

## Dabrafenib and Trametinib Combination Therapy for Melanoma

Dabrafenib (Tafinlar®) and trametinib (Mekinist®) is a BRAF/MEK combination therapy. Dabrafenib is an inhibitor of some mutated forms of BRAF kinase, and trametinib is a MEK1 and MEK2 inhibitor. About half of patients with melanoma have a mutated form of the BRAF protein in their tumors.

Combination MEK/BRAF inhibitor therapy is associated with superior tumor response and patient survival compared with single-agent BRAF inhibitor therapy. Use of the combination also decreases the high rates of secondary cutaneous malignancies associated with single-agent BRAF inhibitory therapy.

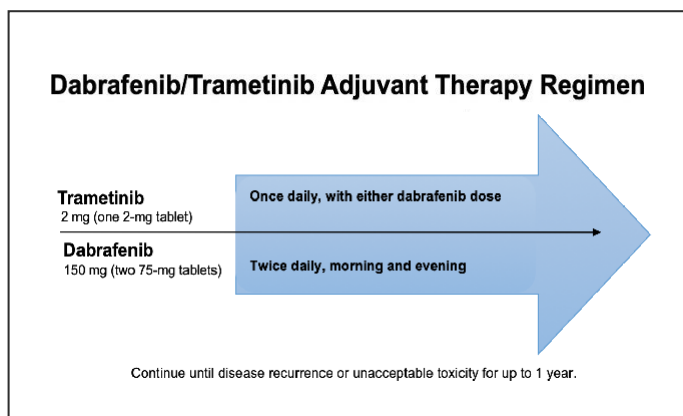
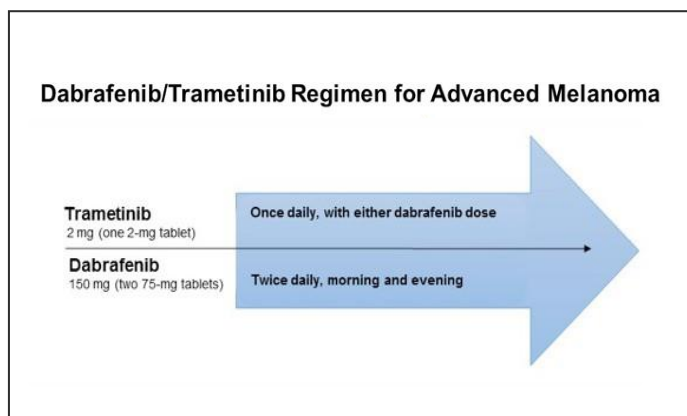
Dabrafenib/trametinib combination therapy received its initial FDA approval for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. More recently, one year of adjuvant therapy of the combination BRAF/MEK inhibitor therapy was found to significantly improve relapse-free survival and have a clinically meaningful benefit on overall survival as compared with placebo.

In April 2018, dabrafenib and trametinib received an additional FDA approval for adjuvant treatment of patients with completely resected stage III melanoma with BRAF V600E or V600K mutations.

This document is part of an overall health care provider toolkit intended to assist providers in optimizing management of melanoma in patients receiving targeted anti-melanoma therapies.

# DRUG-DOSING/ADMINISTRATION

- Both dabrafenib and trametinib are orally administered drugs
- For unresectable or metastatic melanoma (and at the full dose), dabrafenib 150 mg is taken twice daily (once in the morning and once in the evening, 12 hours between doses) for a total daily dosage of 300 mg. Trametinib 2 mg is taken once daily at the same time each day, preferably with either the morning or evening dose of dabrafenib (see left diagram). Dabrafenib/trametinib treatment should continue until disease progression or unacceptable toxicity occurs
- For adjuvant treatment, dabrafenib is also dosed at 150 mg twice daily for a maximum total daily dosage of 300 mg. Trametinib 2 mg is taken once daily at the same time each day. The regimen is continued until disease recurrence or unacceptable toxicity for up to 1 year (see right diagram)



