National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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Updated 7/9/19

Positive Quality Intervention: Overview on Tyrosine Kinase Inhibitors

Description:

Tyrosine kinase inhibitors (TKI) represent a heterogenous class of medications that are FDA indicated for many different types of malignancies. A specific TKI may have different indications, dosing, monitoring, adverse-effect profile, and side-effect management from another of similar mechanism. It is important to understand these differences when counseling patients on expectations and side-effective management.

Background:

TKIs prevent the transfer of the γ-phosphate group from adenosine triphosphate (ATP), which inhibits tumor cell growth and proliferation, ultimately inducing cell apoptosis. Tyrosine kinases (TKs) are categorized as being receptor protein kinases and non-receptor protein kinases. Currently, there have been roughly 90 TKs that have been identified and are classified further into subfamilies depending on the presence or type of receptor and/or ligand. The four main types of TKIs include those that target angiogenesis or vascular endothelial growth factor receptors (VEGFR), breakpoint cluster region-abelson murine leukemia viral oncogene homolog 1 (BCR-ABL), B-cell receptor (BCR), and epidermal growth factor receptors (EGFR).

As seen in table 1 (supplemental material), a single agent may often target multiple types of TKs and thus be indicated in more than one type of cancer. VEGFR inhibitors are FDA indicated in solid organ malignancies, such as renal cell carcinoma (RCC) or GIST. In contrast, BCR-ABL TKIs are FDA indicated in Ph+ chronic myelocytic leukemia (CML) or Ph+ acute lymphoblastic leukemia (ALL). Although these agents fall under the same general classification of TKIs, these agents differ in side-effect profiles, drug-drug interactions, and monitoring parameters.

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PQI Process:

- Verify correct indication:
    - Specific TKIs are indicated for a given disease state, such as vemurafenib for unresectable or metastatic melanoma with a BRAF mutation. These agents should not be used for other indications without literature support. Refer to table 1 for dosing and indication.
    - Some malignancies require a mutation in order to utilize a specific TKI. For example, patients with ALL should have a documented Ph+ status to utilize imatinib. Ibrutinib, comparatively, can be used in patients with CLL without a specific mutation
    - Dosing also varies by indication. For instance, the dose of dasatinib is 100 mg for patients with chronic phase CML but is 140 mg in patients with accelerated phase CML, myeloid, lymphoid blast phase CML, or Ph+ ALL.
- Screen for drug-drug interactions
    - Most have interactions with CYP3A4 inhibitors and inducers. Consult the package insert for guidance on necessary dose adjustments required for concomitant administration or if alternative therapy should be pursued.
    - Some of these agents may also affect warfarin and coagulation. Monitor INR closely in established warfarin patients who initiate TKIs that are known to interact with warfarin.
    - Select agents are affected by acidity (pH status). For example, although imatinib absorption is not affected by pH, PPIs and H2RAs should be avoided with other BCR-ABL inhibitors, such as dasatinib and ponatinib, since they can decrease absorption. Shorter acting agents, such as antacids, are permitted if administration is separated by at least 2 hours.

Patient Centered Activities:

Monitor for adverse events

- VEGFR
    - Patients should monitor blood pressure regularly while starting these agents.
    - Diarrhea can be observed in many patients on these agents. Patients should be counseled on appropriate management with anti-diarrheal agents for uncomplicated symptoms of diarrhea.

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    - For skin rash, patients should be counseled to moisturize regularly, protect their skin from the sun, and avoid irritation as this can exacerbate symptoms. May require OTC or prescription urea if normal moisturization of the skin is inadequate.
- BCR-ABL
    - Monitor weight and fluid status regularly as fluid retention and edema can occur with these agents.
    - Nausea and vomiting can occur more frequently and appropriate anti-emetics should be prescribed for the patient to use as needed.
    - Monitor for suicidal ideation, depression and insomnia for patients who are taking imatinib and dasatinib as this has been reported to occur.
- BCR
    - Ibrutinib: monitor for signs/symptoms of bleeding, rash, GI upset, fatigue, hydration status, and subsequently renal toxicity.
    - Idelalisib: Three black-box-warnings exist for this agent.
        - Patients should be monitored for severe diarrhea and/or colitis. Avoid agents that can cause diarrhea as idelalisib generally responds poorly to antimotility agents.
        - Fatal and/or serous hepatotoxicity occurs in 14% of patients.
        - Patients should be closely monitored for pulmonary symptoms and bilateral interstitial infiltrates.
- EGFR
    - Topical and/or oral antibiotics should be prescribed for patients who develop a mild-to-moderate skin rash.
    - Diarrhea can be observed in many patients on these agents. Patients should be counseled on appropriate management with anti-diarrheal agents for uncomplicated symptoms of diarrhea.
        - Neratinib has a 95% incidence of all-grade diarrhea. Patients starting on neratinib should have concomitant loperamide prophylaxis for the first 52 weeks and as appropriate thereafter. Directions are stated in the package insert.
    - Erlotinib and gefitinib are two specific EGFR inhibitors that are known to potentially interact with warfarin and may need closer monitoring of INR until stabilized on concomitant therapy.

