

Tenosynovial Giant Cell Tumors: Mechanisms for Improving Patient Functionality and Outcomes

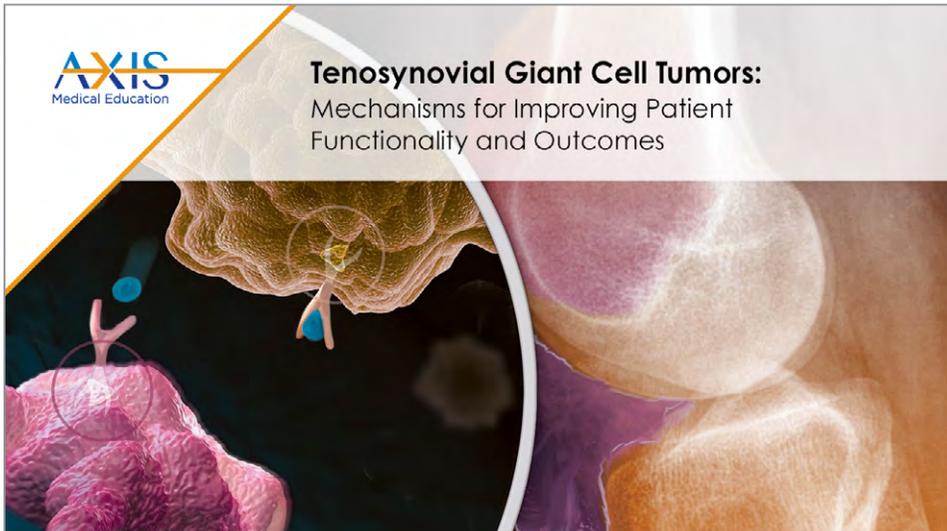
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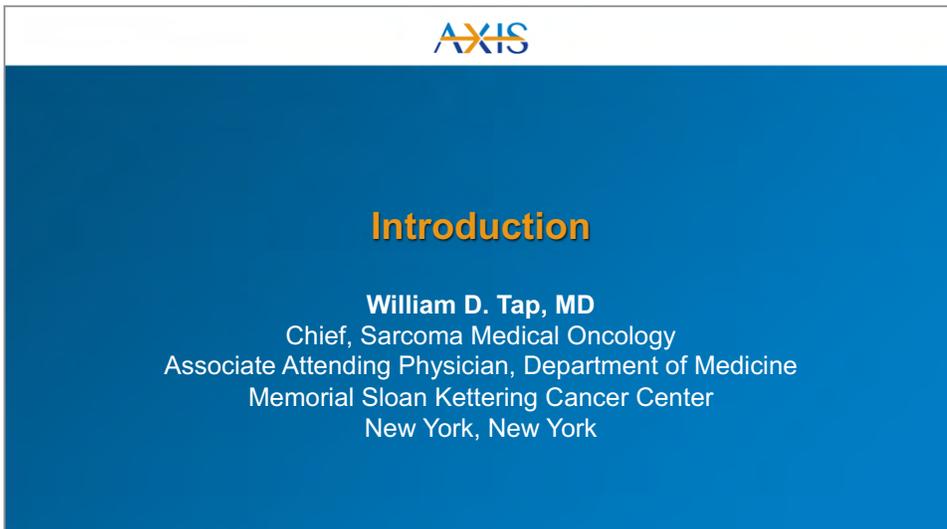
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Tenosynovial Giant Cell Tumors: Mechanisms for Improving Patient Functionality and Outcomes

William D. Tap, MD



- ▶ **William D. Tap, MD:** Hello, and welcome to this educational activity entitled *Tenosynovial Giant Cell Tumors: Mechanisms for Improving Patient Functionality and Outcomes*.



- ▶ I am Dr. William Tap, chief of the Sarcoma Medical Oncology Service and associate attending physician in the Department of Medicine at Memorial Sloan Kettering Cancer Center in New York, New York.



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Disclosure of Conflicts of Interest William D. Tap, MD

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- ▶ Here is my financial disclosure information.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Identify the signs and symptoms of tenosynovial giant cell tumors (TGCTs) to ensure prompt and accurate diagnosis
- Examine when referral to centers of excellence is warranted for more complicated and unresectable cases of TGCT
- Select treatment for TGCT based on available efficacy data, safety data, and current best practices for appropriate use and monitoring
- Discuss treatment goals and preferences with patients with TGCT to ensure an informed and productive shared decision-making process

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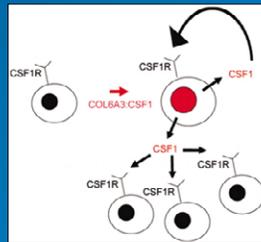
▶ Here are the learning objectives for this activity. Today we will review the latest clinical advances and emerging evidence in tenosynovial giant cell tumor (TGCT) while highlighting the relevance and integration of these new data into current practice.

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Overview of Tenosynovial Giant Cell Tumor

Pigmented Villonodular Synovitis Tenosynovial Giant Cell Tumor

- Rare synovial tumor of joints & tendon sheaths
- Annual incidence in United States ~ 11 per million
 - Often young adults
- Clonal neoplastic process resulting in overexpression of CSF1 in synovium
 - Frequently due to genetic translocation
 - t(1;2) *CSF1:COL6A3*
 - Propagation of neoplastic clone (autocrine)
 - Reactive inflammatory process with **proliferation and recruitment of CSF1 receptor-expressing cells**:
 - Macrophages, giant cells, osteoclasts



CSF1, colony-stimulating factor 1.
West, et al. *PMAS* 2006;103:690-695; National Organization for Rare Disorders, 2017; Giustini et al. *Clin Sarcoma Res.* 2018;8:14.

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▶ TGCT, previously referred to as pigmented villonodular synovitis, is a rare synovial tumor of the joints and tendon sheath. The exact incidence is not clearly identified in the United States or worldwide, but it is estimated that about 600 new cases are diagnosed in the United States each year. Patients are often diagnosed as young adults.

TGCT is a clonal neoplastic process that involves the overexpression of colony-stimulating factor 1 (CSF1) in the synovium. This is frequently due to a genetic translocation; for example, a translocation involving chromosomes 1 and 2 in which the *CSF1* gene is placed next to the promoter of a ubiquitous collagen gene.

With the expression of *CSF1*, you can get propagation of the neoplastic clone in an autocrine fashion. However, the presence of CSF1 can actually recruit reactive inflammatory cells over to the joint that bears CSF1 receptors (CSF1R).

The bulk of tumors that we often deal with in TGCT are inflammatory cells, which can include macrophages, giant cells, and osteoclasts.

PVNS and GCT-TS: High Morbidity

- While usually not metastatic, disease is locally aggressive, and recurrence is common after surgical resection
 - Particularly with diffuse PVNS
- Affects young and middle-aged adults of both sexes with no ethnic predisposition
- Patients diagnosed in their 30s and 40s and can live ~40 years after diagnosis

Gross features:

- Collagen deposition
- Subchondral bone erosions
- Repeat hemarthrosis

Clinical features:

- Usually single joint:
 - Swelling
 - Pain
 - ↓ range of motion
 - Stiffness



Implications:

- Functional impairment
- Narcotic use
- Disability

GCT-TS, giant cell tumor of the tendon sheath; PVNS, pigmented villonodular synovitis.

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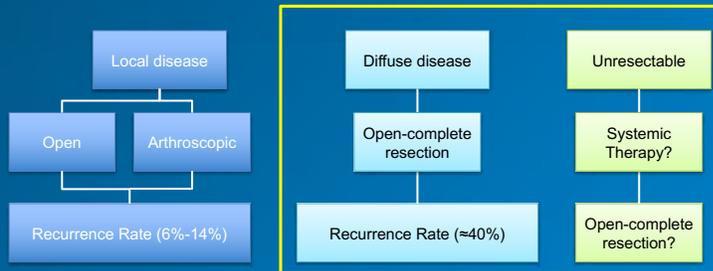
▶ TGCT is a neoplastic process and not a cancer per se; therefore, metastatic disease tends not to develop. It usually affects one joint in the body. It tends to affect younger and middle-aged adults of both sexes with no ethnic predisposition. Disease is usually diagnosed in patients in their thirties and forties, and patients can live long lives with this disease.

For the most part, when the diffuse type of TGCT develops, they can get collagen deposition, subchondral bone erosions, and repeat hemarthroses within the bone. This can cause swelling, pain, and decreased range of motion, as well as stiffness. Most of this is due to the aggregation of the inflammatory cells that are recruited over to the joint, which bears the CSF1R.

Having this type of inflammation can cause functional impairment, narcotic use, and disability. So although TGCT does not necessarily threaten a person's life, it can really change the trajectory of their life by causing this disability and the use of medications to help with pain.

Pigmented Villonodular Synovitis Tenosynovial Giant Cell Tumor

PVNS/TGCT – New Diagnosis



PVNS, pigmented villonodular synovitis; TGCT, tenosynovial giant cell tumor.
Courtesy of William D. Tap, MD.

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► For the most part, there are two forms of TGCT that we will talk about. There is a local disease which is usually a nodular form encapsulated and most often cured with surgery alone. This has very low recurrence rates with the appropriate surgery of about 6% to 14%.

The majority of the disease that we will be talking about today is the diffuse type of the disease, and we'll show some images and examples of this. Patients with diffuse disease tend to need open and complete resections, but even with open resections such as synovectomies, the recurrence rate can be high, approximately 40%.

There are also patients with the diffuse type of TGCT that is not amenable to surgery due to the extent of the disease and the morbidity that surgery may actually convey.

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Making the Tensynovial Giant Cell Tumor Diagnosis

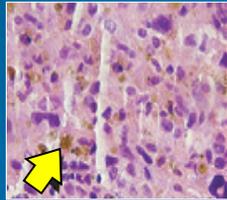
TGCT Represents Two Distinct Clinical Presentations

Localized-TGCT



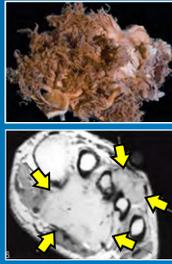
Reprinted from Lucas, 2012.

Hemosiderin Deposition



Reprinted from Richman et al, 2015.

Diffuse-TGCT



Reprinted from Lucas, 2012.

TGCT, tenosynovial giant cell tumor.
Lucas. *Arch Pathol Lab Med.* 2012;136(8):901-906; Richman et al. *J Clin Imaging Sci.* 2015;5:13.

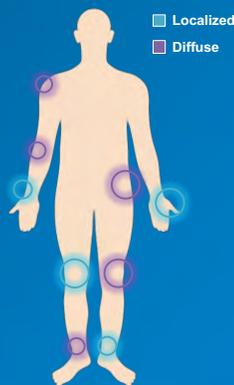
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- ▶ On the next slide we actually show the different types of TGCT. And, again, it is important to know that patients with the localized nodular TGCT are cured almost always with surgery alone, they are not the patients that we will be talking about in this presentation, especially when we talk about medical management. There are extreme cases of this disease, though, that may not be resectable, and these patients could be considered for medications.