- Dabrafenib/trametinib and dabrafenib should be administered on an empty stomach at least 1 hour before or at least 2 hours after eating. Dabrafenib capsules should not be opened, crushed, or broken
- Dabrafenib should be stored at room temperature
- Trametinib must be kept refrigerated
  - » Instruct patients to store trametinib in a refrigerator in the original bottle with the lid closed tightly to protect the medication from heat, light, or moisture
  - » Patients who are traveling should keep trametinib in a refrigerated lunch pack
  - » Temperature excursion data show that trametinib (in an opened bottle) is not damaged by storage outside the refrigerator for as many as 30 days if it is maintained at a temperature below 86°F (30°C). Nurses may advise patients who have inadvertently left trametinib out of the refrigerator to simply keep the medication cool and return it to the refrigerator as soon as possible
- Concurrent administration of strong inhibitors of CYP3A4 or CYP2C8 should be avoided with dabrafenib. Also, dabrafenib is an inducer of CYP3A4, CYP2C8, and several other CYP enzymes; concomitant use of drugs that are sensitive substrates of these CYP enzymes may result in loss of efficacy of these drugs (example, hormonal contraceptives and proton pump inhibitors)

# SIDE EFFECTS AND THEIR MANAGEMENT

- Possible treatment-related adverse events (AEs) should be discussed with patients prior to initiating trametinib/dabrafenib therapy. Patients should be informed of the importance of immediately reporting any health changes that may reflect a treatment-related AE.
- AEs associated with trametinib/dabrafenib therapy can be generally divided into those that are most common (but typically mild-to-moderate in severity) and less common but serious AEs. Table 1 shows the common and less common but serious AEs associated with dabrafenib/trametinib as well as other AEs.

**Table 1. AEs Associated With Dabrafenib/Trametinib**

Category	Examples
Most common	Fever/pyrexia Skin toxicities (rash) Hypertension Chills Cough Headache Peripheral edema Arthralgia/myalgia Anorexia Gastrointestinal <ul style="list-style-type: none"> <li>- Constipation/abdominal pain</li> <li>- Nausea/vomiting</li> </ul>
Less common but serious	New primary cancers <ul style="list-style-type: none"> <li>- Cutaneous (eg, basal cell or squamous cell carcinoma, keratoacanthoma, new melanoma)</li> <li>- Non-cutaneous</li> </ul> Ocular toxicity Cardiovascular <ul style="list-style-type: none"> <li>- Cardiomyopathy (LVEF)</li> <li>- Hemorrhage</li> <li>- Venous thromboembolism (pulmonary embolism, deep vein thrombosis)</li> <li>- Hemolytic anemia</li> </ul> Colitis and gastrointestinal perforation Interstitial lung disease/pneumonitis Renal toxicity

# SIDE EFFECTS AND THEIR MANAGEMENT

(CONTINUED)

- Severe and sometimes moderate AEs are commonly managed by dose interruptions or withdrawal. In certain cases, referral to a cardiology, dermatology, or ophthalmology specialist is warranted

**Table 2: Recommended dose reductions for trametinib and dabrafenib**

<b>Dabrafenib</b>	<b>Dose reduction from 150 mg orally twice daily to</b>
First dose reduction Second dose reduction Third dose reduction Subsequent	100 mg orally twice daily 75 mg orally twice daily 50 mg orally twice daily Permanently discontinue if unable to tolerate 50 mg orally twice daily
<b>Trametinib</b>	<b>Dose reduction from 2 mg once daily to</b>
First dose reduction Second dose reduction Subsequent modification	1.5 mg orally once daily 1 mg orally once daily Permanently discontinue if unable to tolerate 1 mg orally once daily

## Detection and management of AEs and laboratory abnormalities not included in Care Step Pathways for trametinib/dabrafenib

