Taylor & Francis
Taylor & Francis Group

Expert Opinion on Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

Pharmacotherapeutic strategies for epithelioid sarcoma: are we any closer to a non-surgical cure?

Magdalena Meissner, Andrea Napolitano, Khin Thway, Paul Huang & Robin L Jones

To cite this article: Magdalena Meissner, Andrea Napolitano, Khin Thway, Paul Huang & Robin L Jones (2023) Pharmacotherapeutic strategies for epithelioid sarcoma: are we any closer to a non-surgical cure?, Expert Opinion on Pharmacotherapy, 24:12, 1395-1401, DOI: 10.1080/14656566.2023.2224500

To link to this article: https://doi.org/10.1080/14656566.2023.2224500

Published online: 20 Jun 2023.

EXPERT OPINION ON PHARMACOTHERAPY
2023, VOL. 24, NO. 12, 1395–1401
https://doi.org/10.1080/14656566.2023.2224500

Taylor & Francis
Taylor & Francis Group

REVIEW

Pharmacotherapeutic strategies for epithelioid sarcoma: are we any closer to a non-surgical cure?

Magdalena Meissner [a,b], Andrea Napolitano[c], Khin Thway[c,d], Paul Huang [c,d] and Robin L Jones [c,e]

[a]Velindre Cancer Centre, Cardiff, UK; [b]Department of Cancer and Genetics, Cardiff University, Cardiff, UK; [c]Sarcoma Unit, The Royal Marsden NHS Foundation Trust, London, UK; [d]Division of Molecular Pathology, Institute of Cancer Research, London, UK; [e]Division of Clinical Studies, The Institute of Cancer Research, London, UK

ABSTRACT

Introduction: Epithelioid sarcoma (ES) is a rare soft tissue sarcoma subtype, predominantly occurring in children and young adults. Despite optimal management of localized disease, approximately 50% of patients develop advanced disease. The management of advanced ES remains challenging due to limited response to conventional chemotherapy and despite novel oral EZH2 inhibitors that have better tolerability but similar efficacy to chemotherapy.

Areas covered: We performed a literature review using the PubMed (MEDLINE) and Web of Science databases. We have focused on the role of chemotherapy, targeted agents such as EZH2 inhibitors, potential new targets and immune checkpoint inhibitors and combinations of therapies currently undergoing clinical investigation.

Expert opinion: ES is a soft tissue sarcoma with a heterogeneous pathological, clinical, and molecular presentation. In the current era of precision medicine, more trials with targeted therapies and a combination of chemotherapy or immunotherapy with targeted therapies are required to establish optimal treatment for ES.

ARTICLE HISTORY
Received 5 December 2022
Accepted 8 June 2023

KEYWORDS
Epithelioid sarcoma; systemic therapy; chemotherapy; INI1; EZH2 inhibitors

1. Introduction

Epithelioid sarcoma (ES) is a slow-growing type of soft-tissue tumor first named in 1970 by Franz Enzinger [1]. ES is rare and is recognized in less than 1% of all sarcomas and mainly occurs in young to middle age adults (20–40 years) and males [2].

ES can be divided into two variants based primarily on anatomic location and histology (classic and proximal). It is thought that there is a continuum between these variants [3]. The classic ES affects mostly teenagers and young adults; the proximal type is a rarer, more aggressive type and mainly occurs in adults. Histologically, both subtypes are characterized by sheets of uniform epithelioid cells, although they have morphologic differences [4].

Almost half of the patients with ES present with often localized multi-focal disease [5]. In up to 30–50% of cases, ES metastasize to lymph nodes and distant sites, most commonly the lung [6]. The classic ES has multiple lesions with high local recurrence rates. However, the proximal ES often spreads sooner than the classic ES and therefore has a poorer prognosis. ES can appear superficially as single or multiple nodules (nodular ES) or as a mass in deeper tissues [7]. Nodular ES is associated with significantly higher amputation and local relapse rates, and mass ES was found to have a better prognosis with no occurrence of locoregional spread [7]. Livi et al. demonstrated that the dominant prognostic factor was the site of the primary tumor, with the best prognosis for distal limb location [8].

The 5-year overall survival has been reported as 68% [5], with better survival in localized disease compared to regional disease (75% vs 49%, respectively) [5]. Deep, large proximal tumors, older age, male sex, and local recurrence or regional metastases are adverse prognostic factors [9,10]. In addition, Jawad et al. 2009 in their analysis of 441 cases from the SEER Database, reported that none of the patients with metastatic disease survived for five years, and 1-year survival was 46% [5].

1.1. Molecular pathology

INI1 loss was reported in over 90% of ES, which has improved the diagnosis of ES through immunohistochemistry [11–14]. *INI1* is a tumor suppressor gene present in chromosome 22 [15]. This gene encodes a subunit of the SWI/SNF chromatin complex that regulates genes involved in the cell cycle and oncogenic signaling pathways [15]. The loss of INI1 triggers genomic instability, cell cycle advancement, and initiation of abnormal signaling pathways, allowing oncogenesis [16,17]. In addition, INI1 loss causes activation of EZH2, which is considered the key oncogenic driver for ES and has become its main therapeutic target [18,19]. Hornick et al. reported that loss of expression of INI1 is characteristic of classic and proximal ES [13]. However, Rasmussen et al., through functional genomics analysis, uncovered distinguishing features of classic and