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Supplemental Information

Table 1. Common Tyrosine Kinase Inhibitors

Medications	Tyrosine kinase targets	FDA Indications and Dose	Adverse Effects (Common* and notable**)
ALK Inhibitors			
Alectinib (Alecensa)	ALK and RET	**ALK+ metastatic NSCLC** 600 mg twice daily continuously with food	**Common**: Fatigue, myalgias **Notable**: Hepatotoxicity, cardiac toxicity, pulmonary toxicity, visual effects
Brigatinib (Alunbrig)	ALK and FLT3	**ALK+ metastatic NSCLC who have progressed or intolerant to crizotinib** 90 mg daily for 7 days then 180 mg daily continuously if tolerated	**Common**: Visual effects, N/V/D, hyperglycemia, increased CPK **Notable**: Hepatotoxicity, cardiac toxicity, peripheral neuropathy, pulmonary toxicity
Ceritinib (Zykadia)	ALK	**ALK+ metastatic NSCLC** 450 mg daily continuously with food	**Common**: N/V/D, hyperglycemia, fatigue **Notable**: Hepatotoxicity, cardiac toxicity, peripheral neuropathy, pulmonary toxicity, visual effects,
Crizotinib (Xalkori)	ALK and ROS1	**ALK+ metastatic NSCLC** 250 mg twice daily continuously	**Common**: Visual effects, N/V/D, **Notable**: Hepatotoxicity, cardiac toxicity, peripheral neuropathy, pulmonary toxicity
Lorlatinib (Lorbrena)	ALK and ROS1	**ALK+ metastatic NSCLC who have progressed on crizotinib, alectinib, or ceritinib** 100 mg daily continuously	**Common**: edema, PN **Notable**: Hepatotoxicity, ILD, AV block, HLD

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BCR			
Acalabrutinib (Calquence)	BTK inhibitor	**MCL who have received ≥ 1 prior therapy** 100 mg twice daily continuously	**Common**: Diarrhea, fatigue **Notable**: Bleeding, infections, secondary malignancies, afib or flutter
Duvelisib (Copiktra)	PI3K- δ kinase inhibitor	**r/r CLL, SLL, or FL with ≥ 2 prior therapies** 25 mg twice daily continuously Give with PJP prophylaxis during treatment and after discontinuation until CD4+ T cell count > 200 cells/μL	**Common**: Myelosuppression, diarrhea/colitis, URI/pneumonia, skin rash **Notable**: Hepatotoxicity
Ibrutinib (Imbruvica)	BTK inhibitor	**MCL** 560 mg daily continuously **CLL, SLL, WM** 420 mg daily continuously	**Common**: Diarrhea, musculoskeletal pain **Notable**: Bleeding, infections, myelosuppression, renal toxicity, secondary primary malignancies, fatigue
Idelalisib (Zydelig)	PI3K- δ kinase inhibitor	**rCLL, rFL, and rSLL** 150 mg twice daily continuously	**Common**: Diarrhea/colitis **Notable**: Hepatotoxicity, diarrhea/colitis, myelosuppression, GI perforation
BCR-ABL			
Bosutinib (Bosulif)	BCR-ABL; SRC family kinases	**Ph+ CML (chronic)** 400 mg daily continuously with food **Ph+ CML (chronic, accelerated or blast) with resistance or intolerance to prior therapy** 500 mg daily continuously with food	**Common**: Diarrhea, nausea, myelosuppression, skin rash, **Notable**: Fluid retention
Dasatinib (Sprycel)	BCR-ABL; cKIT; ABL2	**CML (chronic)** 100 mg daily continuously **CML (accelerated and blast) and Ph+ ALL** 140 mg daily continuously	**Common**: Myelosuppression, fluid retention **Notable**: Bleeding complications