On the flipside, most of the time when we're talking about the use of medications in the types of surgeries later on in this talk, we will be talking about the diffuse type of TGCT, which is represented on some of the images to the right. Many surgeons talk about this disease as operating in mud, meaning that it is really infiltrated within the joint and can be difficult to encapsulate or resect with clear margins.

Most TGCT Patients Present With Localized Disease

| TGCT type |
|--|
| Localized ~90% of TGCT cases |
| Diffuse ~10% of TGCT cases |



TGCT, tenosynovial giant cell tumor.
Myers and Masi. *Medicine (Baltimore)* 1980;59(3):223-238; Mastboom et al. *Acta Orthop.* 2017;88(6):688-694.

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- ▶ Most patients with TGCT present with localized disease. This comprises about 90% of the cases that are documented. It's only about 10% of the cases that are actually diagnosed with the diffuse type of TGCT.

Joint Signs and Symptoms

- Pain
- Swelling
- Stiffness
- Limited range of motion
- Locking complaints
- Instability
- Giving way

Gelhorn et al. *Clin Ther*. 2016;38(4):778-793.

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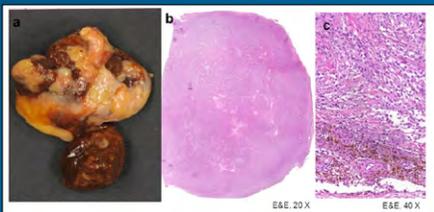
▶ When patients present they often present with local joint swelling, stiffness, pain, decreased range of motion. They can have complaints of the joint locking, instability, or giving way.

Ironically, patients can often present with pain within other joints, and this can often be due to compensation to the main affected joint. For example, if someone often has TGCT within the right knee, they can complain about left hip pain.

Many patients actually get confused with having more polyarthritic symptoms, so it's very important to have the appropriate diagnostic procedures for the main affected joint, and this could be MRI as well as biopsies.

TGCT/PVNS: Outcome of 294 Patients Before the Era of Kinase Inhibitors

TGCT/PVNS Primary Tumor Site Distribution Among 294 Patients



Other Sites
13%



Hip
11%

Knee
60%

Ankle
16%

PVNS, pigmented villonodular synovitis; TGCT, tenosynovial giant cell tumor. Palmerini et al. *Eur J Cancer* 2015;51:210-217. Used with permission.

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▶ There have been data looking at historical evaluations of TGCT. There was a nice collaborative series that was recently published in the *European Journal of Cancer* looking at 294 patients that were evaluated before the use of tyrosine kinase inhibitors. Again, they qualified the different types of TGCT, and, importantly, qualified the types of joints where we can see this disease.

We can see TGCT develop within any joint of the body. By far the most prevalent is the knee, and then we often see them within the ankle and the hip. Other common joints can also be the elbow.

TGCT/PVNS: 5-year Local Failure-Free Survival

5-year LFFS by
Resection Status

76%

Complete

57%

Incomplete

P=0.0007

5-year LFFS by
Presentation of Referral Centers

77%

New diagnosis

12%

First recurrence

P=0.0001

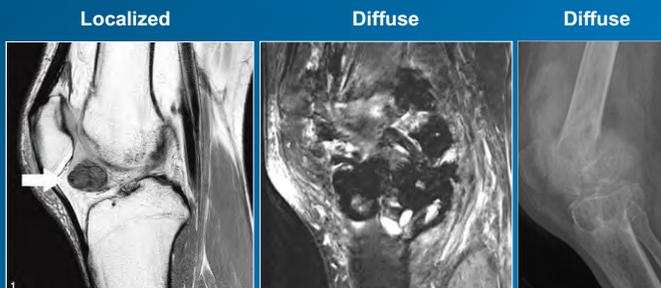
LFFS, local failure-free survival; PVNS, pigmented villonodular synovitis; TGCT, tenosynovial giant cell tumor. Palmerini et al. *Eur J Cancer* 2015;51:210-217.

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▶ One of the hallmarks of this disease is the recurrence rates after surgical resections of the diffuse type of TGCT is high. There is a wide confidence interval, but it is estimated that the recurrence rate can be anywhere between 40% and 60%, depending on where the procedure is done, which joint, and what type of procedure is performed.

However, it is important to understand that surgery still remains one of the main treatment strategies for patients with the diffuse type of TGCT. For many patients it can be curative, and it can actually relieve significant symptoms for a long time.

Localized and Diffuse Tumor Presentation



Left image Lucas DR. *Arch Pathol Lab Med*. 2012;136(8):901-906. Center and right images courtesy of Nicholas Bernthal, MD.

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▶ The next slide shows what localized versus diffuse tumor types can look like on radiographs. On the localized side is a nodular form of TGCT, again nodular, well encapsulated, and can be easily cured with the right type of surgery.

Conversely, when you look at the diffuse type of the disease, you can see the extensive nature of the disease that may require anterior and posterior synovectomies and extensive surgeries that would not necessarily clear the disease.

Small Molecule Inhibitors

Imatinib and Nilotinib

- ▶ Because of the extent of the disease and the fact that some patients have disease that is not amenable to surgery and with the discovery of the overexpression of CSF1 in the biology of this disease, there has been tremendous interest in the use of small molecule inhibitors, or even antibodies, that can target CSF1 signaling. There are drugs that are approved for other malignancies such as imatinib mesylate and nilotinib, which are weak inhibitors of CSF1.

Imatinib in TGCT/PVNS

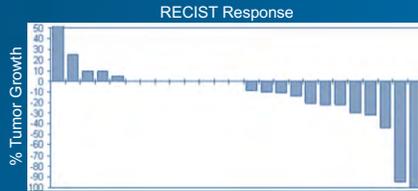
Patient Characteristics

| Characteristic | No. of Patients (%) | Characteristic | No. of Patients (%) |
|------------------------------|---------------------|---|---------------------|
| Total | 29 (100) | Previous Surgery | |
| Median age [range], y | 41 [21-77] | Yes | 20 (69) |
| Sex | | No | 9 (31) |
| Men | 13 (45) | Median no. of operation for surgical patients [range] | 2 [1-9] |
| Women | 16 (55) | Median time since last operation [range], mo | 22 [1-95] |
| Tumor location | | Disease status | |
| Knee | 17 (59) | Localized/locally advanced | 27 (93) |
| Hip | 3 (10) | Metastatic | 2 (7) |
| Foot | 3 (10) | Site of metastasis | |
| Ankle | 3 (10) | Lung | 2 (7) |
| Shoulder | 1 (3) | Bone | 1 (3) |
| Elbow | 1 (3) | | |
| Head and neck | 2 (7) | | |

- ▶ There was a publication in *Cancer* in 2012 that looked at 29 patients who were treated at multiple sites using imatinib mesylate. What you can see from the demographics of this patient population, it is very typical of the types of patients that we see who present with the diffuse type of TGCT, a younger age with a median onset of about 40, a slight preponderance of women over men, and the majority of patients have disease within the knee.

Imatinib in TGCT/PVNS

Best Tumor Shrinkage According to RECIST



Efficacy of Imatinib (N=27)

| Parameter | No. of Patients (%) |
|---|---------------------|
| RECIST Best Response | |
| Overall response rate | 5 (19) |
| CR | 1 (3.7) |
| PR | 4 (14.8) |
| SD | 20 (74.1) |
| PD | 2 (7.4) |
| NE | 2 (-) |
| Symptomatic Response | |
| Assessable | 22 |
| Response | 16 (72.7) |
| Median treatment duration [95% CI], mo | 8 [4-12] |
| Median PFS, mo | 20.9 |

CR, complete response; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; PVNS, pigmented villonodular synovitis; RECIST, Response Evaluation Criteria in Solid Tumors; TGCT, tenosynovial giant cell tumor. Adapted from Cassier et al. *Cancer* 2012;118(6):1649-1655.

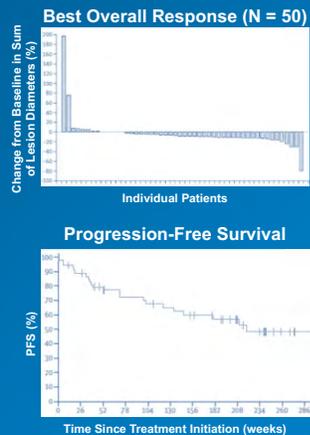
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▶ What you can see from the data is that the best overall RECIST response rate was approximately 18%; in other words, with drugs like imatinib we do not see tremendous decreases in tumor size by RECIST. This is a very diffuse disease, and RECIST as a measurement is not always the best criteria to determine how well tumors are shrinking with the treatment.

What you see here is that some of the responses are durable. But what's also important is that even if patients don't have responses according to RECIST criteria, they can have improvements in symptoms, especially in swelling, pain, and improvements in range of motion and stiffness.

Nilotinib in TGCT/PVNS

- Treatment x 1 year
- 56 patients
- 55% continued for 1 year
- 92% progression-free at 12 weeks
- 77% progression-free at 52 weeks
- ORR = 6%



ORR, overall response rate; PFS, progression-free survival;
PVNS, pigmented villonodular synovitis; TGCT, tenosynovial giant cell tumor.
Adapted from Geldenblom et al. *Lancet Oncol*. 2018;19(5):638-648.

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► There was also a very nice prospective treatment done by our European colleagues looking at nilotinib in patients with diffuse TGCT. In this trial, patients with advanced disease were given nilotinib for 1 year of treatment and then the treatment was discontinued.

What you see is a small overall response rate according to RECIST of 6%. However, the responses were durable even with the cessation of drug, so even when the drug was stopped, many patients did not have disease progression. It is difficult to know if this is the natural history of the disease or if the drug actually helped stabilize the disease over time.

What's important again would be the measurement of improvement in symptoms in this patient population with drugs such as nilotinib and imatinib but use of these drugs off-label can often be very good for our patients. We know the toxicity profile of the drugs, they tend to be very safe to administer, and even if we do not see dramatic decreases in the size of tumors according to RECIST measurements, patients may actually get clinical benefit with improvement in symptoms.

Assessing Clinical Impact of Disease

- Range of motion
 - Objectively measured by goniometer
 - Clinical impact is joint specific
- Knee specific^a
 - Level walking (~65°)
 - Up and down stairs (~80°)
 - In and out of chair (~90°)
 - Most activities of daily living (~110°)



► It is important to look at different measures of how a patient is doing while on treatment. Oftentimes you can see improvements in range of motion. Objectively this can be measured with goniometry by our orthopedic or physical therapy colleagues, and this can often let us know the effect that a drug is having on the patient's mobility and, in turn, quality of life.

