 8/6/22

New Drug Update: Hematologic & Solid Tumor Malignancies

LEAH EDENFIELD, PHARMD, CPP, BCOP
ATRIUM HEALTH WAKE FOREST BAPTIST