CONTACT Magdalena Meissner Magdalena.Meissner@wales.nhs.uk Velindre Cancer Centre, Velindre Road, Cardiff CF14 2TL, UK; Robin L Jones robin.jones4@nhs.net Sarcoma Unit, The Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, UK

Article highlights

- Almost 50% of epithelioid sarcoma recur or develop advanced disease despite optimal management of the localized disease.
- Significant differences exist between proximal and classic ES in terms of prognostic, histological and molecular features, which may require different therapeutic approaches.
- EZH2 inhibitors represent similar efficacy to chemotherapy but better tolerability; combinations of both are under evaluation.
- Molecular profiling of epithelioid sarcoma may help identify new directions in the treatment of epithelioid sarcomas.
- Immune checkpoint inhibitors have not shown significant outcomes in soft tissue sarcomas. Understanding the immunogenicity and immune microenvironment of ES may help identify patients that benefit from immunotherapy or its combinations.

proximal ES [20]. Specifically, molecular sequencing and immunohistochemistry show deletion of INI1 in proximal ES, whilst classic ES demonstrates a pattern of retained dysfunctional INI1 expression [20]. In addition, classic ES has an increased expression of actionable molecular targets, such as *GLI3, FYN,* and *CXCL12* [20]. Preserved expression of INI1 in classic ES allows a different therapeutic approach by targeting *INI1* through BRD7/9 degraders [20]. This needs further investigation as a potential therapeutic option for classic ES.

In addition to the above differences between proximal and classic types, Frezza et al., in their transcriptomic analyses of ES samples, discovered disparities in the expression of multiple regulatory pathways [21]. Proximal ES was characterized by MYC overexpression and genomic signatures that affect the cell cycle, chromatin metabolism, and protein synthesis. In contrast, classic ES demonstrated increased involvement of Notch/Hedgehog and immune regulation pathways linked with class 1 human leukocyte antigens (HLA) overexpression and increased immune infiltration [21].

These observations suggest significant molecular disparities between both types of ES, which may explain differences in response to current therapies and possibly requires new directions for research and clinical trials.

In addition, a study by Hiroshi Kato et al. has demonstrated high specificity and positivity of CA125 expression in epithelioid sarcoma (ES) compared to other sarcomas [22]. CA125 serum levels have been found to correlate with disease progression in ES [23] Measurement of CA125 levels is a well-established test for monitoring disease status and evaluating response to therapy in ovarian cancer and could be possibly be applicable in the management of ES.

1.2. Role of surgery and radiotherapy for localized ES

The standard treatment is the surgical resection of local disease with or without radiotherapy to prevent local recurrence. Livi et al. demonstrated that wide local excision with a radical radiotherapy dose is more effective at preventing local recurrence [8]. This study showed that 35% of patients treated with wide excision developed a local recurrence as opposed to 55% of patients treated with local excision [8]. The lower mortality rates of 21% and 27% were in patients treated with wide excision and local excision, respectively [8]. However, incomplete excision was associated with a high mortality rate of 75% [8]. Despite optimal management of localized disease, approximately 50% of patients develop advanced disease.

The recommended radiation dose after surgery for sarcoma is 60–66 Gy delivered in 1.8–2 Gy fractions. A two-phase technique is commonly employed, with an initial larger volume receiving 50 Gy, followed by a smaller volume receiving 10–16 Gy [24].

Pre-operative radiotherapy is administered at a lower dose of 50 Gy with a smaller treatment volume that covers the pre-operative tumor volume, rather than the post-operative tumor bed. Although it is associated with more acute post-operative complications compared to the standard post-operative treatment, it has been found to have less late toxicity while maintaining equivalent tumor control [25,26]. This approach has become routine in some centers.

2. Chemotherapy in epithelioid sarcoma

2.1. Adjuvant chemotherapy

There are limited published data regarding the efficacy of adjuvant chemotherapy in epithelioid sarcoma, with no definitive evidence to support a role for post-operative chemotherapy. Similarly for more common soft tissue sarcoma subtypes the evidence base for adjuvant chemotherapy is limited, for example the role of adjuvant chemotherapy in uterine leiomyosarcoma remains to be conclusively defined [27]. Further studies are needed are needed to better understand the value of adjuvant chemotherapy in soft tissue sarcomas.

2.2. Palliative chemotherapy

There is no strong evidence of systemic treatment for advanced and metastatic ES. Most available data are based on small studies, case reports, or single patients with ES treated in all-comer soft tissue sarcoma (STS) trials. The summary table (Table 1) presents an overview of key findings from relevant studies and trials.

The biggest multicentre case series reported by Frezza et al. analyzed 115 patients with advanced or metastatic ES [28]. They reported an Objective Response Rate (ORR) of 22% with anthracycline-based regimens and 27% with gemcitabine-based regimens, and median Progression Free Survival (PFS) was 6 and 4 months, respectively [28]. Jones et al. reported a similar PFS of 7.3 months with first-line anthracycline-based regimens [29]. However, their case series of 21 patients demonstrated an ORR of 15% to first-line anthracyclines alone or in combination with ifosfamide [28]. Four prospective EORTC (European Organisation for Research and Treatment of Cancer) clinical trials identified 27 patients with ES out of 976 patients [30]. The ORR in all patients was 22.2%. However, in the first line, there were no responses to single-agent doxorubicin; there was an ORR of 12.5% (1/8) in patients treated with doxorubicin and ifosfamide and of 33.3% (1/3) with trabectedin [30]. The median PFS was 4 months, and the median OS was 11 months [30].