Image courtesy of Nicholas Bernthal, MD.
^aRowe et al. *Gait Posture* 2000;12(2):143-155.

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Assessing Impact of TGCT With PROMIS-Physical Function

- Patient-Reported Outcomes Measurement Information System (PROMIS®)-Physical Function
 - Normalized against the US population
 - 50 represents average physical function
 - ~2 point change has been reported as a minimally important difference in RA^a

Examples of Lower Extremity Questions

| | Without any difficulty | With a little difficulty | With some difficulty | With much difficulty | Unable to do |
|---|------------------------|--------------------------|----------------------|----------------------|--------------|
| Are you able to go up and down stairs at a normal pace? | 5 | 4 | 3 | 2 | 1 |
| Does your health now limit you in bending, kneeling, or stooping? | Not at all | Very little | Somewhat | Quite a lot | Cannot do |
| | 5 | 4 | 3 | 2 | 1 |

► There has also been tremendous interest in developing TGCT-specific patient-reported outcome measures, there is a modification of the PROMIS Physical Function Scale specific to patients with TGCT. This is an important scale that can talk about the health of joints throughout the body, which is important, because TGCT can affect joints in the upper skeleton and in the lower skeleton.

There were standard questions that were modified after speaking with a significant number of patients with TGCT to understand the implications and the impact of these questions on their lives and how the disease can affect them. Understanding how patient's symptoms are improved can really help us to determine how well our treatments are helping them.

RA, rheumatoid arthritis; TGCT, tenosynovial giant cell tumor.

^aHays et al. *Ann Rheum Dis*. 2015;74(1):104-107.

Gelhorn et al. *J Patient Rep Outcomes*. 2019;3(1):8.

Image of PROMIS Item Bank v.1.2-Physical Function (Lower Extremity) questionnaire © 2009-2016 PROMIS Health Organization and PROMIS Cooperative Group.

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Discussion

Quality-of-Life Impact

- Young, working-age population
- Life-altering functional limitations, morbidity, and diminished quality of life
- Broad burden of disease
 - Pain
 - Limited range of movement
 - Swelling
 - Stiffness
- Limitations in ability to work or participate in sports and hobbies

Importance of Early Patient Referral to Center of Excellence

- Misdiagnoses due to nonspecific nature of symptoms, atypical presentations
- Delays in definitive diagnosis
- Underappreciation of importance of referral of patients with more complicated disease to centers of excellence and expert clinicians

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▶ As mentioned earlier, this tends to be a younger, healthy, working population that is affected by TGCT. TGCT is not a malignancy that can affect the length of people's lives but can definitely affect the quality of their lives and their ability to perform their daily living activities or other activities and hobbies that are important to them. This is often caused by pain, swelling, decreased range of motion, and stiffness in a single joint that often requires repeated surgeries and/or the use of medications and narcotics.

It's important that patients with TGCT are referred to centers of excellence that have familiarity with TGCT from a multidisciplinary care aspect. This can often include orthopedic oncologists, now medical oncologists, physical and occupational therapists, as well as physicians who specialize in pain and palliative care. Treatment of symptoms, range of motion, and orthopedic issues alone can really improve quality of life for patients with TGCT.

Surgical Management

- ▶ When we discuss the surgical management of the disease, there is yet to be any specific guidelines regarding the appropriate type of surgical management.

Surgical Outcomes in TGCT

Patient Characteristics

| | Overall Population (N = 1,192) | | Overall Population (N = 1,192) |
|--|--------------------------------|--|--------------------------------|
| Type of surgery (N = 1,163) | | Sex (N = 1,192) | |
| Arthroscopic synovectomy | 159 (14%) | Men | 499 (42%) |
| One-staged open synovectomy | 628 (54%) | Women | 693 (58%) |
| Two-staged open synovectomy | 187 (16%) | Age at initial treatment, y (N = 1,122) | |
| (Tumor) prosthesis | 63 (5%) | 35 (26-48) | |
| Amputation | 3 (<1%) | Tumor localization (N = 1,192) | |
| Wait and see | 76 (7%) | Knee | 758 (64%) |
| Synovectomy not specified | 47 (4%) | Hip | 124 (10%) |
| Tumor size initial treatment (N = 701) | 5.4 (3.0-8.8) | Ankle | 162 (14%) |
| <5 cm | 297 (42%) | Foot | 63 (5%) |
| ≥5 cm | 404 (58%) | Shoulder | 15 (1%) |
| Adjuvant therapy at initial treatment (N = 1,033) | | Elbow | 17 (1%) |
| External beam radiotherapy | 58 (6%) | Wrist | 25 (2%) |
| Yttrium-90 | 60 (6%) | Hand | 13 (1%) |
| Systemic or molecular targeted treatment | 15 (1%) | Other | 15 (1%) |
| Other | 11 (1%) | Bone involvement (N = 847) | |
| None | 889 (86%) | Present | 259 (30%) |
| Admission status (N = 1,192) | | Absent | 588 (70%) |
| Therapy naïve | 910 (76%) | Duration of symptoms, mo (N = 744) | |
| ≥1 surgery elsewhere | 282 (24%) | 18 (6-36) | |

TGCT, tenosynovial giant cell tumor. Mastboom et al. *Lancet Oncol.* 2019;20(6):877-886.

- ▶ There is a very nice publication in *Lancet Oncology* that is looking at surgical practice in patients with advanced TGCT. Demographics are very similar to what we discussed before, a slight preponderance of females and the majority of patients had disease within the knee.

Interestingly and importantly, the majority of patients with the diffuse type of TGCT had either one-staged or two-staged open synovectomies. A minority, only about 14%, had arthroscopic synovectomies, again lending to the diffuse nature of the disease and the requirement to having open procedures to try to clear the extensive nature of this disease.

Surgical Outcomes in TGCT

| Recurrence-free Survival, y | At-Risk Patients Who Received Primary Treatment (N = 966), n (%) | At-Risk Therapy-Naive Patients (N = 758), n (%) |
|-----------------------------|--|---|
| 3 | 474 (62) | 372 (70) |
| 5 | 297 (55) | 227 (64) |
| 10 | 89 (40) | 70 (50) |

| Surgical Outcomes After Treatment for All Patients Who Had Primary Surgery | | Patients With Primary Surgery |
|---|--|-------------------------------|
| First local recurrence after initial treatment at tertiary center (N = 966), n (%) | | |
| Present | | 425 (44%) |
| Absent | | 541 (56%) |
| Total number of recurrence events (N = 425), n (%) | | |
| 1 | | 267 (63%) |
| 2 | | 85 (20%) |
| ≥3 | | 73 (17%) |
| Total number of surgeries (N = 707) | | |
| | | 2.0 (1-5) |
| Total number of surgeries in patients with recurrent disease (N = 425), median (IQR) | | |
| | | 2.7 (1-6) |
| Status at last follow-up (N = 891), n (%) | | |
| No evidence of disease | | 587 (66%) |
| Alive with disease-being followed up | | 190 (21%) |
| Alive with disease-awaiting treatment | | 31 (3%) |
| Death from other disease | | 10 (1%) |
| Lost to follow-up | | 73 (8%) |

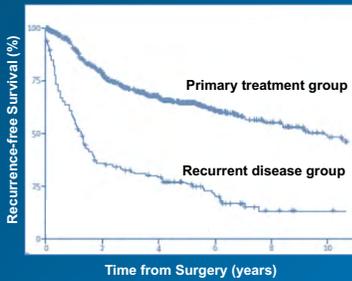
TGCT, tenosynovial giant cell tumor.
Mastboom et al. *Lancet Oncol*. 2019;20(6):877-886.

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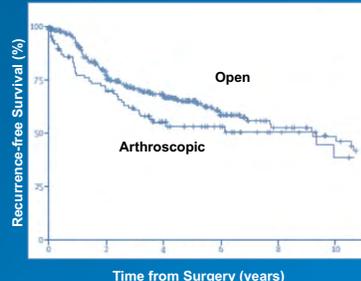
- ▶ What was also found is that the majority of patients do have high levels of recurrence and often require repeat surgical procedures even with large, open procedures. The reason again is that the diffuse type of the disease can be very difficult to clear with a single surgical procedure.

Surgical Outcomes in TGCT: Recurrence-free Survival

Primary vs Recurrent Disease



Open Surgery vs Arthroscopic Synovectomy



TGCT, tenosynovial giant cell tumor.
Adapted from Mastboom et al. *Lancet Oncol*. 2019;20(6):877-886.

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- ▶ When we look at the Kaplan-Meier plots, you can actually look at the recurrence rates of patients with primary treatment of surgery and recurrent treatment of surgery, and the differences between open and arthroscopic procedures.

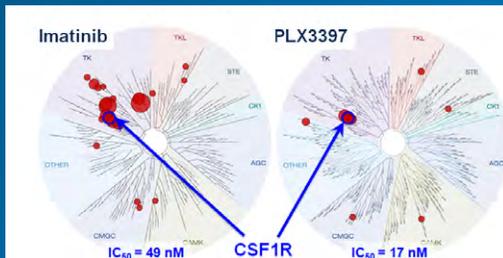
What is important to realize is that the recurrence in patients with primary treatment surgery is actually going to be a lot less than that in patients with recurrent disease. It is one of the main reasons why it's so important with the primary procedure to be treated in the hands of an orthopedic oncologist who is familiar with this disease and can discuss the goals of surgery with the multidisciplinary team.

Targeting the CSF1/CSF1R Axis in Advanced Tenosynovial Giant Cell Tumor

▶ There has been a lot of interest, as mentioned before, in targeting the CSF1/CSF1R axis in advanced TGCT, the diffuse type with medications.

Strong and Specific CSF1R Inhibitors

PLX3397 is a potent and specific inhibitor of CSF1R kinase activity



▶ As we discussed earlier, some data between weak CSF1R inhibitors such as imatinib and nilotinib, we can now switch to some of the stronger and more specific CSF1R inhibitors that have been moving into clinical trials.

There have been early data with monoclonal antibodies as well as small molecule inhibitors. One of the small molecule inhibitors we've been fortunate to work with and develop with TGCT was PLX3397, which is now known as pexidartinib.

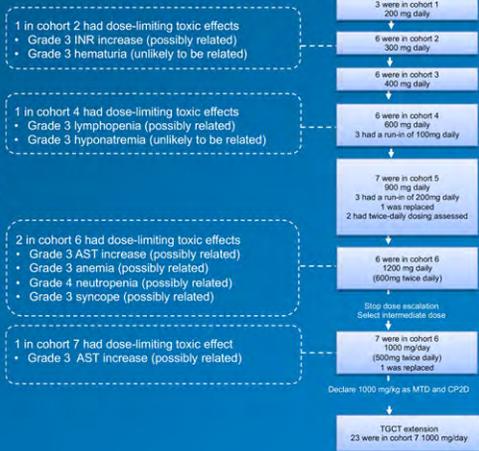
CSF1R, colony-stimulating factor 1 receptor.
Tap et al. *N Engl J Med*. 2015;373(5):428-437.