Adverse event	Common symptoms	Common management/anticipatory guidance*
Anorexia	Decreased appetite (occurs at higher rates in elderly patients)	<ul style="list-style-type: none"> <li>• Monitor weight; query patient about appetite/eating habits; advise dietary modification if necessary</li> <li>• Anticipate treatment hold for intolerable Grade 2 (oral intake altered) or Grade 3/4 (significant weight loss or malnutrition or life-threatening consequences)</li> </ul>
Arthralgias/myalgias	Joint pain swelling, or stiffness, feeling tired	<ul style="list-style-type: none"> <li>• Query patients regarding joint symptoms; standard supportive care (analgesia and anti-inflammatory drugs)</li> <li>• Anticipate treatment hold for intolerable Grade 2 (moderate pain, limiting instrumental ADLs) or Grade 3 (severe pain and self-care ADL limitations)</li> </ul>
Chills	Shaking feeling/cold in absence of fever	<ul style="list-style-type: none"> <li>• Query about symptoms, including symptoms related to serious febrile reactions</li> <li>• Anticipate treatment hold for intolerable Grade 2 (moderate tremors) or Grade 3 (severe or prolonged chills that are not responsive to narcotics)</li> </ul>
Constipation/ Abdominal pain	Infrequent stools/ difficulty stooling, abdominal pain	<ul style="list-style-type: none"> <li>• Increase fluid; fiber; laxatives. Consider appropriate testing to evaluate bowel obstruction</li> <li>• Anticipate treatment hold for intolerable Grade 2 (persistent symptoms of constipation or moderate pain limiting instrumental ADLs) or Grade 3/4 (obstipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences)</li> </ul>
Cough	Dry cough, shortness of breath, DOE	<ul style="list-style-type: none"> <li>• Advise patients to report any symptoms; rule out infectious causes and pneumonitis (interstitial lung disease); monitor oxygen saturation (pulse oximetry) and consider chest x-ray; standard supportive care</li> <li>• Anticipate treatment hold for intolerable Grade 2 (moderate symptoms, limiting instrumental ADLs) or Grade 3 (severe symptoms)</li> </ul>
Deep vein thrombosis	Swelling, leg pain, shortness of breath	<ul style="list-style-type: none"> <li>• Advise patients to seek medical care if they have acute onset arm/leg swelling</li> <li>• Anticipate treatment hold of trametinib for Grade 2 (uncomplicated DVT) and permanent discontinuation if not improved after 3 weeks; no dose modification for dabrafenib for uncomplicated venous thromboembolism</li> </ul>

## Detection and management of AEs and laboratory abnormalities not included in Care Step Pathways for trametinib/dabrafenib

(Continued)

Adverse event	Common symptoms	Common management/anticipatory guidance*
Edema	Swelling of limbs, etc	<ul style="list-style-type: none"> <li>Occurs at higher rates in elderly patients. Advise patients to report swelling; standard supportive care; cardiac workup may be indicated</li> <li>Anticipate treatment hold for intolerable Grade 2 (moderate swelling, limiting instrumental ADLs) or Grade 3 (severe swelling, gross deviation from anatomic contour)</li> </ul>
Embryo-fetal toxicity	—	<ul style="list-style-type: none"> <li>Trametinib/dabrafenib can cause fetal harm. Females and males of child-bearing potential should use effective nonhormonal birth control during trametinib/dabrafenib treatment and for 4 months after stopping trametinib/dabrafenib treatment</li> </ul>
Fatigue	Unrelenting exhaustion not relieved by rest	<ul style="list-style-type: none"> <li>Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematological and biochemical abnormalities; standard supportive care</li> <li>Anticipate treatment hold for fatigue not relieved by rest and limiting ADLs (Grade 2/3)</li> </ul>
Headache	Pain and/or change in vision	<ul style="list-style-type: none"> <li>May be multifactorial. For severe or persistent symptoms, consider other causes such as bleeding in the brain, uncontrolled hypertension, dehydration, new CNS disease, or other causes; consider brain MRI and evaluations for hypertension</li> <li>Anticipate treatment hold for intolerable Grade 2 (moderate pain) or Grade 3 (severe pain, limiting self-care ADLs)</li> </ul>
Hemolytic anemia (in patients with G6PD deficiency)	Yellow skin, weakness or dizziness, shortness of breath	<ul style="list-style-type: none"> <li>Monitor patients with G6PD deficiency for signs of hemolytic anemia. Advise patients to report any symptoms</li> </ul>
Hemorrhage	Red or black/tarry stools; blood in urine; headaches; coughing or vomiting blood; abdominal pain; unusual vaginal bleeding; fatigue; dizziness or weakness	<ul style="list-style-type: none"> <li>Standard supportive care; medical intervention as indicated</li> <li>Anticipate treatment hold for intolerable Grade 2 (moderate bleeding) or Grade 3/4 (severe bleeding requiring transfusion or radiologic, endoscopic, or operative intervention or life-threatening consequences)</li> </ul>