Pink et al., through a retrospective multi-institutional analysis, reported an ORR of 58% (7/12) to the combination of gemcitabine and docetaxel, regardless of the line of treatment, with a median PFS of 8 months in all patients [31]. However, for gemcitabine-based chemotherapy, Frezza et al. reported a lower ORR (27%) with a median PFS of 4 months [28]. Also, they have not observed any differences in response rates between gemcitabine in monotherapy or in combination with docetaxel [28].

A most recent retrospective multicentre real-world study involving 74 patients with ES showed the real effectiveness of conventional chemotherapy of ORR of 15% in the first-line treatment and 9% in the second line and beyond [32]. However, over half of patients (51.4%) experienced significant adverse events during chemotherapy, with febrile neutropenia being the most common. Nevertheless, this study provided valuable insight into conventional chemotherapy's activity and safety in advanced ES. Overall, a small proportion of patients with ES can benefit from these chemotherapies. However, this must be weighed against the potential toxicity of these treatments.

There have also been a few case reports of the benefit of vinorelbine. One patient with metastatic ES achieved a complete resolution of pulmonary metastases with a durable response for four years, and one achieved a PR over 27 months [33,34]. Therefore, vinorelbine, a relatively well-tolerated chemotherapy option, could be considered for patients with metastatic ES.

In combination, these retrospective studies indicate that anthracycline- and gemcitabine-based schedules have activity in ES. However, the durability of response is brief, and these agents can have considerable toxicity.

3. Approved targeted therapies in ES

As discussed above, INI1 loss leads to oncogenic dependency on EZH2. This has led to considerable interest in evaluating EZH2 inhibitors in ES. In 2020, the Food and Drug Administration (FDA) approved the EZH2 inhibitor tazemetostat based on the results of a phase 2 basket trial (NCT02601950), which demonstrated clinical efficacy and good tolerability in patients with ES [35]. The primary endpoint in the ES cohort was ORR. All patients received oral tazemetostat. The ORR was 15%; 26% of patients had stable disease at 8 months, and the progression-free survival rate at 12 months was 21% [36]. The ORR was mainly demonstrated in 25% of patients who received tazemetostat in the first-line setting compared to 8% of patients with second-line or beyond [36]. The ORR for tazemetostat is similar to anthracycline- or gemcitabine-based regimens in ES, as reported in a retrospective multicentre real-world study [32]. However, tazemetostat was well tolerated, with mostly grade 1–2 side effects and few dose reductions or suspensions [36]. Importantly, tazemetostat did not cause grade 3 or 4 nausea, thrombocytopenia or neutropenia frequently related to chemotherapy [35]. Based on this information, a phase 1b/3 randomized trial (NCT04204941) was developed. Currently, this trial randomizes ES patients to receive doxorubicin plus tazemetostat or single-agent doxorubicin in a first-line setting.

Pazopanib was the first targeted therapy available for the treatment of ES. However, Frezza et al.'s study demonstrated no radiological responses in any 18 patients treated with pazopanib with a median PFS of 3 months [28]. In

Table 1. Summary of the main treatments for ES.

Therapy type	Efficacy	References
Chemotherapy regimens		
Anthracycline-based chemotherapy	ORR 22%, PFS 6 months	[28]
	ORR 15%, PFS 7.3 months	[29]
Gemcitabine-based chemotherapy	ORR 27%, PFS 4 months	[28]
	ORR 58%(7/12 Pts), PFS 8 months	[31]
Doxorubicin + Ifosfamide	ORR 12.5% (1/8 Pts), PFS 4 months, OS 11 months	[30]
Trabectedin	ORR 33.3% (1/3 Pts), PFS 4 months, OS 11 months	[30]
Vinorelbine	1 Pt – CR for 4 years, 1 Pt – PR for 27 months	Case reports [33,34]
Targeted Therapies		
Tazemetostat	ORR 15%; PFS at 12 months 21%	[32,35,36]
Pazopanib	18 Pts – No OR, PFS 3 months	[28,30,37,38]
Dasatinib	ORR 28%(2/7 pts); PFS 7.9 months OS 21% at 2 years	[39]
Sunitinib	1 Pt – SD for 32 months	Case report [40]
Chemotherapy combination with targeted therapy		
Doxorubicin + Tazemetostat	Awaiting results of phase 1b/3 randomized trial	NCT04204941
Immunotherapy		
Pembrolizumab	1 Pt – PR for 12 months	[41]
Nivolumab	1 Pt – PR for 4 months	[42]
	1 Pt – PD	
	1 Pt – PD	[43]
Immunotherapy combinations		
Ipilimumab + Nivolumab	1 Pt – CR	[44]
Axitinib + Pembrolizumab	1 Pt – PR for 6 months	[45]
Nivolumab + Sunitinib	7 Pts – No OR	[46]
Dasatinib + Ipilimumab	1 Pt – No OR	[47]
Durvalumab + Tazemetostat	Awaiting results of phase 2 CAIRE trial	NCT04705818

Objective Response Rate (ORR), Objective Response (OR), Progression-Free Survival (PFS), And Overall Survival (OS), Pt/Pts – Patient/Patients, PR – Partial Response, CR – Complete Response, PD – Progressive Disease.

contrast, there have been sporadic reports of successful treatment with pazopanib [37,38], and Touati et al. reported an ORR of 100% (2/2) to pazopanib in the first line and 11% (1/9) in second line [30].