Pexidartinib

Targeting CSF1-Driven Signaling by PLX3397

- o Oral small molecule tyrosine kinase inhibitor
- o Potently and selectively inhibits CSF-1R, a primary growth driver of abnormal cells in the synovium that causes TGCT
- o Traps the kinase in the autoinhibited conformation

Phase 1 Dose-Escalation Process



CSF1R, colony-stimulating factor 1 receptor.
Tap et al. *N Engl J Med* 2015;373:428-437.



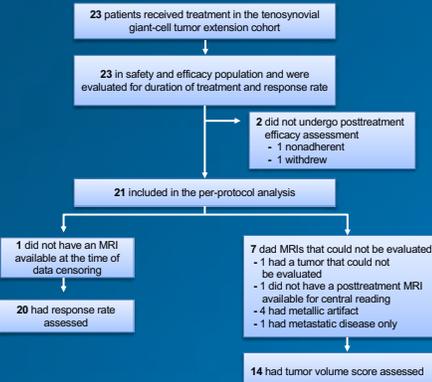
► Pexidartinib is a highly specific CSF1R inhibitor that is exceedingly strong. It is a multitargeted tyrosine kinase inhibitor so it will also target genes, such as mutant and wild-type KIT.

There was a phase 1 clinical trial looking at pexidartinib in advanced patients with cancer. This had a typical 3+3 dose escalation scheme. We bring on the dose escalation scheme to show some of the toxicity of the drug.

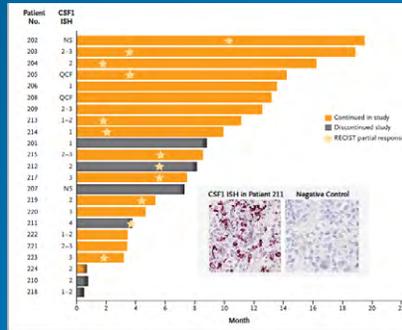
What was seen with escalating doses were certain cytopenias, edema, as well as inflammation within the liver as noted by elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Elevations in AST and ALT, as we will discuss, are very common with many drugs that target CSF1R.

Phase 1 Trial: PLX3397

Disposition of Patients in the Extension Cohort



Clinical Outcomes in the Extension Cohort and Confirmation of CSF1 Expression



CSF1, colony-stimulating factor 1.
Tap et al. *N Engl J Med* 2015;373:428-437. © Massachusetts Medical Society. Used with permission.

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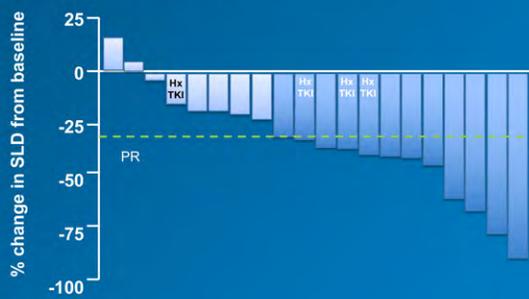
► What was important in the phase 1 clinical trial is after the recommended phase 2 dose of 1,000 mg per day in divided doses was established, there was an exploratory extension cohort in a group of patients with TGCT.

What is seen here in this swim plot is the extensive responses that were noted in this small cohort of patients who had very advanced disease. Not only did numerous patients have responses, but the responses were durable, as seen on the plot, some of which lasting over years.

Almost 5 years after publication of the original data, the updated data from this clinical trial are being worked on and will be published; however, there are patients who remain on treatment with stable disease.

Phase 1 Trial: PLX3397

Tumor Response Rates in Per Protocol Efficacy Population



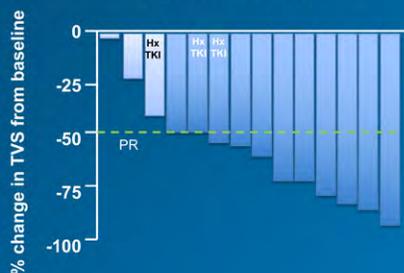
SLD, sum of longest diameters.
Adapted from Tap et al. *N Engl J Med* 2015;373:428-437.

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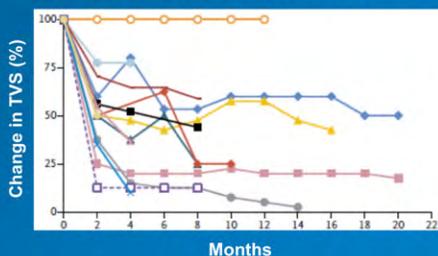
► If we look at the waterfall plot, we can see that there were a significant number of responses according to RECIST criteria. As mentioned, RECIST is not the best measurement, especially early on, to determine efficacy by a response rate in this disease; however, it was striking to see a waterfall plot showing that over 40% of the patients were having a RECIST response. Importantly, several patients who had treatment with tyrosine kinase inhibitors also had very nice responses.

Phase 1 Trial: PLX3397

Tumor Response Rates Based on Tumor Volume Score



Change in Tumor Volume Score in 14 Patients



TVS, tumor volume score. Tap et al. *N Engl J Med* 2015;373:428-437. © Massachusetts Medical Society. Used with permission.

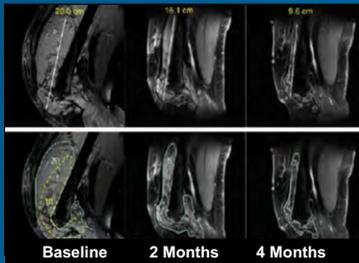


► The spider plot, which is shown on the next slide, shows that many of these responses can happen very quickly, often within the first few months. This led to the point that the drugs can actually block and decrease the inflammatory process, which can happen early in treatment. The responses are also durable.

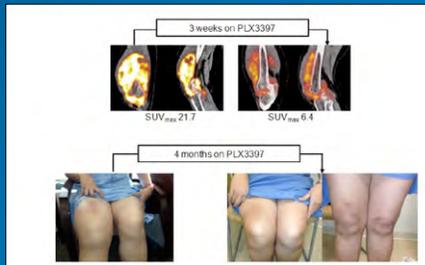
What is noted in the left figure, which is another waterfall plot, is looking at a special tumor volume score that was developed specifically to measure TGCT. The tumor volume score has a partial response when we see 50% decrease in the tumor volume, and what you notice is when measuring the tumor volume of this disease you can actually see a tremendous increase in the response rates even when we have a high bar of response of greater than 50%.

Phase 1 Trial: PLX3397

Objective Response on MRI



Example of an Objective Response



▶ The next slide shows some of the changes that we saw radiographically and clinically. When you look at the objective response rates on the MRI in the left-hand panel, you see a patient that has an extensive tumor burden within the anterior and posterior aspects of the knee.

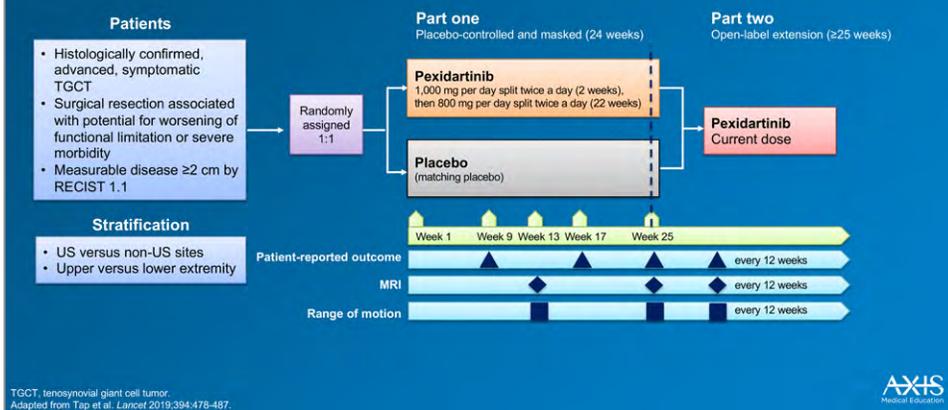
What we show you in the above panel is the unidimensional measurements of RECIST. As you can see, RECIST does not nearly identify the extent of the tumor within the joint.

The lower panel below that at baseline is showing the tumor volume score measuring the volumetrics of the disease. What you can see in just 2 to 4 months is a tremendous decrease in the tumor burden. This is not only allowing for a RECIST response, but also a partial response according to the tumor volume score as well.

On the right-hand panel is the depiction of a PET scan with the patient. The disease often has very tremendous and intense FDG uptake, this is again due to the inflammatory nature of the disease. What is seen in just 3 weeks is a tremendous decrease in the FDG uptake of the tumor mass.

And, finally, below is a patient who was actually treated in the phase 1 clinical trial. She had extensive disease within the right knee, and there were suggestions of an amputation for her. However, with just 4 months of treatment, you can see tremendous response within the patient and improvement in clinical symptoms such as swelling, pain, and range of motion.

Phase 3 ENLIVEN Trial: Pexidartinib



► This encouraging data led to the development of the ENLIVEN study. The ENLIVEN study was designed to do several things. The first was to actually understand the efficacy of this drug, the other was to understand the natural history of TGCT and what does the application of a drug where we could see significant shrinkage of a tumor in a patient mean to that patient; in other words, are we seeing improvements in clinical symptoms.

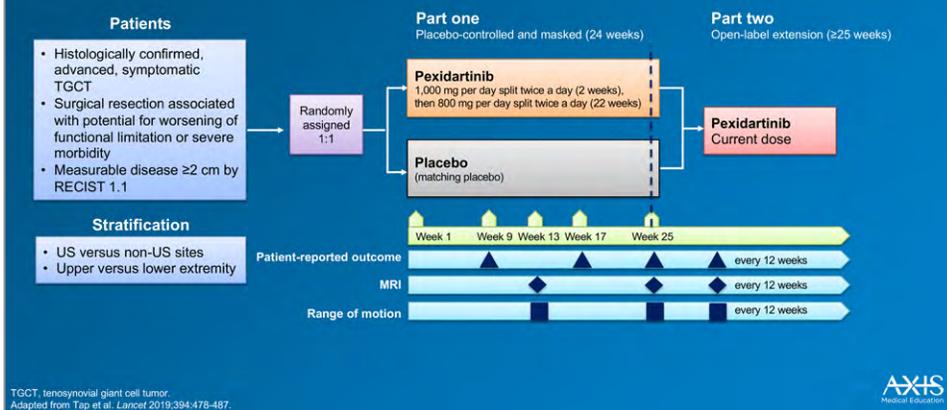
So this study enrolled patients with histologically confirmed, advanced, and symptomatic TGCT for whom surgical resection could be associated with potential of worsening functional limitations or severe morbidity. Patients were required to have measurable disease of at least greater than 2 cm according to RECIST criteria.