## Detection and management of AEs and laboratory abnormalities not included in Care Step Pathways for trametinib/dabrafenib

(Continued)

Adverse event	Common symptoms	Common management/anticipatory guidance*
Hyperglycemia	Fatigue, polyuria, polydipsia, headaches	<ul style="list-style-type: none"> <li>• Monitor fasting glucose/Hemoglobin A1C (particularly in patients with pre-existing diabetes/hyperglycemia); advise patients to report increased thirst/increased urination; provide anti-diabetic medication</li> <li>• Anticipate treatment hold for intolerable Grade 2 (fasting glucose &gt;160 to 250 mg/dL) or Grade 3/4 (fasting glucose &gt;250 mg/dL)</li> </ul>
Nausea/Vomiting	Vomiting, queasiness, RUQ or LUQ pain	<ul style="list-style-type: none"> <li>• For most cases, standard supportive care will be adequate</li> <li>• May indicate hepatotoxicity; check LFTs/lipase/amylase</li> <li>• Anticipate treatment hold for intolerable Grade 2 (oral intake decreased or 3 -5 episodes vomiting in 24 hours) or Grade 3/4 (inadequate oral intake or ≥6 episodes vomiting in 24 hours or life-threatening consequences)</li> </ul>
Pulmonary embolism	Shortness of breath/ chest pain	<ul style="list-style-type: none"> <li>• Advise patients to seek medical care if they have shortness of breath, chest pain; appropriate workup, including imaging and CT angiogram</li> <li>• Anticipate treatment hold of trametinib and permanent discontinuation if not improved after 3 weeks or for life-threatening PE</li> <li>• Anticipate treatment hold of dabrafenib and permanent discontinuation if no recovery to Grade 0–1</li> <li>• Anticipate anticoagulant therapy for at least 6 months</li> </ul>
Pneumonitis (interstitial lung disease)	New cough, dyspnea, hypoxia, pleural effusion or infiltrates	<ul style="list-style-type: none"> <li>• Advise patients to report any new or worsening symptoms of lung or breathing problems (shortness of breath/cough)</li> <li>• Anticipate permanent discontinuation of trametinib; do not modify the dose of dabrafenib</li> </ul>
Renal toxicity	Decreased urine, blood in urine, swelling of ankles, decrease in appetite	<ul style="list-style-type: none"> <li>• Measure serum creatinine before treatment initiation and periodically during treatment; monitor kidney function</li> <li>• Anticipate treatment hold with intolerable Grade 2 (eGFR or CrCl 59 to 30 mL/min/1.73 m<sup>2</sup>) or Grade 3/4 (eGFR or CrCl ≤29 mL/min/1.73 m<sup>2</sup>)</li> </ul>

\*When treatment holds are required, resume therapy at a lower dose level following improvement to Grade 0 to 1. Permanently discontinue targeted therapies in case of persistent intolerable Grade 2 events, persistent Grade 3 events, and persistent or recurrent Grade 4 events unless otherwise specified