4. Other potential targets and non-approved therapies

Certain signaling pathways have been linked with ES pathogenesis and are possible targets for new treatments. Imura et al. reported hyperactivation of the AKT/mTOR pathway in cells with loss of INI1 and consequently reduced cell proliferation when mTOR was blocked with anti-mTOR specific siRNAs [48]. This led to studying everolimus, an mTOR inhibitor, in ES. However, mTOR inhibition caused an increase in the activation of AKT and c-MET [48]. This suggests that inhibiting one pathway can be insufficient. The inhibition of multiple pathways with AKT and c-MET inhibitors might need to be considered.

EGFR overexpression was also identified in both ES subtypes [49,50]. Erlotinib, a tyrosine kinase inhibitor to EGFR, was investigated and demonstrated tumor growth delay in vivo. However, Erlotinib did not cause tumor arrest due to sustained AKT activation [49]. Subsequently, the researchers investigated the effects of the combination of EGFR inhibitor with mTOR inhibitor in vivo and in vitro models of ES. They reported a significant benefit with inhibition of both pathways compared to the blockade of a single pathway [49]. Furthermore, Imura et al. also demonstrated that combining a selective c-MET inhibitor with an mTOR inhibitor leads to a stronger blockage of ES xenograft growth than either agent alone [48].

Dysregulation of adhesion protein has also been reported in ES. Dysadherin is a cell membrane glycoprotein involved in the downregulation of E-cadherin, which is responsible for cancer development and metastasis [51,52]. Interestingly, greater levels of dysadherin have been found in proximal ES cell lines, which could contribute to a worse prognosis of proximal ES [53]. Therefore, both glycoproteins are potential targets for the treatment of ES.

Cyanamide Pan-TEAD·YAP1 Covalent Antagonists represent a promising new approach for the treatment of cancer, including sarcoma. The TEAD·YAP/TAZ pathway plays a crucial role in the regulation of various biological processes, including tissue and immune homeostasis, organ size control, tumorigenesis, and metastasis [54]. Dysregulation of this pathway has been implicated in various types of cancer, promoting tumor growth and metastasis. Small molecules that target the TEAD palmitate-binding cavity have been discovered, which is a key site of interaction between TEADs and YAP/TAZ [54]. By inhibiting this interaction, the small molecules suppress the transcriptional activity of TEADs and the expression of target genes involved in tumor growth, metastasis, and other biological processes [54]. In vitro studies have shown that these small molecules have potent anticancer activity against several types of cancer cells, including sarcoma [54]. These small molecules represent a promising new class of anticancer agents that could have significant clinical impact in the future.

Dasatinib (multi-kinase inhibitor) efficacy in ES was investigated in a single-arm SARC0009 trial; 28% (2/7) patients achieved ORR (according to Choi criteria) with a median PFS of 7.9 months [39]. However, OS was only 21% at 2 years [39].

Finally, a case reporting long-term stable disease of more than 32 months on sunitinib in the third line of treatment has been published [40].

All these promising targets and combinations of targeted agents in preclinical studies must be studied in clinical trials to assess safety, tolerability, and efficacy in ES.

5. Immunotherapy

Immunotherapy has changed the practice for many solid tumors. However, the value of immunotherapy in STS has not been established yet. Forrest et al. investigated PD-L1 expression in 30 INI1-negative sarcomas, including ES [55]. Forty-seven percent of these sarcomas were PD-L1 positive (using a threshold of ≥1% positivity in tumor cells or Tumor Infiltrating Lymphocytes (TILs)), and all four patients with ES were PD-L1 positive [55]. In the study of Boxberg et al., 20% (1/5) of ES were PD-L1 positive (defined as positive PD-L1 staining of any percentage) [56]. In the study of Kim et al., all seven ES were PD-L1 positive (using a threshold of >10% positivity in tumor cells), PD-L1 expression was linked to shorter 5-year OS, and it was an independent negative prognostic factor, which supports a role as a potential therapeutic target [57].

There are ongoing clinical trials with immune checkpoint inhibitors targeting the PD – 1/PD-L1 and CTLA – 4/CD80/86 for STS, including ES. Here, we will focus on the limited data for ES patients from these clinical trials or case reports.

In the KEYNOTE – 051 study, there was an 18-year-old patient with PD-L1-positive (PD-L1 40% positivity in the tumor cells) ES who achieved partial response (PR) for almost 12 months with pembrolizumab [41]. In a retrospective series with nivolumab, a 24-year-old man with a proximal ES metastatic to the lung achieved PR after four cycles; however, he progressed after four additional cycles, and another patient with ES had disease progression at the first evaluation of nivolumab [42].

5.1. Immunotherapy combinations

In order to improve the efficacy of immune monotherapy for STS, multiple combination strategies have been explored in various clinical trials. These combinations include CTLA – 4 checkpoint inhibitors, targeted therapies, and epigenetic or anti-angiogenic agents, intending to boost the anti-tumor immune response.

In the randomized clinical trial Alliance A091401 (NCT02500797), a combination of nivolumab with or without the anti-CTLA4 ipilimumab was investigated for all metastatic sarcomas, including ES [43]. However, only one patient with ES was included and did not respond to single-agent nivolumab. In contrast, Pecora et al. reported one patient that had a complete response to a combination of ipilimumab and nivolumab previously treated with tazemetostat and chemotherapy [44]. This indicates that further molecular investigations are needed to identify immune biomarkers of response. The combination of ipilimumab

and nivolumab is currently being evaluated in a phase 3 trial (NCT04741438) for rare subtypes of sarcoma, including ES, and a phase 2 trial (NCT04416568) for INI1-negative pediatric cancers.