They were randomly assigned in a 1:1 fashion to receive either pexidartinib or placebo. The pexidartinib was started at 1,000 mg per day for 2 weeks, and then was dose-reduced to 800 mg per day in split doses for 22 weeks.

Alternatively, patients could be randomized to placebo. It was thought that the placebo group was important because we truly did not understand the natural history of this disease and needed to know that the effects of the drug were actually meaningful for the patients.

Because a placebo group was involved in this clinical trial, there were 2 parts to the clinical trial. One was the randomization between pexidartinib and placebo, but after 24 weeks all patients regardless of what they were on could then receive

Phase 3 ENLIVEN Trial: Pexidartinib

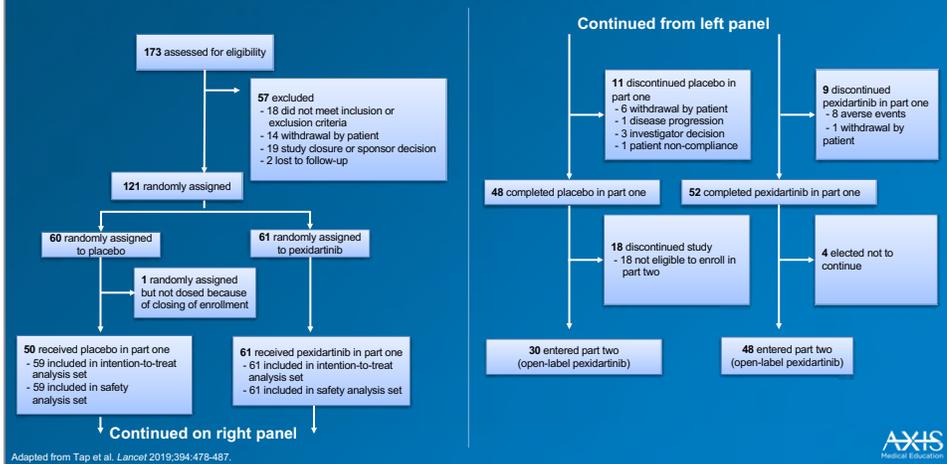


pexidartinib at their current dose. This would allow patients in the placebo group to enter into a part of the trial in which they received open-label pexidartinib.

What was also important in this study is we not only looked at responses according to RECIST, so radiographic measurements with MRI, but we also looked at the tumor volume score, and then specific patient-reported outcomes, as well as subjective and objective measures looking at pain and range of motion to understand the true worth of the drug.

The primary endpoint of this study was the RECIST response rate at week 25.

Phase 3 ENLIVEN Trial: Pexidartinib



▶ In total there were approximately 120 patients who ended up being treated; 60 were randomized in part 1 to placebo and 61 were randomized in part 1 to pexidartinib.

As we'll talk about a little later, the study was stopped early. The reason was that there was a case of mixed cholestatic hepatotoxicity that was identified. This put a hold on clinical trial enrollment when these 120 patients were already enrolled, and only allowed those patients on placebo who had already received pexidartinib to continue. We'll talk a little bit about this unique toxicity of the drug a little later on.

Phase 3 ENLIVEN Trial: Pexidartinib

| Characteristic | Pexidartinib (n = 61) | Placebo (n = 59) |
|------------------------------|-----------------------|------------------|
| Age (y) | 44.0 (22-75) | 45.0 (18-79) |
| Sex | | |
| Men | 26 (43%) | 23 (39%) |
| Women | 35 (57%) | 36 (61%) |
| Race | | |
| White | 52 (85%) | 54 (92%) |
| Black | 3 (5%) | 1 (2%) |
| Asian | 1 (2%) | 2 (3%) |
| Native American | 2 (3%) | 0 |
| Hawaiian or Pacific Islander | 2 (3%) | 2 (3%) |
| Multiracial | 1 (2%) | 0 |
| Geographic region | | |
| US | 23 (38%) | 22 (37%) |
| Non-US | 38 (62%) | 37 (63%) |
| Disease location | | |
| Knee | 34 (56%) | 39 (66%) |
| Ankle | 14 (23%) | 7 (12%) |
| Hip | 6 (10%) | 7 (12%) |
| Wrist | 2 (3%) | 2 (3%) |
| Foot | 2 (3%) | 1 (2%) |
| Shoulder | 1 (2%) | 1 (2%) |
| Spine | 1 (2%) | 1 (2%) |
| Elbow | 1 (2%) | 0 |
| Finger | 0 | 1 (2%) |

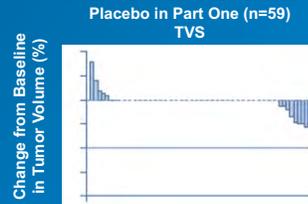
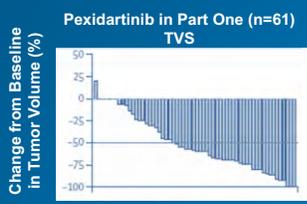
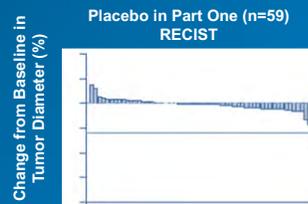
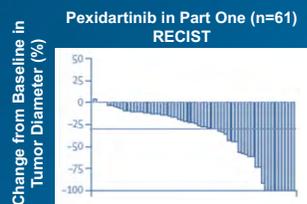
| Characteristic | Pexidartinib (n = 61) | Placebo (n = 59) |
|---|-----------------------|------------------|
| Previous surgeries for TGCT | | |
| 0 | 29 (48%) | 28 (48%) |
| 1 | 13 (21%) | 12 (20%) |
| 2 | 7 (12%) | 12 (20%) |
| ≥3 | 12 (20%) | 7 (12%) |
| Previous systemic therapy | | |
| No previous systemic therapy | 53 (87%) | 56 (95%) |
| Nilotinib | 1 (2%) | 0 |
| Imatinib | 7 (12%) | 3 (5%) |
| Tumor sum of longest diameters (mm) | 101.3 (63.1) | 105.5 (73.5) |
| Tumor volume score | 14.8 (21.2) | 12.1 (16.2) |
| Range of motion in affected joint relative to reference standard (%) | 62.5% (24.8) | 62.9% (21.8) |
| Concomitant analgesic use | 38 (62%) | 36 (61%) |

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Tap et al. *Lancet* 2019;394:478-487.

▶ The demographics were very similar to what we've discussed. The majority of patients had disease within the knee. They were younger, with a median age of about 44, only a slight preponderance of women over men. The majority of patients had surgeries for TGCT, and a few patients had received nilotinib and imatinib. Most of the patients by design of the study were required to have symptoms, either pain or stiffness or limitations with range of motion. In addition, most of the patients were also using concomitant analgesics when they enrolled in the study.

Phase 3 ENLIVEN Trial: Pexidartinib



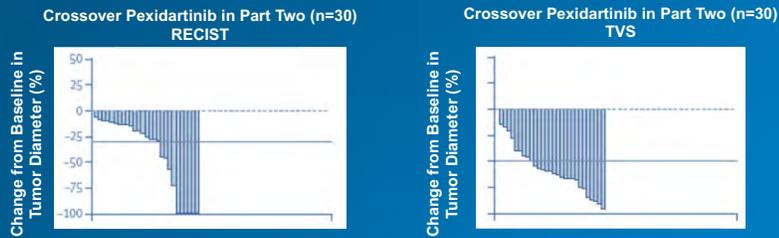
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TVS, tumor volume score. Adapted from Tap et al. *Lancet* 2019;394:478-487.

▶ The next slide shows the waterfall plots of the best response rate, again at week 25, which was the primary endpoint. And when we look at response, we see an overall response rate of approximately 39% in the treatment group versus 0% in the placebo group. Importantly, when you look at the placebo group, you can see the natural history of this disease where we notice that no patients within a 24-week period actually had disease progression according to RECIST.

When we look at the tumor volume score, again volumetric measurements of this disease where a partial response is defined as a decrease in greater than 50% of the tumor, we can see a significant number of patients, approximately 56%, had a partial response according to the tumor volume score. Again looking at the tumor volume score, we see very little, if any, progression or actual responses according to tumor volume score in the placebo group.

Phase 3 ENLIVEN Trial: Pexidartinib



TVS, tumor volume score.
Adapted from Tap et al. *Lancet* 2019;394:478-487.

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▶ The next slide shows the response rates of the patients who were on placebo in part 1 and in part 2 received pexidartinib for 24 weeks. What you can see are very similar response rates according to RECIST and the tumor volume score.

These patients started with 800 mg per day in divided doses as opposed to receiving the 1,000 mg per day in divided doses for the first 2 weeks. Because they have similar response rates, this another reason why the FDA-approved dose for pexidartinib is 800 mg per day in divided doses.

Phase 3 ENLIVEN Trial: Pexidartinib

Tumor Response by RECIST and TVS at Week 25

| Results | Pexidartinib (n = 61), n (%) | Placebo (n = 59), n (%) | Difference Between Groups (%) |
|--|---------------------------------|----------------------------|----------------------------------|
| Response rate based on RECIST for part one (primary endpoint) | | | |
| Overall response | 24 (39%) | 0 | 39%; P < .0001 |
| Complete response | 9 (15%) | 0 | - |
| Partial response | 15 (25%) | 0 | - |
| Stable disease | 24 (39%) | 46 (78%) | - |
| Progressive disease | 1 (2%) | 1 (2%) | - |
| Not evaluable | 12 (20%) | 12 (20%) | - |
| Response rate based on TVS for part one | | | |
| Overall response | 34 (56%) | 0 | 56%; P < .0001 |
| Complete response | 3 (5%) | 0 | - |
| Partial response | 31 (51%) | 0 | - |
| Stable disease | 14 (23%) | 45 (76%) | - |
| Progressive disease | 1 (2%) | 2 (3%) | -- |
| Not evaluable | 12 (20%) | 12 (20%) | - |

RECIST, Response Evaluation Criteria for Adverse Events, version 1.1; TVS, tumor volume score.
Adapted from Tap et al. *Lancet* 2019;394:478-487.

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▶ The next slide shows a table summarizing the results of the overall and best responses according to RECIST and the tumor volume score. Again, in part 1 of the study, which was the primary endpoint, what you can actually see is the overall response rate is 39% according to RECIST versus 0% for placebo, and the tumor volume score of the overall response rate for pexidartinib is 56% versus 0% for placebo.

