Cancer Association of South Africa (CANSA)

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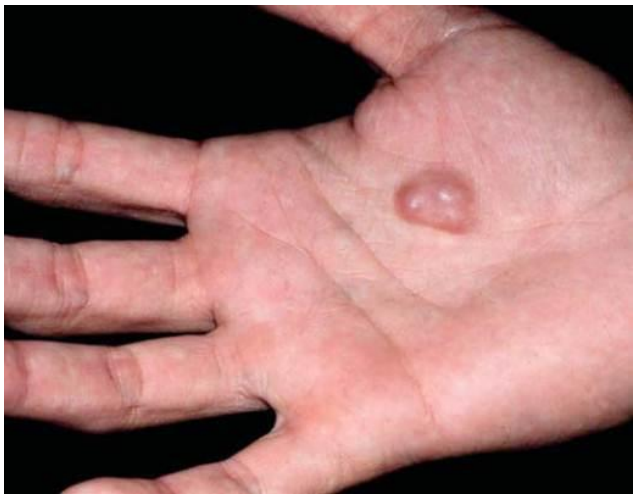
Fact Sheet on Epithelioid Sarcoma

Introduction

Epithelioid Sarcoma (ES) is a rare soft tissue sarcoma in children and young adults (usually 20-39 year olds) involving the upper extremities 60% of the time. The name was given by Enzinger in 1970 to a group of soft tissue sarcomas that were confused with a variety of malignant and benign conditions, especially granulomatous process, synovial sarcoma and ulcerating squamous cell carcinoma. In 1997, a "proximal type variant" of epithelioid sarcoma was described arising in the deep parts of the pelvis, perineum, and proximal extremities. It consists of large epithelioid carcinoma–like and/or rhabdoid cells and has a more aggressive clinical course compared to tumours located distally.[10] This variant is also referred to as "large cell epithelioid sarcoma" due to presence of large rhabdoid cells.



[Picture Credit: Epitheloid Sarcoma Picture]

Epithelioid Sarcoma is a slow growing tumour with a high rate of recurrence and metastasis. Slow growth of the tumour, paucity of symptoms, benign appearance in early stage imaging studies, and indistinctive pathologic findings in some cases makes the diagnosis of epithelioid sarcoma challenging. The rarity of the disease also makes performing large controlled clinical trials to evaluate different treatment options almost impossible.

Epithelioid Sarcoma (ES)

Epithelioid Sarcoma is a rare, slow-growing type of soft tissue cancer. Most cases begin in the soft tissue under the skin of a finger, hand, forearm, lower leg or foot, though it can start in other areas of the body. It occurs more frequently in men. Typically, epithelioid sarcoma starts as a small firm growth or lump that's painless. It usually starts out as a single growth, but multiple growths may occur by the time a person seeks medical help. Sometimes this sarcoma appears as ulcers that don't heal, looking like open wounds over the growths.

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Almost 40 years after Enzinger's first characterization of ES as a distinct clinicopathologic entity, ES is still of uncertain histogenesis (without a normal counterpart cell and a characteristic cytogenetic finding). However, it remains a distinct clinicopathologic entity with characteristic histomorphology, immunophenotype, and ultrastructure. The correct diagnosis of ES is essential because it can easily be misdiagnosed as another benign and less-aggressive malignant epithelioid lesions. Generally, the presence of large polygonal cells with prominent nucleoli and abundant necrosis on histology warrants the consideration of ES in the differential diagnosis. However, an immunohistochemical confirmation is a must for definitive diagnosis.

Needs, T. & Fillman, E.P. 2021.
"Epithelioid sarcoma was first described by Enzinger in 1970 as a rare soft tissue sarcoma that mimics granulomatous disease, carcinoma, and synovial sarcoma. The tumor typically presents as a painless, slow-growing soft tissue swelling in the distal extremity of young adult males. It is locally invasive and frequently metastasizes to regional lymph nodes and distant sites, most commonly to the lungs. Complete surgical resection is curative in low-stage disease; however, a risk of recurrence and late metastasis remains. Epithelioid sarcomas are tumors of purportedly mesenchymal origin that show ultrastructural and immunophenotypic evidence of epithelial differentiation. The mixed differentiation of epithelioid sarcoma can make the differential diagnosis challenging from a histopathologic perspective. The differential diagnosis is narrowed by the somewhat unique epithelioid sarcoma immunophenotype expressing cytokeratin, epithelial membrane antigen, and CD34. Epithelioid sarcoma is one of only a few tumors that characteristically lacks INI-1/SMARCB1 expression."