A combination of checkpoint inhibitors with anti-angiogenic agents has been supported by preclinical studies that VEGF blocks T-cell development and might contribute to tumor-induced immune suppression [58]. A phase 2 clinical trial evaluated a combination of axitinib and pembrolizumab in STS and reported prolonged (6 months) partial response in one patient with ES [45]. In contrast, no objective responses were observed in seven patients with ES who received the combination of nivolumab with sunitinib in the phase 1b/2 trial [46] and in one patient with ES who received the combination of dasatinib and ipilimumab [47].

Several preclinical studies reported that the EZH2 inhibitors have the potential to modulate the immunogenicity of a tumor and anti-tumor immune response [59]. Tazemetostat could potentially be used as an immunomodulator [59,60]. Multiple studies reported that EZH2 inhibitors could bypass primary and secondary resistance to PD-L1 inhibitors in multiple cancer types [61–63]. The ongoing phase 2 CAIRE clinical trial (NCT04705818) investigates the combination of anti-PD-L1 (durvalumab) and tazemetostat in solid tumors, including soft-tissue sarcoma.

We hope that all the ongoing clinical trials improve our understanding of the immunogenicity of ES and provide more information on the effects of immunotherapy combinations in ES to allow us to identify patients with ES that will benefit from specific immunotherapy combinations.

6. Conclusion

In summary, ES is a rare type of soft tissue sarcoma with heterogeneity in clinical presentation and behavior. Diagnosing ES has improved through loss of INI1 expression. However, management of advanced ES remains challenging due to limited response to chemotherapy. Tazemetostat, an EZH2 inhibitor, provides patients with oral systemic therapy with better tolerability than chemotherapy but with similar efficacy. Ongoing trials will provide more information on whether the combination of tazemetostat with chemotherapy or immunotherapy might have a better effect in patients with ES. There are limited data on the effects of immunotherapy in patients with ES. However, more molecular investigations are required to identify those patients that will benefit from immune monotherapy and those that will require a potential combination of multiple treatments. Furthermore, more research is needed to identify novel targets to help improve treatment options for patients with rare soft tissue sarcoma like ES.

7. Expert opinion

Epithelioid sarcoma represents a rare and heterogenous patient population group in terms of anatomical location, histology, molecular and immune characteristics. Nevertheless, over 40 years of research in ES has provided several insights into this difficult-to-manage disease:

A combination of retrospective studies indicated that anthracycline- and gemcitabine-based schedules have activity in epithelioid sarcoma. However, the durability of response is brief, and these agents can have considerable toxicity. Molecular classification could help identify patients most likely to respond to chemotherapy.

Tazemetostat (an EZH2 inhibitor) as a single agent is less toxic than conventional chemotherapy. However, in terms of efficacy, tazemetostat has similar efficacy to standard chemotherapy. Therefore, the results of ongoing clinical trials that assess the combination of tazemetostat with chemotherapy are eagerly awaited. In addition, due to recent developments in the genomics of ES, the treatment with single-agent tazemetostat might be less effective for patients with classic ES with dysfunctional INI1, who might require a different therapeutic approach. This needs to be explored in future clinical trials. In addition, tazemetostat has the potential to modulate tumor immunogenicity and anti-tumor immune response and therefore is being further evaluated in combination with immunotherapy.

Other targeted therapies, such as mTOR and EGFR inhibitors, are under investigation. Hyperactivation of the AKT/mTOR pathway and a high level of EGFR expression have been identified in ES. However, blocking one pathway might be insufficient to stop cancer growth, and combinations might be more effective and should be evaluated in future clinical trials.

Higher levels of dysadherin (downregulator of E-cadherin cell-mediated adhesion) have been identified in cell lines from proximal ES. Dysadherin and a complete loss of E-cadherin promote metastasis, and therefore, both glycoproteins are potential targets for the treatment of ES.

Immunotherapy in ES is still under evaluation. However, several patients from case reports and clinical trials have benefited from immune checkpoint inhibitors. The ongoing trials with single-agent checkpoint inhibitors or combinations with targeted therapies will inform future direction. In addition, we need more studies evaluating both the immunogenicity and microenvironment of ES to discover immune biomarkers that identify patients who will benefit from immune checkpoint inhibitors on their own and who will require a combination of immunotherapy with additional therapy.

The goal of epithelioid sarcomas research has been to discover effective treatment options to improve patient outcomes. In the current era of precision medicine, chemotherapy or immunotherapy might be combined with targeted agents, or combinations of multiple targeted therapies may be used to prolong survival and provide a better quality of life by reducing toxicity. Immunotherapy has radically changed the oncology landscape, but the benefit in epithelioid sarcomas is yet to be conclusively proven. Identifying specific immune biomarkers to enrich for patients more likely to benefit or discovering alternative pathways of immune suppression may help develop new drugs for this type of disease.