## CLINICAL PEARLS

- Before beginning targeted therapy, patients who previously received immunotherapy should be monitored carefully for possible overlapping toxicities. Several AEs are observed with both targeted and immunotherapy including rash, diarrhea, and liver enzyme elevation and may result in cumulative toxicities.
- Potential drug-drug interactions are an important component of dabrafenib/trametinib therapy for melanoma
- Dabrafenib is metabolized by CYP3A4 and 2C8 and also induces CYP3A4&2C8 and several other enzyme systems. Therefore, dabrafenib efficacy can be reduced by other concomitantly administered agents sharing metabolic pathways. It can also lower the concentrations and efficacy of concomitant drugs as well including hormonal birth control.
- Patients should be encouraged to have all their medications filled by a single pharmacy to ensure familiarity with the full medication list and to avoid polypharmacy issues.
- Patients should have a full skin exam prior to starting therapy and throughout therapy. Patients should be referred to a dermatologist for any new skin lesions.
- New skin cancers often initially present as a new wart, skin sore or reddish bump that bleeds or dose not heal, and/or as a change in size or color of a mole. Patients should be made aware of this association and advised to immediately report any skin changes to the healthcare team
- Advise patients to take pictures of any skin lesions for documentation



## QUESTIONS & ANSWERS

### Q. How long do the fevers last?

**A.** During the trials, pyrexia with BRAF/MEK inhibitor therapy occurred in about two thirds of patients. Fevers usually start after about 30 days of treatment, but can start within a couple of days lasting 2-3 days, and typically improving after 6 months. Your patient must contact the oncology team if they begin to experience fevers. For low-grade fevers of 99-101°F, they can take antipyretics as directed by the provider. Also make sure your patient is drinking plenty of water. For a fever higher than 101°F, the oncology team member most likely will hold the BRAF inhibitor (and may hold the MEK inhibitor as well), and if the patient's temperature is higher than 104°F, he/she will hold both medications and see the patient in clinic. The patient might need supportive care such as IV hydration and to begin low dose prednisone as recommended by the prescribing information. Some patients might need a dose holiday and dose reduction until fevers resolve. Keeping well hydrated is very important, especially with higher temperatures, to avoid dehydration.

### Q. How long will the patient be on BRAF/MEK inhibitor therapy?

**A.** In the unresectable or metastatic disease setting, likely patients will continue therapy for as long as their disease is responding to therapy and they are tolerating the medications. During the clinical trials, the patients who had to stop therapy were those who had disease progression or had moderate-to-severe drug toxicities who affected their quality of life and required persistent drug holidays, dose reduction, or discontinuation.

In the adjuvant setting, patients will continue therapy for a duration of 1 year, as long as their disease has not reoccurred and they are tolerating the medications. During the clinical trials, the patients who had to stop therapy were those who had disease recurrence or had moderate- to-severe drug toxicities that affected their quality of life and required persistent drug holidays, dose reduction, or discontinuation.

## ADDITIONAL RESOURCES

- Czupryn M, & Cisneros, J. BRAF/MEK inhibitor therapy: consensus statements from the faculty of the Melanoma Nursing Initiative on managing adverse events and potential drug interactions. *Clin J Oncol Nurs*. 2017; 21 (suppl): 11-29.
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- How to Take Tafinlar + Mekinist. Available at: <https://www.us.tafinlarmekinist.com/advanced-melanoma/about-treatment/dosing-and-administration/>.
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- Mavropoulos JC, Wang TS. Managing the skin toxicities from new melanoma drugs. *Curr Treat Options Oncol*. 2014;15:218-301.
- Mekinist®. [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2024. Available at: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/mekinist.pdf>.
- Rubin KM. Care and management of unique toxicities associated with MAPK pathway- targeted therapies in patients with advanced melanoma. *Clin J Oncol Nurs*. 2017 Dec 1;21(6):699-709. doi: 10.1188/17.CJON.699-709.
- TAF + MEK website for melanoma, non-small cell lung cancer and pediatric low-grade glioma. <https://us.tafinlarmekinist.com/>. Novartis Pharmaceuticals. Accessed 2024.
- Tafinlar® (dabrafenib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2024. Available at: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/tafinlar.pdf>.
- Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol*. 2015;7:122-136.

