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ASO PERSPECTIVES

NIRO or No-go? Positioning a Novel Systemic Treatment Option for Desmoid Tumours

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Desmoid tumours (DT), also known as aggressive fibromatosis, are locally aggressive tumours with no known potential for metastases or dedifferentiation. Although they lack the capacity to establish metastases, desmoids are locally aggressive and have a high rate of recurrence even after complete resection. In the recent years, data have been provided about the natural course of the disease and a paradigm shift towards a more conservative approach has taken place. Active surveillance has become the initial strategy in the management of DT.[1–3] Only some 30-40% of patients with sporadic DT experience persistent progression and pain and need an active therapy, whereas a much greater proportion of FAP associated DT are to be actively treated for the less indolent natural course.

Systemic therapy has increasingly been adopted in patients with progressing DT or for management of intra-abdominal DT for which local therapy options may cause unacceptable morbidity. Beside nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal therapy, whose activity has never been really proven in retrospective/prospective studies, systemic chemotherapies have long remained the only effective treatment for this disease (Table 1).[4–10] More recently, systemic therapies in the form of tyrosine-kinase inhibitors, such as Imatinib initially, but with limited activity,[11–14] and sorafenib[15] and pazopanib[16] afterwards with a good balance between favourable treatment response and acceptable side effects profile, have also been adopted (Table 2). However, despite this, there are presently no evidence-based or consensus-based guidelines as to the appropriate sequence of agents for systemic therapy. The initial choice of therapy depends on several factors, including but not limited to: (i) the urgency of the clinical situation, (ii) tumour location, and (iii) the preference of the patient.[1]

Nirogacestat, an investigational oral, selective, small molecule gamma secretase inhibitor (GSI) that targets the Notch pathway,[17] has been recently evaluated in a phase 3 trial, DeFi, for adults with progressing desmoid tumours. The positive results of this study, initially presented at the European Society of Medical Oncology (ESMO) Annual Congress in 2022[18] and now published in full,[19] were awaited with great excitement offering symptomatic/progressing patients another option in the treatment of their disease. Compared with placebo, Gounder and colleagues were able to show that Niro offered significant reduction in risk of disease progression (hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.15–0.55; $p < 0.001$) and rates of objective response (41 vs. 8%; $p < 0.001$).[19] Moreover, improvement in symptomatology as registered by objectively validated scales were observed early and sustained in patients treated with nirogacestat as opposed to placebo. Whilst no head-to-head comparison was made with contemporary treatment options, results of this trial compare favourably to other agents studied and/or approved in this disease (Tables 1, 2) and—given its favourable toxicity profile—it may well become the first-line treatment in the management of the disease.

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TABLE 1 Results of selected clinical trials/reports on cytotoxics in treatment of desmoid tumours

Publication	*N*	Treatment	Planned dose	Duration of treatment	Response	Duration of response (mo)
de Camargo et al.[7]	6	Doxorubicin	NR	NR	3 PR	NR
de Camargo et al.[7]	22	Pegylated liposomal doxorubicin	NR	NR	3 PR 1 SD	9–40 months of follow-up with no progression seen
Constantinidou et al.[8]	12	Pegylated liposomal doxorubicin	40–50 mg/m^2 Q4weeks	Up to 6 months	4 PR 10 SD	9–45
Palassini et al.[9]	75	Methotrexate + vinorelbine	Methotrexate 30 mg/m^2 + vinorelbine 20 mg/m^2 weekly	38 cycles over 13.9 months	1 CR 35 PR 38 SD 1 PD	52–145 months
Skapek et al.[10]	26	Methotrexate + vinorelbine	Methotrexate 30 mg/m^2 + vinblastine 5 mg/m^2 weekly	2.5 to 12 (median 10 months)	1 CR 4 PR, 3 MR 10 SD, 8 PD	2.1–71

N number of patients; *NR* not reported; *PR* partial response; *SD* stable disease; *CR* complete response; *MR* minor response

TABLE 2 Selected results of tyrosine-kinase inhibitor and gamma-secretase inhibitor clinical trials in desmoid tumours