There is a need for further research focusing on finding new targets and effective therapies. Furthermore, we need to identify and validate biomarkers for targeted agents such as

tazemetostat and immune markers to be able to identify patients who will most likely benefit from specific therapy and avoid exposure to the unnecessary toxicities of ineffective therapies. This is challenging in ES due to the rarity of this tumor type. Standard clinical trials in this field can be difficult to initiate and, therefore, are not attractive to pharmaceutical companies to maintain engagement. Often clinical trials include all soft tissue sarcomas, and the number of ES patients is not representative of the population. New adaptive designs and biomarker-driven clinical trials will help us evaluate new treatments more efficiently. International collaboration and database maintenance should be integrated to increase involvement in clinical trials and accelerate future research.

Declaration of interest

R Jones declares receipt of grants/research support from MSD, GlaxoSmithKline and receipt of Consultations fees from Adaptimmune, Astex, Athenex, Bayer, Boehringer Ingelheim, Blueprint, clinigen, Eisai, Epizme, Daiichi, Deciphera, Immunedesign, Immunicum, Karma Oncology, Lilly, Merck, Mundipharma, PharmaMar, Springworks, SynOx, Tracon, and UptoDate. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Magdalena Meissner http://orcid.org/0000-0001-5897-0219
Paul Huang http://orcid.org/0000-0003-3972-5087
Robin L Jones http://orcid.org/0000-0003-4173-3844

References

1. Enzinger FM. Epithelioid sarcoma. A sarcoma simulating a granuloma or a carcinoma. Cancer. 1970 Nov;26(5):1029–1041. doi: 10.1002/1097-0142(197011)26:5<1029:AID-CNCR2820260510>3.0.CO;2-R
2. Ziegler A, Vens M. Generalized estimating equations. notes on the choice of the working correlation matrix. Methods Inf Med. 2010;49(5):421–425. discussion 426-32. doi: 10.3414/ME10-01-0026
3. Rakheja D, Wilson KS, Meehan J, et al. "Proximal-type" and classic epithelioid sarcomas represent a clinicopathologic continuum: case report. Pediatr Dev Pathol. 2005 Jan;8(1):105–114.
4. Alves A, Constantinidou A, Thway K, et al. The evolving management of epithelioid sarcoma. Eur J Cancer Care (Engl). 2021 Nov;30(6):e13489.
5. Jawad MU, Extein J, Min ES, et al. Prognostic factors for survival in patients with epithelioid sarcoma: 441 cases from the SEER database. Clin Orthop Relat Res. 2009 Nov;467(11):2939–2948.
6. Ross HM, Lewis JJ, Woodruff JM, et al. Epithelioid sarcoma: clinical behavior and prognostic factors of survival. Ann Surg Oncol. 1997 Sep;4(6):491–495.
7. Baratti D, Pennacchioli E, Casali PG, et al. Epithelioid sarcoma: prognostic factors and survival in a series of patients treated at a single institution. Ann Surg Oncol. 2007 Dec;14(12):3542–3551.
8. Livi L, Shah N, Paiar F, et al. Treatment of epithelioid sarcoma at the royal marsden hospital. Sarcoma. 2003;7(3–4):149–152. doi: 10.1080/13577140310001644760
9. Chase DR, Enzinger FM. Epithelioid sarcoma. diagnosis, prognostic indicators, and treatment. Am J Surg Pathol. 1985 Apr;9(4):241–263. doi: 10.1097/00000478-198504000-00001
10. Spillane AJ, Thomas JM, Fisher C. Epithelioid sarcoma: the clinicopathological complexities of this rare soft tissue sarcoma. Ann Surg Oncol. 2000 Apr;7(3):218–225. doi: 10.1007/BF02523657
11. Biegel JA, Zhou JY, Rorke LB, et al. Germ-line and acquired mutations of INI1 in atypical teratoid and rhabdoid tumors. Cancer Res. 1999 Jan 1;59(1):74–79.
12. Brenca M, Rossi S, Lorenzetto E, et al. SMARCB1/INI1 genetic inactivation is responsible for tumorigenic properties of epithelioid sarcoma cell line VAESBJ. Mol Cancer Ther. 2013 Jun;12(6):1060–1072.
13. Hornick JL, Dal Cin P, Fletcher CD. Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. Am J Surg Pathol. 2009 Apr;33(4):542–550. doi: 10.1097/PAS.0b013e3181882c54
14. Modena P, Lualdi E, Facchinetti F, et al. SMARCB1/INI1 tumor suppressor gene is frequently inactivated in epithelioid sarcomas. Cancer Res. 2005 May 15;65(10):4012–4019. doi: 10.1158/0008-5472.CAN-04-3050
15. Wang X, Haswell JR, Roberts CW. Molecular pathways: sWI/SNF (BAF) complexes are frequently mutated in cancer–mechanisms and potential therapeutic insights. Clin Cancer Res. 2014 Jan 1;20(1):21–27. doi: 10.1158/1078-0432.CCR-13-0280
16. Jagani Z, Mora-Blanco EL, Sansam CG, et al. Loss of the tumor suppressor snf5 leads to aberrant activation of the hedgehog-gli pathway. Nat Med. 2010 Dec;16(12):1429–1433.
17. Mora-Blanco EL, Mishina Y, Tillman EJ, et al. Activation of β-catenin /TCF targets following loss of the tumor suppressor SNF5. Oncogene. 2014 Feb 13;33(7):933–938. doi: 10.1038/onc.2013.37
18. Phelan ML, Sif S, Narlikar GJ, et al. Reconstitution of a core chromatin remodeling complex from SWI/SNF subunits. Mol Cell. 1999 Feb;3(2):247–253.
19. Wilson BG, Wang X, Shen X, et al. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. Cancer Cell. 2010 Oct 19;18(4):316–328. doi: 10.1016/j.ccr.2010.09.006
20. Rasmussen SV, Jin JX, Bickford LR, et al. Functional genomic analysis of epithelioid sarcoma reveals distinct proximal and distal subtype biology. Clin Transl Med. 2022 Jul;12(7):e961.
21. Frezza AM, Sigalotti L, Savio ED, et al. Epitheliod sarcoma: molecular insights into proximal versus classic variant. J Clin Oncol. 2020;38(15_suppl):e23552–e23552. doi: 10.1200/JCO.2020.38.15_suppl.e23552
22. Kato H, Hatori M, Kokubun S, et al. CA125 expression in epithelioid sarcoma. Jpn J Clin Oncol. 2004 Mar;34(3):149–154.
23. Kawashima H, Hoshino M, Ogose A, et al. CA125 expression in epithelioid sarcoma: production and secretion by epithelioid sarcoma cells in vitro and clinical feature. Cancer Res. 2008;68(9_Supplement):2191–2191.
24. Haas RL, Delaney TF, O'Sullivan B, et al. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? Int J Radiat Oncol Biol Phys. 2012 Nov 1;84(3):572–580. doi: 10.1016/j.ijrobp.2012.01.062
25. Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. Radiother Oncol. 2005 Apr;75(1):48–53.
26. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002 Jun 29;359(9325):2235–2241. doi: 10.1016/S0140-6736(02)09292-9
27. Bogani G, Fucà G, Maltese G, et al. Efficacy of adjuvant chemotherapy in early stage uterine leiomyosarcoma: a systematic review and meta-analysis. Gynecol Oncol. 2016 Nov;143(2):443–447.
28. Frezza AM, Jones RL, Lo Vullo S, et al. Anthracycline, gemcitabine, and pazopanib in epithelioid sarcoma: a multi-institutional case series. JAMA Oncol. 2018 Sep 1;4(9):e180219. doi: 10.1001/jamaoncol.2018.0219
29. Jones RL, Constantinidou A, Olmos D, et al. Role of palliative chemotherapy in advanced epithelioid sarcoma. Am J Clin Oncol. 2012 Aug;35(4):351–357.