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Imatinib (Gleevec)	BCR-ABL; cKIT; ABL2	**Ph+ CML (chronic), MDS/MPD, ASM (c-Kit mutation status unknown), GIST, HES or CEL** 400 mg daily continuously **Ph+ CML (accelerated and blast), Ph+ ALL (relapsed/refractory),** 600 mg daily continuously **ASM (associated with eosinophilia)** 100 mg daily continuously **DFSP** 800 mg daily continuously	**Common**: N/V/D, edema, myalgias, fluid retention
Nilotinib (Tasigna)	BCR-ABL; cKIT; ABL2	**Adult and Pediatric Pts with newly diagnosed Ph+ CML (chronic)** 300 mg twice daily continuously on an empty stomach **Adult and Pediatric Pts with resistant or intolerant Ph+ CML (chronic and accelerated)** 400 mg twice daily continuously on an empty stomach	**Common**: Myelosuppression, fatigue **Notable**: QT-prolongation, electrolyte abnormalities,
Ponatinib (Iclusig)	BCR-ABL; VEGF; SRC; cKIT; ABL2	**Ph+ CML (chronic, accelerated and blast) in pts with no other indicated TKI, T315I-positive CML or Ph+ ALL** 45 mg once daily continuously	**Common**: HTN, fluid retention, myelosuppression **Notable**: Arterial thromboembolic events, hepatotoxicity, cardiac arrhythmias, fluid retention, bleeding,
EGFR			
Afatinib (Gilotrif)	EGFR	**EGFR mutation+ metastatic NSCLC, previously treated metastatic Squamous NSCLC** 40 mg daily continuously	**Common**: Skin rash, pruritis, diarrhea **Notable**:, Pulmonary toxicity, hepatic toxicity
Dabrafenib (Tafinlar)	BRAF	**Adjuvant, unresectable or metastatic Melanoma metastatic (BRAF V600E or V600k mut+), NSCLC (BRAF V600E mut+), or ATC (BRAF V600E mut+)**	**Common**: Keratoacanthomas, skin reactions, pyrexia, hyperglycemia, bleeding

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		150 mg twice daily continuously -Recommended to be given in combination with trametinib	**Notable**: SCC, uveitis, cardiomyopathy
Dacomitinib (Vizimpro)	EGFR and HER2	**EGFR mutation+ Metastatic NSCLC** 45 mg daily continuously	**Common**: Diarrhea, skin rash, **Notable**: Pulmonary toxicity
Encorafenib (Braftovi)	BRAF	**Unresectable or metastatic Melanoma (BRAF V600E or V600k mut+)** 450 mg daily continuously -Recommended to be given in combination with binimetinib	**Common**: Skin reaction **Notable**: SCC and keratoacanthomas, uveitis, bleeding
Erlotinib (Tarceva)	EGFR	**EGFR mutation+ metastatic NSCLC** 150 mg daily continuously on an empty stomach **Locally advanced, unresectable, or metastatic pancreatic Cancer** 100 mg daily continuously on an empty stomach	**Common**: Skin rash, diarrhea **Notable**: Pruritis, pulmonary toxicity, hepatic toxicity, anorexia
Gefitinib (Iressa)	EGFR	**Metastatic, EGFR+ NSCLC** 250 mg daily continuously	**Common**: Skin rash **Notable**: HTN, elevations in LFTs, asthenia and anorexia
Lapatinib (Tykerb)	EGFR and HER2	**HER2+ metastatic breast cancer** 1,250 mg daily on days 1-21 on an empty stomach in combination with capecitabine **ER/PR+, HER2+ metastatic breast cancer** 1,500 mg daily continuously on an empty stomach in combination with letrozole	**Common**: Diarrhea **Notable**: Cardiac toxicity, myelosuppression, fatigue, hepatotoxicity
Neratinib (Nerlynx)	EGFR, HER2, and HER4	**Extended adjuvant treatment of early stage HER2+ breast cancer after adjuvant trastuzumab based therapy** 240 mg daily with food for one year	**Common**: Diarrhea **Notable**: Fatigue, muscle spasms, hepatotoxicity, skin rash
Osimertinib (Tagrisso)	EGFR	**EGFR mutation+ metastatic NSCLC first line or previously treated EGFR T790M mutation+ metastatic NSCLC** 80 mg daily continuously	**Common**: Skin rash, diarrhea **Notable**: Pruritis, ,