Phase 3 ENLIVEN Trial: Pexidartinib

Range of Motion and Patient-Reported Outcomes

| Parameter | Pexidartinib (n = 61) | Placebo (n = 59) | Difference Between Groups (%) |
|---|--------------------------|---------------------|----------------------------------|
| Range of motion assessment | | | |
| Baseline assessment | n = 61 | n = 58 | - |
| Mean at baseline | 62.5% | 62.9% | - |
| Change from baseline to week 25 | 15.1% | 6.2% | 8.9%; P = .0043 |
| PROMIS-Physical Function scale | | | |
| Baseline assessment | n=60 | n=57 | - |
| Mean score at baseline | 37.5 | 38.9 | - |
| Change from baseline to week 25 | 4.1 | -0.9 | 5.0; P = .0019 |
| Worst stiffness NRS score | | | |
| Baseline assessment | n=59 | n=58 | - |
| Mean score at baseline | 5.6 | 5.9 | - |
| Change from baseline to week 25 | -2.5 | -0.3 | -2.2; P < .0001 |
| Response based on Pain-30 | | | |
| Valid mean worse pain NRS at baseline and week 25 | 33 (54%) | 35 (59%) | - |
| Pain-30 response | 19 (31%) | 9 (15%) | 15.9%; P = .052 |

NRS, numeric rating scale; Pain-30, at least a 30% improvement in mean pain score without a 30% or greater increase in analgesic use; PROMIS, Patient-Reported Outcomes Measurement Information System; Adapted from Tap et al. *Lancet* 2019;394:478-487.

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► What was also important when we look at the secondary endpoints looking at range of motion, PROMIS Physical Function, and worse stiffness, there were improvements across the board in the patients who received pexidartinib in part 1 that were all statistical and clinically meaningful for patients. This is critical to show that the extensive decreases in tumor size that I mentioned in the previous slide were clinically meaningful for patients.

There was not a statistically meaningful decrease in pain, but pain can be a very difficult endpoint to capture in patients with TGCT. There are several reasons for this. First is that many times the majority of the pain is not only caused by the tumor bulk in patients with TGCT, but it can be also due to the sequelae of the disease over time, the destruction of the joint as well as from surgeries. So even though a drug may decrease the tumor size in the patient and may have resolution of a TGCT-specific pain, patients still may remain in pain because of other types of pathology within the joint.

The other thing is that many patients even on placebo had slight improvements in pain measures, and that is because they were coming to centers that had a disease management team that specialized in TGCT and they could benefit from palliative care as well as physical therapy consultations that would allow them to have better control of their pain over time. So a very difficult endpoint to measure in patients with TGCT.

Phase 3 ENLIVEN Trial: Pexidartinib

| n (%) | Part one | | | | | | Part two | | | | | |
|---|---------------------|--------------|----------|----------------|--------------|--------|---------------------|--------------|--|-------------------------------|--------------|--|
| | Pexidartinib (n=81) | | | Placebo (n=80) | | | Pexidartinib (n=81) | | | Crossover pexidartinib (n=30) | | |
| | Any Grade | Grade 3 or 4 | | Any Grade | Grade 3 or 4 | | Any Grade | Grade 3 or 4 | | Any Grade | Grade 3 or 4 | |
| Skin disorders | | | | | | | | | | | | |
| Hair color changes | 41 (67%) | 0 | 2 (3%) | 0 | 25 (83%) | 0 | | | | | | |
| Pruritus | 10 (16%) | 0 | 2 (3%) | 0 | 8 (27%) | 0 | | | | | | |
| Rash | 8 (13%) | 1 (2%) | 2 (3%) | 0 | 6 (20%) | 0 | | | | | | |
| Rash maculopapular | 6 (10%) | 0 | 1 (2%) | 0 | 2 (7%) | 0 | | | | | | |
| Erythema | 1 (2%) | 0 | 0 | 0 | 5 (17%) | 0 | | | | | | |
| Gastrointestinal disorders | | | | | | | | | | | | |
| Nausea | 23 (38%) | 0 | 24 (41%) | 0 | 6 (20%) | 0 | | | | | | |
| Diarrhea | 12 (20%) | 0 | 15 (25%) | 0 | 8 (27%) | 0 | | | | | | |
| Abdominal pain | 10 (16%) | 0 | 6 (10%) | 0 | 1 (3%) | 0 | | | | | | |
| Vomiting | 12 (20%) | 1 (2%) | 3 (5%) | 0 | 1 (3%) | 0 | | | | | | |
| Dry mouth | 6 (10%) | 0 | 2 (3%) | 0 | 4 (13%) | 0 | | | | | | |
| Constipation | 7 (12%) | 0 | 3 (5%) | 0 | 3 (10%) | 0 | | | | | | |
| Stomatitis | 4 (7%) | 0 | 1 (2%) | 0 | 3 (10%) | 0 | | | | | | |
| General disorders | | | | | | | | | | | | |
| Fatigue | 33 (54%) | 0 | 21 (36%) | 0 | 5 (17%) | 0 | | | | | | |
| Asthenia | 6 (10%) | 0 | 3 (5%) | 0 | 5 (17%) | 0 | | | | | | |
| Facial oedema | 8 (13%) | 0 | 1 (2%) | 0 | 6 (20%) | 1 (3%) | | | | | | |
| Peripheral oedema | 8 (13%) | 0 | 2 (3%) | 0 | 5 (17%) | 0 | | | | | | |
| Investigations | | | | | | | | | | | | |
| AST increase | 24 (39%) | 6 (10%) | 0 | 0 | 5 (17%) | 1 (3%) | | | | | | |
| ALT increase | 17 (28%) | 6 (10%) | 1 (2%) | 0 | 7 (23%) | 2 (7%) | | | | | | |
| Alkaline phosphatase increase | 9 (15%) | 4 (7%) | 0 | 0 | 1 (3%) | 1 (3%) | | | | | | |
| LDH increase | 7 (12%) | 1 (2%) | 0 | 0 | 3 (10%) | 0 | | | | | | |
| Nervous disorders | | | | | | | | | | | | |
| Dysgeusia | 15 (25%) | 0 | 1 (2%) | 0 | 7 (23%) | 0 | | | | | | |
| Headache | 11 (18%) | 0 | 11 (19%) | 0 | 5 (17%) | 0 | | | | | | |
| Dizziness | 6 (10%) | 1 (2%) | 9 (15%) | 0 | 4 (13%) | 0 | | | | | | |
| Musculoskeletal disorders | | | | | | | | | | | | |
| Arthralgia | 14 (23%) | 2 (3%) | 15 (25%) | 1 (2%) | 6 (20%) | 0 | | | | | | |
| Pain in extremity | 4 (7%) | 0 | 4 (7%) | 1 (2%) | 3 (10%) | 0 | | | | | | |
| Eye disorders | | | | | | | | | | | | |
| Periorbital oedema | 11 (18%) | 1 (2%) | 1 (2%) | 0 | 3 (10%) | 0 | | | | | | |
| Eyelid oedema | 1 (2%) | 0 | 0 | 0 | 3 (10%) | 0 | | | | | | |
| Metabolic or nutritional disorders | | | | | | | | | | | | |
| Decreased appetite | 10 (16%) | 0 | 6 (10%) | 0 | 3 (10%) | 0 | | | | | | |
| Vascular disorders | | | | | | | | | | | | |
| Hypertension | 9 (15%) | 3 (5%) | 6 (10%) | 0 | 6 (20%) | 2 (7%) | | | | | | |

Data are n (%).
AST, aspartate amino-transferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.
Adapted from Tap et al. Lancet 2019;394:472-487.

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Overall, pexidartinib in the ENLIVEN study was well tolerated. There are some side effects that we typically see with this drug as we can see with many tyrosine kinase inhibitors. Some of the side effects that were noted in high populations but lower grades in patients were hair color changes. Pexidartinib can turn skin colors lighter as well as turn hair gray. This is a reversible side effect that happens as long as patients are on the drug. You can also see some rashes, some edema, as well as some hypertension.

Importantly, as mentioned earlier, we often see increases in transaminases such as an AST and ALT elevation in patients with the use of pexidartinib. This can be mitigated by dose modifications and interruptions and is almost always reversible.

However, there were several cases of a more severe mixed cholestatic hepatotoxicity in which we also saw increases of alkaline phosphatase and bilirubin. It is uncertain as to the etiology of these type of changes but in 1 patient it was profound, lasting for many months and requiring liver dialysis. It is a type of a vanishing bile duct syndrome that can be seen as being idiopathic because we truly do not understand what causes this.

Phase 3 ENLIVEN Trial: Pexidartinib

| n (%) | Part one | | | | | | Part two | | | | | |
|---|---------------------|--------------|----------|----------------|--------------|--------|---------------------|--------------|--|-------------------------------|--------------|--|
| | Pexidartinib (n=31) | | | Placebo (n=30) | | | Pexidartinib (n=30) | | | Crossover pexidartinib (n=30) | | |
| | Any Grade | Grade 3 or 4 | | Any Grade | Grade 3 or 4 | | Any Grade | Grade 3 or 4 | | Any Grade | Grade 3 or 4 | |
| Skin disorders | | | | | | | | | | | | |
| Hair color changes | 41 (67%) | 0 | 2 (3%) | 0 | 25 (83%) | 0 | | | | | | |
| Pruritus | 10 (16%) | 0 | 2 (3%) | 0 | 8 (27%) | 0 | | | | | | |
| Rash | 8 (13%) | 1 (2%) | 2 (3%) | 0 | 6 (20%) | 0 | | | | | | |
| Rash maculopapular | 6 (10%) | 0 | 1 (2%) | 0 | 2 (7%) | 0 | | | | | | |
| Erythema | 1 (2%) | 0 | 0 | 0 | 5 (17%) | 0 | | | | | | |
| Gastrointestinal disorders | | | | | | | | | | | | |
| Nausea | 23 (38%) | 0 | 24 (41%) | 0 | 6 (20%) | 0 | | | | | | |
| Diarrhea | 12 (20%) | 0 | 15 (25%) | 0 | 8 (27%) | 0 | | | | | | |
| Abdominal pain | 10 (16%) | 0 | 6 (10%) | 0 | 1 (3%) | 0 | | | | | | |
| Vomiting | 12 (20%) | 1 (2%) | 3 (5%) | 0 | 1 (3%) | 0 | | | | | | |
| Dry mouth | 6 (10%) | 0 | 2 (3%) | 0 | 4 (13%) | 0 | | | | | | |
| Constipation | 7 (12%) | 0 | 3 (5%) | 0 | 3 (10%) | 0 | | | | | | |
| Stomatitis | 4 (7%) | 0 | 1 (2%) | 0 | 3 (10%) | 0 | | | | | | |
| General disorders | | | | | | | | | | | | |
| Fatigue | 33 (54%) | 0 | 21 (36%) | 0 | 5 (17%) | 0 | | | | | | |
| Asthenia | 6 (10%) | 0 | 3 (5%) | 0 | 5 (17%) | 0 | | | | | | |
| Facial oedema | 8 (13%) | 0 | 1 (2%) | 0 | 6 (20%) | 1 (3%) | | | | | | |
| Peripheral oedema | 8 (13%) | 0 | 2 (3%) | 0 | 5 (17%) | 0 | | | | | | |
| Investigations | | | | | | | | | | | | |
| AST increase | 24 (39%) | 6 (10%) | 0 | 0 | 5 (17%) | 1 (3%) | | | | | | |
| ALT increase | 17 (28%) | 6 (10%) | 1 (2%) | 0 | 7 (23%) | 2 (7%) | | | | | | |
| Alkaline phosphatase increase | 9 (15%) | 4 (7%) | 0 | 0 | 1 (3%) | 1 (3%) | | | | | | |
| LDH increase | 7 (12%) | 1 (2%) | 0 | 0 | 3 (10%) | 0 | | | | | | |
| Nervous disorders | | | | | | | | | | | | |
| Dysgeusia | 15 (25%) | 0 | 1 (2%) | 0 | 7 (23%) | 0 | | | | | | |
| Headache | 11 (18%) | 0 | 11 (19%) | 0 | 5 (17%) | 0 | | | | | | |
| Dizziness | 6 (10%) | 1 (2%) | 9 (15%) | 0 | 4 (13%) | 0 | | | | | | |
| Musculoskeletal disorders | | | | | | | | | | | | |
| Arthralgia | 14 (23%) | 2 (3%) | 15 (25%) | 1 (2%) | 6 (20%) | 0 | | | | | | |
| Pain in extremity | 4 (7%) | 0 | 4 (7%) | 1 (2%) | 3 (10%) | 0 | | | | | | |
| Eye disorders | | | | | | | | | | | | |
| Periorbital oedema | 11 (18%) | 1 (2%) | 1 (2%) | 0 | 3 (10%) | 0 | | | | | | |
| Eyelid oedema | 1 (2%) | 0 | 0 | 0 | 3 (10%) | 0 | | | | | | |
| Metabolic or nutritional disorders | | | | | | | | | | | | |
| Decreased appetite | 10 (16%) | 0 | 6 (10%) | 0 | 3 (10%) | 0 | | | | | | |
| Vascular disorders | | | | | | | | | | | | |
| Hypertension | 9 (15%) | 3 (5%) | 6 (10%) | 0 | 6 (20%) | 2 (7%) | | | | | | |