Incidence of Epithelioid Sarcoma (ES)
The South African National Cancer Registry (2017) does not provide any information on Epitheloid Sarcoma.

Epitheloid Sarcoma has been shown to be the second most common soft tissue sarcoma in the hand and the sixth most common soft tissue sarcoma in the upper extremity. This tumour is more common in males (1.8:1) and affects the young adult population.

Signs and Symptoms of Epithelioid Sarcoma (ES)
Individuals who have Epithelioid Sarcoma usually notice a lump or mass somewhere in the soft tissue of their body. The mass can range in size from quite small to large. One can feel and sometimes see the tumour. Sores or ulcers may also appear over the mass or lump.

Epithelioid sarcoma can be present for months or even years before a person notices a mass. In most cases, Epithelioid Sarcoma does not spread. If it does spread, lymph nodes, the lungs and bones are the most common sites of metastases.

Diagnosis of Epithelioid Sarcoma (ES)
Epithelioid Sarcoma is often difficult to diagnose.

The following may assist in making a diagnosis:
Tests and procedures used in diagnosis of epithelioid include:

- Imaging**.** Magnetic Resonance Imaging (MRI) is typically the method of imaging because of the level of detail it provides. Sometimes other imaging tests, such as Computed Tomography (CT) or Positron Emission Tomography (PET), may be used.
- Biopsy**.** The doctor performs a biopsy using a long, thin needle to remove a sample of the suspected sarcoma or a larger lump for testing in a laboratory. Sometimes a biopsy sample is removed during surgery. A pathologist analyses the sample to determine whether it is cancer, and if so, the type and whether it is aggressive.

There are no consistent or specific cytogenetic findings in ES, but several cases display chromosomal abnormalities in the 22q region. Additionally, inactivation of a tumour-suppressor gene *SMARCB1/INI1*, located at band 22q11, has been found in proximal, but not classic type, ES.

Treatment of Epithelioid Sarcoma (ES)
Epithelioid Sarcoma may be treated by means of:

Surgery
The patient may have a wide resection with margins, to remove the tumour and some tissue around the tumour. If the doctor is concerned that the cancer has also spread to nearby lymph nodes, they may also be removed. Amputation of part of the affected limb may be necessary in severe cases.

Radiation Therapy
Patients may have radiation treatment before surgery to reduce the size of the tumour. After surgery, additional radiation therapy may be used to help kill any tumour cells left behind in the body. Two types of radiation are sometimes used - regular radiation or proton radiation. Proton radiation has less side effects because it kills the tumour but does not hurt organs and healthy tissue.

Chemotherapy
If the tumour is large or has spread to other areas, the doctor may recommend chemotherapy or other types of drugs to help kill the cancer cells.

Tazemetostat, an orally available, first-in-class EZH2 inhibitor, may become a new treatment option for patients with Epithelioid Sarcoma, according to interim data from an ongoing phase 2 study presented by Epizyme at the European Society for Medical Oncology (ESMO) 2018 Congress in Munich, Germany.

Hoy, S.M. 2020.
"Tazemetostat (Tazverik™), a first-in-class, small molecule enhancer of zeste homolog 2 (EZH2) inhibitor, received accelerated approval in January 2020 in the USA for the treatment of adults and adolescents aged ≥ 16 years with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection. Developed by Epizyme, in collaboration with Eisai, it is the first therapy to be approved specifically for the treatment of epithelioid sarcoma in the USA. The recommended dosage regimen is 800 mg twice daily, administered orally with or without food, until disease progression or unacceptable toxicity. Tazemetostat is also undergoing clinical development in various countries worldwide for use in several other tumour types, including diffuse large B-cell lymphoma and mesothelioma, with the US FDA accepting a New Drug Application and granting priority review for its use in the treatment of follicular lymphoma. This article summarizes the milestones in the development of tazemetostat leading to this first approval for the

treatment of adults and adolescents aged ≥ 16 years with locally advanced or metastatic epithelioid sarcoma not eligible for complete resection."

The prognosis for patients with epithelioid sarcoma is poor, because a substantial number of patients present with extensive disease, lymph node metastases, and/or distant metastases. Treatment consists of radical surgical excision of the tumour and, if indicated, therapeutic lymph node dissection. In patients who have large tumours, isolated limb perfusion may be useful.

Accelerated Approval of New Drug by the United States Food and Drug Administration (FDA)
The U.S. Food and Drug Administration (FDA) granted accelerated approval to Tazverik (tazemetostat) for the treatment of adults and pediatric patients aged 16 years and older with metastatic (when cancer cells spread to other parts of the body) or locally advanced (when cancer has grown outside the organ it started in, but has not yet spread to distant parts of the body) epithelioid sarcoma not eligible for complete resection (surgically removing all of a tissue, structure, or organ). Epithelioid sarcoma is a rare sub-type of soft tissue sarcoma that often occurs in young adults.