30. Touati N, Schöffski P, Litière S, et al. European organisation for research and treatment of cancer soft tissue and bone sarcoma group experience with advanced/metastatic epithelioid sarcoma patients treated in prospective trials: clinical profile and response to systemic therapy. Clin Oncol. 2018 Jul;30(7):448–454. R Coll Radiol. doi: 10.1016/j.clon.2018.02.065
31. Pink D, Richter S, Gerdes S, et al. Gemcitabine and docetaxel for epithelioid sarcoma: results from a retrospective, multi-institutional analysis. Oncology. 2014;87(2):95–103. doi: 10.1159/000362602
32. Gounder MM, Merriam P, Ratan R, et al. Real-world outcomes of patients with locally advanced or metastatic epithelioid sarcoma. Cancer. 2021 Apr 15;127(8):1311–1317. doi: 10.1002/cncr.33365
33. Anderson SE, Keohan ML, D'Adamo DR, et al. A retrospective analysis of vinorelbine chemotherapy for patients with previously treated soft-tissue sarcomas. Sarcoma. 2006;2006:15947. doi: 10.1155/SRCM/2006/15947
34. Tariq Z, Ghose A, Bawany MZ, et al. A case report of complete remission of pulmonary metastases from epithelioid sarcoma to navelbine chemotherapy. Am J Ther. 2012 Mar;19(2):e95–7.
35. Gounder M, Schöffski P, Jones RL, et al. 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.
36. Stacchiotti S, Schoffski P, Jones R, et al. Safety and efficacy of tazemetostat, a first-in-class EZH2 inhibitor, in patients (pts) with epithelioid sarcoma (ES) (NCT02601950). J Clin Oncol. 2019;37(15_suppl):11003–11003. doi: 10.1200/JCO.2019.37.15_suppl.11003
37. Nakamura T, Matsumine A, Kawai A, et al. The clinical outcome of pazopanib treatment in Japanese patients with relapsed soft tissue sarcoma: a Japanese musculoskeletal oncology group (JMOG) study. Cancer. 2016 May 1;122(9):1408–1416. doi: 10.1002/cncr.29961
38. Irimura S, Nishimoto K, Kikuta K, et al. Successful treatment with pazopanib for multiple lung metastases of inguinal epithelioid sarcoma: a case report. Case Rep Oncol. 2015 Sep;8(3):378–384.
39. Schuetze SM, Bolejack V, Choy E, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. Cancer. 2017 Jan 1;123(1):90–97. doi: 10.1002/cncr.30379
40. Penot P, Bouaziz JD, Battistella M, et al. Stabilization of multiple metastatic epithelioid sarcoma under treatment with sunitinib malate. Br J Dermatol. 2013 Apr;168(4):871–873.
41. Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1-2 trial. Lancet Oncol. 2020 Jan;21(1):121–133.
42. Paoluzzi L, Cacavio A, Ghesani M, et al. Response to anti-PD1 therapy with nivolumab in metastatic sarcomas. Clin Sarcoma Res. 2016;6(1):24. doi: 10.1186/s13569-016-0064-0
43. D'Angelo SP, Mahoney MR, Van Tine BA, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol. 2018 Mar;19(3):416–426.
44. Pecora A, Halpern S, Weber M, et al. Rapid and complete response to combination anti-ctla-4 and anti-pd-1 checkpoint inhibitor therapy in a patient with stage iv refractory end-stage epithelioid sarcoma: a case report. J Immunother. 2020 Nov;43(9):286–290.
45. Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. Lancet Oncol. 2019 Jun;20(6):837–848.
46. Martin-Broto J, Hindi N, Grignani G, et al. Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial. J Immunother Cancer. 2020 Nov;8(2):e001561.
47. D'Angelo SP, Shoushtari AN, Keohan ML, et al. Combined KIT and CTLA-4 blockade in patients with refractory gist and other advanced sarcomas: a phase ib study of dasatinib plus ipilimumab. Clin Cancer Res. 2017 Jun 15;23(12):2972–2980. doi: 10.1158/1078-0432.CCR-16-2349