# PATIENT RESOURCES

## ADDITIONAL INFORMATION RESOURCES

**AIM at Melanoma Foundation** (Ask an Expert program, patient symposia, drug resources, etc)  
<https://www.aimatmelanoma.org/>

**American Cancer Society: Targeted therapy for melanoma skin cancer**  
<https://www.cancer.org/cancer/melanoma-skin-cancer/treating/targeted-therapy.html>

## FINANCIAL ASSISTANCE

**Resources from Novartis**  
Novartis Patient Assistance Program (financial and other support)  
1-800-282-7630  
[www.us.tafinlarmekinist.com/advanced-melanoma](http://www.us.tafinlarmekinist.com/advanced-melanoma)

**Cancer Financial Aid Coalition**  
Facilitates communication, educates and advocates for patients.  
[www.cancerfac.org](http://www.cancerfac.org)

**Centers for Medicare and Medicaid Services (CMS)**  
Apply to determine if you are eligible for government assistance.  
[www.cms.gov](http://www.cms.gov) or [www.medicare.gov](http://www.medicare.gov)  
800-633-4227

**Lazarex Foundation**  
Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.  
[www.lazarex.org](http://www.lazarex.org)

**NeedyMeds**  
Database to search for free or low-cost medications, help with medical transportation and other resources.  
[www.needy meds.org](http://www.needy meds.org)

**Patient Advocate Foundation**  
Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability. Patient must meet their eligibility for financial assistance.  
[www.patientadvocate.org](http://www.patientadvocate.org)  
800-532-5274

**The Sam Fund for Young Adult Survivors of Cancer**  
Assists cancer survivors ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.  
[www.thesamfund.org](http://www.thesamfund.org)  
[info@thesamfund.org](mailto:info@thesamfund.org)

## PRESCRIPTION ASSISTANCE

### **CancerCare Co-Payment Assistance Foundation**

Helps with the cost of medication. Availability of funds for patients with Stage IV melanoma subject to availability.

[www.cancercapecopay.org](http://www.cancercapecopay.org)

1-866-552-6729

### **Medicine Assistance Tool**

Database to search for patient assistance resources offered by pharmaceutical companies.

[www.medicineassistancetool.org/](http://www.medicineassistancetool.org/)

### **Patient Advocate Foundation Co-Pay Relief**

Provides direct financial support to patients who medically qualify. Availability of funds for patients with Stage IV melanoma subject to availability.

[www.copays.org](http://www.copays.org)

1-866-512-3861

### **Good Days**

Formerly known as the Chronic Disease Fund. Provides assistance with insurance co-pays, and prescription medications. Availability of funds for patients with Stage IV melanoma subject to availability.

[www.mygooddays.org](http://www.mygooddays.org)

### **HealthWell Foundation**

For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Availability of funds for patients with Stage IV melanoma subject to availability. Patient must also meet eligibility for financial assistance.

[www.healthwellfoundation.org](http://www.healthwellfoundation.org) or

[grants@healthwellfoundation.org](mailto:grants@healthwellfoundation.org)

1-800-675-8416

### **The Assistance Fund, Inc**

Provides prescription copay and financial assistance, including health insurance premiums. Availability of funds for patients with Stage IV melanoma subject to availability.

[www.theassistancefund.org](http://www.theassistancefund.org)

1-855-845-3663

### **PAN Foundation**

Provides financial assistance to cover out-of-pocket treatment costs. Availability of funds for patients with Stage IV melanoma subject to availability.

[www.panfoundation.org](http://www.panfoundation.org)

1-866-316-PANF (7263)

### **Patient Assistance Program**

Comprehensive database of patient assistance programs offering free medications.

[www.rxassist.org](http://www.rxassist.org)

[info@rxassist.org](mailto:info@rxassist.org)

## HOUSING

### **American Cancer Society – Hope Lodge**

Provides free housing during treatment appointments. Requires a referral from your social worker.

[www.cancer.org/](http://www.cancer.org/)

1-800-227-6333

## TRANSPORTATION (AIR AND GROUND)

### **Medicaid**

Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.

1-877-633-8747

### **Mercy Medical Angels**

Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance.

[www.mercymedical.org/](http://www.mercymedical.org/)

### **Pilots for Patients**

Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.

[www.pilotsforpatients.org](http://www.pilotsforpatients.org)

318-322-5112