Data are n (%).

AST, aspartate amino-transferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.
Adapted from Tap et al. *Lancet* 2019;394:478-487.

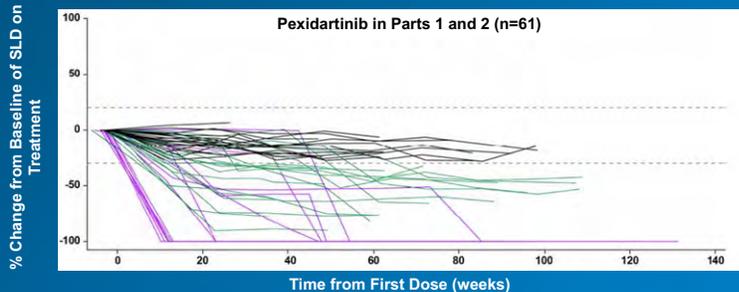
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This is the side effect that caused the data monitoring committee of the ENLIVEN study to put the trial on hold after it was almost all accrued so we could look at the data of the total clinical development of pexidartinib. It is also what has prompted the FDA to have a specific Risk Evaluation and Mitigation Strategy (REMS) program associated with the drug to ensure safety, and that both patients and clinicians prescribing the drug are informed to this very rare but potentially serious side effect. We will discuss this slightly later.

Otherwise, most of the side effects that were seen on the trial were reversible and an early grade.

Phase 3 ENLIVEN Trial: Pexidartinib

Spider Plot of Percentage Change from Baseline over Time in the Sum of Longest Diameters According to RECIST 1.1



SLD, sum of longest diameters.

Tap et al. *Lancet* 2019;394:478-487. Used with permission.

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► This spider plot not only shows the rapidity of responses that we can see, but also that the responses are maintained with the use of the drug, and that with continued use of the drug you see improvements. Patients really benefited with pexidartinib, especially those who were symptomatic and had diffuse TGCT as the study required enrolled.

Pexidartinib Response



Courtesy of William D. Tap, MD.

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▶ An example of a patient with an extreme form of the disease is on the next slide. This is a woman from Italy who had been dealing with TGCT within the wrist for well over 10 years. The patient had over 20 surgeries and was dependent on red blood cell transfusions because of the inflammatory nature of the disease.

There was a rapid decrease in tumor mass and redefinition of the joints and fingers after treatment of just several months. The patient continues on treatment to this day and has had a dramatic response.

Pexidartinib Hepatotoxicity

Patients with Elevated Liver Enzymes and Total Bilirubin (safety population)

| Liver Function | Part 1 | | Part 2 |
|--|---------------------------------|----------------------------|---|
| | Pexidartinib (N = 61), n (%) | Placebo (N = 59), n (%) | Crossover Pexidartinib (N = 30), n (%) |
| AST or ALT ≥ 3 x ULN | 20 (33) | 0 | 4 (13) |
| ALP ≥ 2.5 x ULN | 5 (8) | 1 (2) | 0 |
| Tbili ≥ 2 x ULN | 3 (5) | 0 | 0 |
| Tbili ≥ 2 x ULN and AST or ALT ≥ 3 x ULN | 3 (5) | 0 | 0 |

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, alanine aminotransferase; Tbili, total bilirubin; ULN, upper limit of normal.
Tap et al. *Lancet* 2019;394:478-487.

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▶ The next slide highlights some of the hepatotoxicity that I mentioned before. It is critical to understand the very rare toxicity of the cholestatic hepatotoxicity, where you need to look for elevations in alkaline phosphatase when treating patients, and discerning this from the type of inflammation in which we see elevations of AST and ALT. The transaminase elevations are known and reversible and a normal toxicity that we often see with tyrosine kinase inhibitors that target CSF1R.

The cholestatic hepatotoxicity is different and a very rare toxicity that needs to be discussed when discussing the pros and cons and the rationale for this drug in patients with the diffuse type of TGCT.

Pexidartinib FDA Approval: August 2019

| | |
|--|--|
| Indication | Treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery |
| Recommended Dosage | 400 mg (2 capsules) orally twice daily on an empty stomach until disease progression or unacceptable toxicity |
| Warnings | Hepatotoxicity and embryo-fetal toxicity |
| Most Common Adverse Reactions (>20%) | Increased LDH, increased AST, hair color changes, fatigue, increased ALT, decreased neutrophils, increased cholesterol, increased alkaline phosphatase, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia, and decreased phosphate |
| NCCN Guideline® Recommendation | Category 1 recommendation for TGCT/PVNS |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; NCCN, National Comprehensive Cancer Network. Turalio prescribing information, 2019; von Mehren et al. NCCN Clinical Practice Guidelines in Oncology, Soft Tissue Sarcoma, Version 4.2019. NCCN.org.



► After the ENLIVEN study, pexidartinib received FDA approval for patients with TGCT. It is the first in-class drug for this rare disease.

The recommended dosage is 400 mg twice a day on an empty stomach until disease progression or unacceptable toxicity. Because of the presence of the mixed cholestatic hepatotoxicity, although rare, many experts are making the decision to actually start at a lower dose from 800 mg and titrating up based on safety and need.

The warnings again are hepatotoxicity, as we discussed, and embryo-fetal toxicity. The most common adverse reactions are increases in AST, ALT, hair color changes, fatigue, and some cytopenias.

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology has recommended pexidartinib as a Category 1 for the treatment of TGCT.

Risk Evaluation and Mitigation Strategy Program

- Hepatotoxicity
 - Can cause serious and potentially fatal liver injury
- Due to risk of hepatotoxicity, pexidartinib is available only through a restricted program under a REMS
- REMS program requirements:
 - Prescribers must be certified
 - Patients must enroll in REMS patient registry
 - Pharmacies must be certified and dispense only to authorized patients

REMS, risk evaluation and mitigation strategy.
Turalio prescribing information, 2019; <https://www.turaliorems.com/#Main>.

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▶ The cholestatic hepatotoxicity can be serious and cause potentially fatal liver injury. So due to the risk for hepatotoxicity, pexidartinib is available only through a restricted program under a REMS. The REMS program requires that prescribers must be certified and educated about the drug, the disease, as well as this rare hepatotoxicity. Patients must also enroll in the REMS registry, and pharmacies who dispense the drug must be certified and dispense only to authorized prescribers and patients.

Pexidartinib Patient Monitoring: Hepatotoxicity

| Liver Test Monitoring AST, ALT, total bilirubin, direct bilirubin, ALP, and GGT | | | |
|--|---------------|---------------|----------------|
| Baseline | First 8 Weeks | Next Month | Subsequently |
| prior to initiation | weekly | every 2 weeks | every 3 months |

- Avoid in patients with preexisting increased serum transaminases, total bilirubin, or direct bilirubin (>ULN) or patients with active liver or biliary tract disease including increased ALP
- Taking with food may increase risk of hepatotoxicity (increases drug exposure by 100%)
 - Administer on an empty stomach, either 1 hour before or 2 hours after a meal or snack
- Withhold and dose reduce, or permanently discontinue based on severity of hepatotoxicity
- Monitor liver tests weekly for the first month after rechallenge

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal. Turalio prescribing information, 2019.

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▶ There is also some very specific hepatotoxicity monitoring. Patients need to get liver function tests, including an AST, ALT, total bilirubin, direct bilirubin, an alkaline phosphatase, and a gamma glutamyl transferase prior to initiation, and then weekly for the first 8 weeks, and then every 2 weeks for the subsequent month, and then every 3 months.

The drug should be avoided in patients with preexisting increased serum transaminase levels, total bilirubin, or direct bilirubin, or patients with active liver or biliary tract disease including increased alkaline phosphatase levels.

Patients have to be careful to not take this drug with food, which may increase the risk for hepatotoxicity by increasing drug exposure by 100%.

The drug should be withheld or dose-reduced or permanently discontinued based on the severity or type of hepatotoxicity. It's important to monitor liver tests weekly for the first month after a rechallenge.

Patient Case Review

► So I'd like to just go over a brief case report of a patient who was treated in the phase 1 trial with pexidartinib.

60-year-old Presents for Medical Management of TGCT, Referred by Orthopedic Oncology

- 15 years ago: underwent a left total knee replacement
 - Path c/w PVNS (TGCT)
- 13 years ago: developed recurrent disease, pain, and swelling
- 11 years ago: underwent a left anterior synovectomy
- 10 years ago: residual disease with progression, worsening pain and swelling. Decreased ROM. Underwent an anterior and posterior synovectomy followed by radiation
- Over the past 10 years:
 - 7+ procedures at various times due to worsening disease and symptoms
 - Often found relief for 6+ months; varied in time and frequency

► This was a patient with diffuse TGCT. Fifteen years previously, he underwent a left total knee replacement; pathology was consistent with TGCT. Then 13 years ago recurrent disease, pain, and swelling developed, 11 years ago underwent a left anterior synovectomy, 10 years ago residual disease was identified with progression, worsening pain, and swelling. The patient had decreased range of motion and underwent an anterior and posterior synovectomy followed by radiation. Then over the past 10 years the patient had over 7 procedures at various times due to worsening disease and symptoms.