"Epithelioid sarcoma accounts for less than one percent of all soft tissue sarcomas," said Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Oncologic Diseases in the FDA's Center for Drug Evaluation and Research. "Until today, there were no treatment options specifically for patients with epithelioid sarcoma. The approval of Tazverik provides a treatment option that specifically targets this disease. When we brought Tazverik's application to the Oncologic Drugs Advisory Committee last month, the committee voted unanimously that the benefits of the drug outweighed the risks."

Tazverik blocks activity of the EZH2 methyltransferase, which may help keep the cancer cells from growing. Most cases of epithelioid sarcoma begin in the soft tissue under the skin of an extremity, though it can start in other areas of the body. Surgical removal is considered the main treatment when the cancer is localized to one area of the body. Chemotherapy or radiation may also be given. However, there is a high likelihood for local and regional spread of the disease even with treatment and approximately 50% of patients have metastatic disease at the time of diagnosis. Metastatic disease is considered life-threatening to the patient.

Wollina, U., Schönlebe, J., Haroske, G., Unger, L., Kittner, T., Tchernev, G., Chokoeva, A.A. & Lotti, T. 2015. "Epithelioid sarcoma is a rare malignant soft tissue sarcoma. We present a 36-year-old male patient with a primary tumour on his wrist and subcutaneous spread in a sporotrichoid pattern along the upper extremity. Early surgical treatment with micrographic control of all margins provides best long term outcome as long as a solitary lesion is present. In case of cutaneous and internal spread of the disease treatment options are only palliative. Early diagnosis, therefore, is most crucial."

Clinical Trials
Epithelioid sarcoma can be challenging to treat. In some situations, the doctor may recommend participating in a clinical trial.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The *South African National Clinical Trials Register* provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Gounder, M., Schöffski, P., Jones, R.L., Agulnik, M., Cote, G.M., Villalobos, V.M., Attia, S., Chugh, R., Chen, T.W., Jahan, T., Loggers, E.T., Gupta, A., Italiano, A., Demetri, G.D., Ratan, R., Davis, L.E., Mir, O., Dileo, P., Van Tine, B.A., Pressey, J.G., Lingaraj, T., Rajarethinam, A., Sierra, L., Agarwal, S. & Stacchiotti, S. 2020.

Background: Epithelioid sarcoma is a rare and aggressive soft-tissue sarcoma subtype. Over 90% of tumours have lost INI1 expression, leading to oncogenic dependence on the transcriptional repressor EZH2. In this study, we report the clinical activity and safety of tazemetostat, an oral selective EZH2 inhibitor, in patients with epithelioid sarcoma.

Methods: In this open-label, phase 2 basket study, patients were enrolled from 32 hospitals and clinics in Australia, Belgium, Canada, France, Germany, Italy, Taiwan, the USA, and the UK into seven cohorts of patients with different INI1-negative solid tumours or synovial sarcoma. Patients eligible for the epithelioid sarcoma cohort (cohort 5) were aged 16 years or older with histologically confirmed, locally advanced or metastatic epithelioid sarcoma; documented loss of INI1 expression by immunohistochemical analysis or biallelic SMARCB1 (the gene that encodes INI1) alterations, or both; and an Eastern Cooperative Oncology Group performance status score of 0-2. Patients received 800 mg tazemetostat orally twice per day in continuous 28-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was investigator-assessed objective response rate measured according to the Response Evaluation Criteria in Solid Tumors, version 1.1. Secondary endpoints were duration of response, disease control rate at 32 weeks, progression-free survival, overall survival, and pharmacokinetic and pharmacodynamic analyses (primary results reported elsewhere). Time to response was also assessed as an exploratory endpoint. Activity and safety were assessed in the modified intention-to-treat population (ie, patients who received one or more doses of tazemetostat). This trial is registered with ClinicalTrials.gov, NCT02601950, and is ongoing.

Findings: Between Dec 22, 2015, and July 7, 2017, 62 patients with epithelioid sarcoma were enrolled in the study and deemed eligible for inclusion in this cohort. All 62 patients were included in the modified intention-to-treat analysis. Nine (15% [95% CI 7-26]) of 62 patients had an objective response at data cutoff (Sept 17, 2018). At a median follow-up of 13·8 months (IQR 7·8-19·0), median duration of response was not reached (95% CI 9·2-not estimable). 16 (26% [95% CI 16-39]) patients had disease control at 32 weeks. Median time to response was 3·9 months (IQR 1·9-7·4). Median progression-free survival was 5·5 months (95% CI 3·4-5·9), and median overall survival was 19·0 months (11·0-not estimable). Grade 3 or worse treatment-related adverse events included anaemia (four [6%]) and weight loss (two [3%]). Treatment-related serious adverse events occurred in two patients (one seizure and one haemoptysis). There were no treatment-related deaths.