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			pulmonary toxicity, QT-prolongation, fatigue, cardiomyopathy
Vandetanib (Caprelsa)	EGFR, VEGFR, RET, SRC	**Symptomatic or progressive medullary thyroid cancer** 300 mg daily continuously	**Common**: Skin rash, diarrhea, HTN **Notable**: Pruritis, N/V, fatigue, bleeding, QT-prolongation
Vemurafenib (Zelboraf)	BRAF	**Unresectable or metastatic Melanoma (BRAF V600E or V600k mut+)** 960 mg twice daily continuously -Recommended to be given in combination with cobimetinib	**Common**: SCC and keratoacanthomas, skin reactions, photosensitivity **Notable**: QTc prolongation
VEGFR			
Axitinib (Inlyta)	VEGFR	**RCC after failure on 1 prior therapy** 5 mg twice daily continuously	**Common**: N/V/D, HTN **Notable:** Arterial and venous thrombosis, bleeding, GI perforation, slow wound-healing,
Cabozantinib (Cabometyx)	VEGFR; RET; FLT3; cKIT	**RCC, HCC** 60 mg daily continuously on an empty stomach	**Common**: Diarrhea, nausea, HTN **Notable**: Rash, dry skin, alopecia, hair color changes, HFS, vomiting, mucositis, fatigue, bleeding
Lenvatinib (Lenvima)	VEGFR; cKIT; RET	**Metastatic differentiated thyroid cancer** 24 mg daily continuously **RCC** 18 mg daily continuously in combination with everolimus **HCC** 12 mg daily continuously if > 60 kg 8 mg daily continuously if < 60 kg	**Common**: HTN, N/V/D, fatigue **Notable:** Mucositis, bleeding, arterial thromboembolic events, hepatotoxicity
Pazopanib (Votrient)	VEGFR; cKIT	**RCC, soft tissue sarcoma who have received prior therapy** 800 mg once daily continuously on an empty stomach	**Common**: Diarrhea, HTN, hair color changes, **Notable**: N/V, fatigue, bleeding

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Regorafenib (Stivarga)	VEGFR; cKIT; BRAF; RET; Abl	**Metastatic colorectal cancer, GIST, HCC** 160 mg daily on days 1-21 of a 28-day cycle with a low fat meal (< 30% fat, and < 600 calories)	**Common**: Rash, diarrhea **Notable**: HTN, HFS, bleeding, nausea, fatigue, hepatotoxicity
Sorafenib (Nexavar)	VEGFR; cKIT; FLT-3; RET; BRAF	**RCC, HCC, and thyroid carcinoma** 400 mg BID continuously on an empty stomach	**Common**: Diarrhea, skin rash, **Notable**: HTN, bleeding, wound-healing complications, cardiovascular events
Sunitinib (Sutent)	VEGFR; cKIT; FLT-3; RET	**GIST and advanced RCC** 50 mg daily 2 weeks on, then 1 weeks off **Adjuvant RCC** 50 mg daily 2 weeks on, then 1 weeks off for nine 6-week cycles **pNET** 37.5 mg daily continuously	**Common**: Bleeding **Notable**: HTN, skin rash, cardiovascular events, hepatotoxicity

*Common adverse events are noted as ≥ 20-30% reported in the package insert, **notable = rare or serious adverse events, AE = adverse events; VEGFR = vascular endothelial growth factor receptors; BCR-ABL = breakpoint cluster region-abelson murine leukemia viral oncogene homolog 1; BCR = B-cell receptor; epidermal growth factor receptors; RCC = renal cell carcinoma; GIST = gastrointestinal stromal tumor; pNET = pancreatic neuroendocrine tumors; HCC = hepatocellular carcinoma; CML = chronic myeloid leukemia; Ph+ = Philadelphia chromosome positive; ALL = acute lymphoblastic leukemia; MDS/MPD = Myelodysplastic/myeloproliferative diseases; ASM = aggressive systemic mastocytosis; HES = hypereosinophilic syndrome; CEL = chronic eosinophilic leukemia; DFSP – dermatofibrosarcoma protuberans; MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; SLL = small lymphocytic leukemia; NSCLC = non-small cell lung cancer; HTN = hypertension; N/V/D = nausea/vomiting/diarrhea; LFTs = liver function tests; SCC = squamous cell carcinomas, r = relapsed, mut = mutation, r/r = relapsed/refractory, PRES = posterior reversible encephalopathy syndrome, HFS = hand foot syndrome, ATC = anaplastic thyroid cancer, ILD = interstitial lung disease, AV = atrioventricular, HLD = hyperlipidemia