Presents to Orthopedic Oncology at Tertiary Care Center

- MRI demonstrated large multifocal masses c/w TGCT, multiple bone erosions
- PET/CT indicated multiple FDG avid soft tissue masses in the distal thigh and proximal leg c/w metabolically active and recurrent TGCT
- SUV max 26
- CT component showed extensive TGCT in the knee with extraarticular nodules in adjacent subcutaneous tissue
- Tumor displaced but did not encase the popliteal neurovascular bundle

CT, computed tomography; MRI, magnetic resonance imaging; c/w, consistent with; PET, positron emission tomography; SUV, maximum standardized uptake value; TGCT, tenosynovial giant cell tumor.

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▶ The MRI demonstrated large multifocal masses consistent with TGCT as well as multiple bone erosions. The patient underwent a PET/CT scan, which showed multiple FDG avid soft tissue masses in the distal thigh and proximal leg consistent with metabolically active and recurrent TGCT. The SUV max of one of the tumors was 26. The CT component showed extensive TGCT in the knee with extraarticular nodules in adjacent subcutaneous tissue. The tumor displaced but did not encase the popliteal neurovascular bundle.

Exam

- Wheelchair bound for medical oncology visit
- Significant swelling within knee, decreased range of motion, constant pain +4 at rest, +7 with movement
- Midline incision, extensive posterior incision in boat race fashion
- 0-60 ROM both passive and active
- LLE circumference
 - 7 cm above the knee: 51 vs 48 cm
 - Knee joint: 54 vs 56 cm
 - 8 cm distal to the knee joint: 48 vs 38 cm
- Several palpable SQ tumors
- Normal motor and sensory exam and +2 distal pulses

ROM, range of motion; LLE, lower left extremity; SQ, subcutaneous.

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▶ So on exam when the patient presented to a medical oncology clinic, he was wheelchair-bound and had significant swelling within the knee with decreased range of motion, constant pain that he reported at 4+ at rest and 7+ with movement. Range of motion was 0 to 60 degrees, both passive and active. The left lower extremity circumference at 7 cm above the knee was 51 versus 48 cm, and at the knee joint 54 versus 56 cm, and 8 cm distal to the knee joint was 48 versus 38 cm. There were several palpable subcutaneous tumors. There was normal motor and sensory exam and 2+ distal pulses.

Biopsy

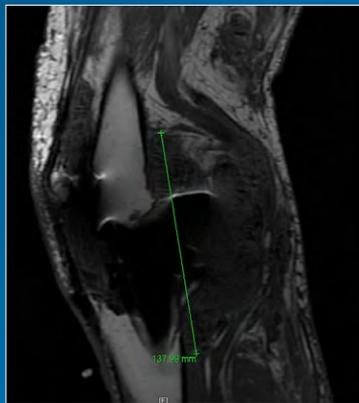
- Due to prior radiation and extent of disease, a CT-guided biopsy was performed
- Cytology showed atypical rare giant cells
- Core c/w recurrent TGCT

▶ Due to the prior radiation and the extent of the disease, a CT-guided biopsy was performed. The cytology showed atypical rare giant cells and the core was consistent with recurrent TGCT.

CT, computed tomography; c/w, consistent with; TGCT, tenosynovial giant cell tumor.

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MRI: Sagittal T1

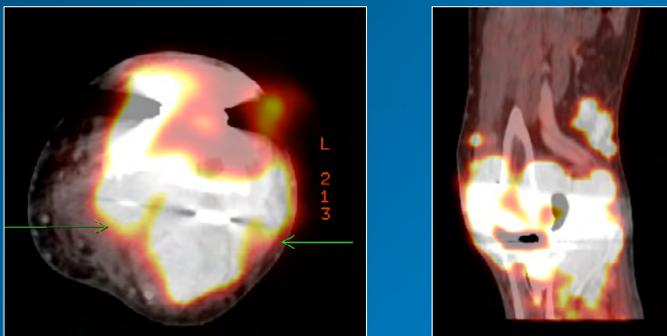


▶ An MRI with the sagittal T1-weighted images is depicted here, showing the extent of the disease.

MRI, magnetic resonance imaging.
Courtesy of William D. Tap, MD.

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PET



PET, positron emission tomography.
Courtesy of William D. Tap, MD.

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- ▶ The following slide shows the PET avidity of these tumors and the extent of the disease as mirrored by PET scan.

CT Scan



CT, computed tomography.
Courtesy of William D. Tap, MD.

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- ▶ And then the CT scan not only depicting the prior joint replacement, but also the extent of the disease specifically more discernable in the posterior aspect of the joint.

The patient did very well with treatment and had tremendous shrinkage of the disease and improvement in symptoms.

Patient Perspectives

- Encouraging oral therapy compliance
- Patient counseling and care coordination
- Shared decision making
 - Process of communication in which clinicians and patients work together to make optimal healthcare decisions that align with what matters most to patients
 - Optimal decision takes into account evidence-based information about available options, the provider's knowledge and experience, and the patient's values and preferences
 - National Quality Forum's 6 fundamentals to guide shared decision making in healthcare organizations:
 1. Promote leadership and culture
 2. Enhance patient education and engagement
 3. Provide healthcare team knowledge and training
 4. Take concrete actions for implementation
 5. Track, monitor, and report
 6. Establish accountability for organizations, clinicians, and patients

National Quality Forum. *National Quality Partners Playbook™: Shared Decision Making in Healthcare*. Washington DC: National Quality Forum; 2018.



▶ It is very important to make shared clinical decisions to understand the risks and benefits of a drug. Again, patients can be younger and even the risk of rare but significant toxicities are important to discuss. Understanding all options, not only medically but also surgically, are critical in making these informed decisions, and having the appropriate disease management team supporting the patient is very important.

Key Takeaways

- Diffuse TGCT is a rare, and for some patients, very devastating disease
 - Surgery is the mainstay of treatment
 - Medical management should be considered for symptomatic patients who are not surgical candidates
- It is critical for patients to be fully informed about the risks and benefits of all treatment options and to be involved in the decision making process



▶ So in conclusion, the diffuse type of TGCT is a rare and for some patients very devastating disease. Surgery, again, remains the mainstay of treatment.

But for patients who often have diffuse type TGCT who are very symptomatic and not necessarily amenable to surgical resection, the considerations of medical management can be very important for them.

Again, it is critical for patients to be able to have multidisciplinary discussions regarding all options regarding care and the risks and benefits of treatments.

Thank You

Thank you for participating in this activity!

- ▶ So that concludes today's discussion. I thank you for participating in this activity.

REFERENCES

- Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer* 2012;118(6):1649-55.
- Cassier PA, Italiano A, Gomez-Roca CA, et al. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. *Lancet Oncol.* 2015;16(8):949-956.
- Goldenberg H, Cropet C, Chevreau C, et al. Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2018;19(5):639-648.
- Gelhorn HL, Tong S, McQuarrie K, et al. Patient-reported symptoms of tenosynovial giant cell tumors. *Clin Ther.* 2016;38(4):778-793.
- Gelhorn HL, Ye X, Speck RM, et al. The measurement of physical functioning among patients with Tenosynovial Giant Cell Tumor (TGCT) using the Patient-Reported Outcomes Measurement Information System (PROMIS). *J Patient Rep Outcomes* 2019;3(1):6.
- Giustini N, Bernthal NM, Bukata SV, et al. Tenosynovial giant cell tumor: case report of a patient effectively treated with pexidartinib (PLX3397) and review of the literature. *Clin Sarcoma Res.* 2018;8:14.
- Hays RD, Spritzer KL, Fries JF, et al. Responsiveness and minimally important difference for the Patient-Reported Outcomes Measurement Information System (PROMIS) 20-item physical functioning short form in a prospective observational study of rheumatoid arthritis. *Ann Rheum Dis.* 2015;74(1):104-107.
- Lucas DR. Tenosynovial giant cell tumor: case report and review. *Arch Pathol Lab Med.* 2012;136(8):901-906.
- Mastboom MJL, Verspoor FGM, Verschoor AJ, et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. *Acta Orthop.* 2017;88(6):688-694.
- Mastboom MJL, Palmerini E, Verspoor FGM, et al. Surgical outcomes of patients with diffuse-type tenosynovial giant-cell tumours: an international, retrospective, cohort study. *Lancet Oncol.* 2019;20(6):877-886.
- Myers BW, Masi AT. Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. *Medicine (Baltimore)* 1980;59(3):223-238.
- National Organization for Rare Disorders. 2017. Tenosynovial giant cell tumor. <https://rarediseases.org/rare-diseases/tenosynovial-giant-cell-tumor/>.
- National Quality Forum. *National Quality Partners Playbook™: Shared Decision Making in Healthcare*. Washington DC: National Quality Forum; 2018.
- Palmerini E, Staals EI, Maki RG, et al. Tenosynovial giant cell tumour/pigmented villonodular synovitis: outcome of 294 patients before the era of kinase inhibitors. *Eur J Cancer* 2015;51:210-217.
- PROMIS Item Bank v1.2-Physical Function (Lower Extremity) questionnaire © 2008-2016 PROMIS Health Organization and PROMIS Cooperative Group.
- Richman DM, Bresler SC, Rosenthal MG, et al. Malignant tenosynovial giant cell tumor of the leg: a radiologic-pathologic correlation and review of the literature. *J Clin Imaging Sci.* 2015;5:13.
- Rowe PJ, Myles CM, Walker C, et al. Knee joint kinematics in gait and other functional activities measured using flexible electrogoniometry: how much knee motion is sufficient for normal daily life? *Gait Posture* 2000;12(2):143-155.
- Tap WD, Wainberg ZA, Anthony SP, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med.* 2015;373:428-437.
- Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet* 2019;394:478-487.
- Turalio (pexidartinib) [prescribing information]. August 2019. Basking Ridge, New Jersey: Daiichi Sankyo, Inc. <https://dsi.com/prescribing-information-portal/getPIContent?productName=Turalio&inline=true>.
- Turalio (pexidartinib) REMS. <https://www.turaliorems.com/#Main>.
- US Food & Drug Administration. August 2, 2019. FDA approves pexidartinib for tenosynovial giant cell tumor. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pexidartinib-tenosynovial-giant-cell-tumor>.
- von Mehren M, Kane JM, Benjamin RS, et al. NCCN Clinical Practice Guidelines in Oncology. Soft tissue sarcoma. Version 4.2019. ©2019 National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.
- West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. *PNAS* 2006;103:690-695.

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