Publication	*N*	Treatment	Comparator (if any)	Dosage (daily total)	Duration of treatment	ORR (%)	6 months PFS (%)	12 months PFS (%)	24 months PFS (%)
Heinrich et al.[11]	19	Imatinib	Nil	800 mg	325 days	16	53	37	NE
Penel et al.[12]	35	Imatinib	Nil	400 mg	1 year	11	80	67	55
Chugh et al.[13]	49	Imatinib	Nil	200–600 mg	Until PD	6	84	66	NE
Kasper et al.[14]	38	Imatinib	Nil	800 mg	2 years	19	65	59	45
Gounder et al.[15]	50	Sorafenib	Placebo	400 mg	Until PD	33	NE	89	81
Toulmonde et al.[16]	46	Pazopanib	Methotrexate-vinblastine	800 mg	1 year	37	84	86	67
Kummar et al.[17]	17	Nirogacestat	Nil	300 mg	Until PD	29	100	100	100
Kasper et al.[18, 19]	70	Nirogacestat	Placebo	300 mg	Until PD	41	NE	NE	NE

N number of patients; *ORR* objective response rate; *PFS* progression-free survival; *PD* disease progression; *NE* not evaluated

Of concern, however, is that 75% of women of child-bearing potential (27/36) assigned to Niro were observed to have ovarian dysfunction, defined as a composite adverse event associated with changes in female reproductive hormone levels and clinical manifestations. This issue is particularly important in this disease, which tends to afflict a younger population than other cancers. Whilst the physiological explanation of this remains uncertain, it does appear that in majority of cases ovarian dysfunction was temporary. Ovarian dysfunction resolved in all affected patients who discontinued nirogacestat for any reason (n = 11). Ovarian dysfunction also resolved spontaneously in 64% of patients (9 of 15 patients) whose treatment with nirogacestat was still ongoing at time of reporting. Further studies will need to be performed for us to better understand whether there are potentially any medium to long-

term impacts of ovarian dysfunction in relation to say cardiovascular or bone health, let alone the implications of this on issues pertaining to family planning. Finally, no long-term data about the possible side effects of this class of drugs are presently available and this remains a concern in a disease, which is mostly not fatal.

Clouding the above is of course the unknown factor of optimal duration of therapy. Albeit the local aggressiveness, it remains a disease with no metastatic potential, The natural history is variable and spontaneous regressions are also seen. Presently, there is no clear consensus on the optimal duration of treatment. In prior trials with low dose metronomic chemotherapy the treatment was planned for a maximum of 24 months. In more contemporary clinical practice with tyrosine kinase inhibitors, such as sorafenib and pazopanib, we continue to experiment with how long a patient requires the drug to achieve optimal disease control. The approach of treat until treatment plateau and reinstitution of treatment upon symptomatic progression is commonly employed by most colleagues in the field. However, given the lack of data on long-term toxicity of the chronic administration of this class of drugs, one may well speculate that the longer the treatment the higher the risk of developing unpredictable side effects (the risk of permanent infertility included). Ideally, a trial incorporating randomised discontinuation upon treatment plateau and rechallenge at subsequent progression should be considered, like what was done with GIST some years ago.[20]

Finally, positive findings in a clinical trial and subsequent regulatory approval does not guarantee accessibility to treatment. Novel therapeutic agents, such as nirogacestat, may potentially be hampered by nonclinical or nonscientific factors, including the cost of treatment itself. These costs may be further amplified in treatments of longer durations, and, short of a randomized treatment discontinuation study, we are unable to ascertain what the most optimal treatment duration is. Moreover, as patients suffering from desmoids rarely die of the disease, the traditional metrics for health authorities to assess treatment utility, including Quantity-of-Life Years (QALY) gained, may not be clear cut. Interestingly, most of the systemic therapies being employed in desmoid tumours are not formally registered for this specific indication, as many of the agents were not originally designed with desmoid tumours in mind. Thus, it may very well be possible that on the contrary, while appropriate registration of a contemporary and effective treatment may finally be possible with these encouraging results, we may assist at the paradox of lack of reimbursement in countries with a social welfare if the price of the drug was set too high.

The DeFI trial[18,19] has confirmed that randomized studies are possible also in rare diseases and has proven strong clinical activity of nirogacestat in adults with desmoid, and most encouraging as this is a first-in-class compound. The most ideal positioning of nirogacestat in the treatment algorithm of desmoid tumours remains uncertain. A global consensus meeting is already planned in 2023 to update the current treatment recommendations.[1] What is certain is that systemic treatment for desmoids shall only be limited to patients who have disease progression, and initial close observation to assess the disease's trajectory both in terms of growth and symptoms in asymptomatic or minimally symptomatic patients remains the most appropriate treatment paradigm. During this period, reassurance, acknowledgement of patients' concurrent anxiety and distress is of paramount importance.

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