Interpretation: Tazemetostat was well tolerated and showed clinical activity in this cohort of patients with advanced epithelioid sarcoma characterised by loss of INI1/SMARCB1. Tazemetostat has the potential to improve outcomes in patients with advanced epithelioid sarcoma. A phase 1b/3 trial of tazemetostat plus doxorubicin in the front-line setting is currently underway (NCT04204941).
Funding: Epizyme.

Medical Disclaimer

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Sources and References Consulted and/or Utilised

Epitheloid Sarcoma
https://www.mayoclinic.org/diseases-conditions/epithelioid-sarcoma/cdc-20392420
http://sarcomahelp.org/epithelioid-sarcoma.html
https://www.archivesofpathology.org/doi/full/10.1043/1543-2165-133.5.814
https://www.frontiersin.org/articles/10.3389/fonc.2015.00186/full
http://www.pathologyoutlines.com/topic/softtissueepithelioidsarcoma.html
https://academic.oup.com/ajcp/article/131/2/222/1766026
https://www.cincinnatichildrens.org/health/e/epithelioid-sarcoma
https://www.mycancergenome.org/content/disease/epithelioid-sarcoma/
https://www.malacards.org/card/epithelioid_sarcoma
https://www.uptodate.com/contents/search?search=Epithelioid%20Sarcoma
https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/cncr.22037
https://www.sciencedirect.com/topics/medicine-and-dentistry/epithelioid-sarcoma
https://www.cancertherapyadvisor.com/home/cancer-topics/sarcoma/tazemetostat-shows-promise-in-epithelioid-sarcoma/

Epitheloid Sarcoma Picture
https://www.orthobullets.com/pathology/8076/epithelioid-sarcoma

Gounder, M., Schöffski, P., Jones, R.L., Agulnik, M., Cote, G.M., Villalobos, V.M., Attia, S., Chugh, R., Chen, T.W., Jahan, T., Loggers, E.T., Gupta, A., Italiano, A., Demetri, G.D., Ratan, R., Davis, L.E., Mir, O., Dileo, P., Van Tine, B.A., Pressey, J.G., Lingaraj, T., Rajarethinam, A., Sierra, L., Agarwal, S. & Stacchiotti, S. 2020. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. *Lancet Oncol*. 2020 Nov;21(11):1423-1432.

Hoy, S.M. 2020. Tazemetostat: first approval. *Drugs*. 2020 Apr;80(5):513-521.

Jensen, D.B., Nielsen, N.H., Nielsen, P.L. & Krag, C. 1991. Epitheloid sarcoma – an overlooked diagnosis? *UgeskrLaeger*. 1991 Jun 24;153(26):1873-4.

Joseph, F., Sobanko, M.D., Lindsay Meijer, B.S. & Nigra, T.P. 2009. Epitheloid sarcoma: a review and update. *Journal of Clin and Aesth Dermatol.* Sobanko JF, Meijer L, Nigra TP. Epithelioid sarcoma: a review and update. *J Clin Aesthet Dermatol*. 2009;2(5):49–54.

Needs, T. & Fillman, E.P. 2021. Epithelioid Sarcoma. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2021 Jan 9.

Ortoli JC, Mansouri S, Veron C, Servant JM, Marinho E, Aractingi S. 1998. Epitheloid sarcoma manifesting as chronic plantar arch ulceration. *Ann Dermatol Venereol.* 1998 Mar;125(3):179-81.

Rajeev, L.K., Asati, V., Babu, S., Babu, G. & Champaka, G. 2018. Epitheloid sarcoma presenting as recurrent thumb ulcer: a lesson to learn. Indian *J Surg Oncol.* 2018 Jun;9(2):251-253. doi: 10.1007/s13193-018-0727-9. Epub 2018 Mar 20.

United States Food and Drug Administration
https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-option-specifically-patients-epithelioid-sarcoma-rare-soft-tissue

Wollina, U., Schönlebe, J., Haroske, G., Unger, L., Kittner, T., Tchernev, G., Chokoeva, A.A. & Lotti, T. 2015. Nodular epitheloid sarcoma of the upper limb. A case report and review of the literature. *J Biol Regul Homeost Agents*. 2015 Jan-Mar;29(1 Suppl):23-6.