48. Imura Y, Yasui H, Outani H, et al. Combined targeting of mTOR and c-MET signaling pathways for effective management of epithelioid sarcoma. Mol Cancer. 2014 Aug 7;13(1):185. doi: 10.1186/1476-4598-13-185
49. Xie X, Ghadimi MP, Young ED, et al. Combining EGFR and mTOR blockade for the treatment of epithelioid sarcoma. Clin Cancer Res. 2011 Sep 15;17(18):5901–5912. doi: 10.1158/1078-0432.CCR-11-0660
50. Cascio MJ, O'Donnell RJ, Horvai AE. Epithelioid sarcoma expresses epidermal growth factor receptor but gene amplification and kinase domain mutations are rare. Mod Pathol. 2010 Apr;23(4):574–580. doi: 10.1038/modpathol.2010.2
51. Sakharpe A, Lahat G, Gulamhusein T, et al. Epithelioid sarcoma and unclassified sarcoma with epithelioid features: clinicopathological variables, molecular markers, and a new experimental model. Oncology. 2011;16(4):512–522. doi: 10.1634/theoncologist.2010-0174
52. Ino Y, Gotoh M, Sakamoto M, et al. Dysadherin, a cancer-associated cell membrane glycoprotein, down-regulates E-cadherin and promotes metastasis. Proc Natl Acad Sci U S A. 2002 Jan 8;99(1):365–370. doi: 10.1073/pnas.012425299
53. Izumi T, Oda Y, Hasegawa T, et al. Prognostic significance of dysadherin expression in epithelioid sarcoma and its diagnostic utility in distinguishing epithelioid sarcoma from malignant rhabdoid tumor. Mod Pathol. 2006 Jun;19(6):820–831.
54. Bum-Erdene K, Yeh IJ, Gonzalez-Gutierrez G, et al. Small-molecule cyanamide pan-tead·yap1 covalent antagonists. J Med Chem. 2023 Jan 12;66(1):266–284. doi: 10.1021/acs.jmedchem.2c01189
55. Forrest SJ, Al-Ibraheemi A, Doan D, et al. Genomic and immunologic characterization of ini1-deficient pediatric cancers. Clin Cancer Res. 2020 Jun 15;26(12):2882–2890. doi: 10.1158/1078-0432.CCR-19-3089
56. Boxberg M, Steiger K, Lenze U, et al. PD-L1 and PD-1 and characterization of tumor-infiltrating lymphocytes in high grade sarcomas of soft tissue - prognostic implications and rationale for immunotherapy. Oncoimmunology. 2018;7(3):e1389366. doi: 10.1080/2162402X.2017.1389366
57. Kim C, Kim EK, Jung H, et al. Prognostic implications of PD-L1 expression in patients with soft tissue sarcoma. BMC Cancer. 2016 Jul 8;16(1):434. doi: 10.1186/s12885-016-2451-6
58. Ohm JE, Gabrilovich DI, Sempowski GD, et al. VEGF inhibits T-cell development and may contribute to tumor-induced immune suppression. Blood. 2003 Jun 15;101(12):4878–4886. doi: 10.1182/blood-2002-07-1956
59. Aspeslagh S, Morel D, Soria JC, et al. Epigenetic modifiers as new immunomodulatory therapies in solid tumours. Ann Oncol. 2018 Apr 1;29(4):812–824. doi: 10.1093/annonc/mdy050
60. Qiu J, Sharma S, Rollins RA, et al. The complex role of EZH2 in the tumor microenvironment: opportunities and challenges for immunotherapy combinations. Future Med Chem. 2020 Aug;12(15):1415–1430.
61. Zingg D, Arenas-Ramirez N, Sahin D, et al. The histone methyltransferase ezh2 controls mechanisms of adaptive resistance to tumor immunotherapy. Cell Rep. 2017 Jul 25;20(4):854–867. doi: 10.1016/j.celrep.2017.07.007
62. Zhou L, Mudianto T, Ma X, et al. Targeting EZH2 enhances antigen presentation, antitumor immunity, and circumvents anti-pd-1 resistance in head and neck cancer. Clin Cancer Res. 2020 Jan 1;26(1):290–300. doi: 10.1158/1078-0432.CCR-19-1351
63. Morel KL, Sheahan AV, Burkhart DL, et al. EZH2 inhibition activates a dsRNA-STING-interferon stress axis that potentiates response to PD-1 checkpoint blockade in prostate cancer. Nat Cancer. 2021 Apr;2(4):444–456.