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References:

1. Alecensa (alectinib) [prescribing information]. South San Francisco, CA: Genentech USA Inc; June 2018
2. Alunbrig (brigatinib) [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals Inc; December 2018.
3. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther. 2005;315(3):971-9.
4. Bosulif (bosutinib) [prescribing information]. New York, NY: Pfizer; October 2018.
5. Braftovi (encorafenib) [prescribing information]. Boulder, CO: Array BioPharma Inc; January 2019.
6. Cabometyx (cabozantinib) [prescribing information]. South San Francisco, CA: Exelixis, Inc; January 2019.
7. Calquence (acalabrutinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2017.
8. Caprelsa (vandetanib) [prescribing information]. Cambridge, MA: Sanofi Genzyme; October 2018.
9. Chu E, Jr. VT. Physicians' Cancer Chemotherapy Drug Manual 2019. Jones & Bartlett Learning; 2018.
10. Copiktra (duvelisib) [prescribing information]. Needham, MA: Verastem, Inc; September 2018.
11. Gilotrif (afatinib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; January 2018.
12. Gleevec (imatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; July 2018.
13. Iclusig (ponatinib hydrochloride) [prescribing information]. Cambridge, MA: ARIAD Pharmaceuticals Inc; December 2017.
14. Imbruvica (ibrutinib) [prescribing information]. Sunnyvale, CA: Pharmacyclics; August 2018.
15. Inlyta (axitinib) [prescribing information]. New York, NY: Pfizer Inc; August 2018.
16. Iressa (gefitinib) [prescribing information]. Wilmington, DE: AstraZeneca; August 2018.
17. Lenvima (lenvatinib) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; December 2018.
18. Lorbrena (lorlatinib) [prescribing information]. New York, NY: Pfizer Labs; November 2018.
19. National Comprehensive Care Network. Acute Lymphoblastic Leukemia (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed January 27, 2019
20. National Comprehensive Care Network. Soft Tissue Sarcoma (Version 1.2019). https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed January 27, 2019
21. Nerlynx (neratinib) [prescribing information]. Los Angeles, CA: Puma Biotechnology, Inc.; June 2018.
22. Nexavar (sorafenib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; December 2017.

23. Short NJ, Kantarjian H, Jabbour E, Ravandi F. Which tyrosine kinase inhibitor should we use to treat Philadelphia chromosome-positive acute lymphoblastic leukemia?. Best Pract Res Clin Haematol. 2017;30(3):193-200.
24. Sprycel (dasatinib) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; December 2018.
25. Stivarga (regorafenib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; June 2018.
26. Sutent (sunitinib) [prescribing information]. New York, NY: Pfizer Labs; November 2017.
27. Tafinlar (dabrafenib) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; May 2018.
28. Tagrisso (osimertinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals; August 2018.
29. Tarceva (erlotinib) [prescribing information]. South San Francisco, CA: Genetech USA Inc; October 2016.
30. Tasigna (nilotinib) [prescribing information]. East Hanover, NJ: Novartis; July 2018.
31. Tykerb (lapatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; December 2018.
32. Vizimpro (dacomitinib) [prescribing information]. New York, NY: Pfizer Labs; October 2018.
33. Von mehren M, Joensuu H. Gastrointestinal Stromal Tumors. J Clin Oncol. 2018;36(2):136-143.
34. Votrient (pazopanib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2017.
35. Worden, FP, BCOP AJ, PharmD BL. Cancer Pharmacology and Pharmacotherapy Review, Study Guide for Oncology Boards and MOC Exams. Demos Medical; 2016.
36. Xalkori (crizotinib) [prescribing information]. New York, NY: Pfizer Labs; January 2019.
37. Zelboraf (vemurafenib) [prescribing information]. South San Francisco, CA: Genentech USA Inc; November 2017.
38. Zydelig (idelalisib) [prescribing information]. Foster City, CA: Gilead Sciences Inc; October 2018.
39. Zykadia (ceritinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2019.