

Sarcoma

Oral presentations (Thu, 27 Sep, 09.00–11.00)

Sarcoma

7500

ORAL

Impact of independent review on efficacy outcomes in a randomised multicenter trial of trabectedin given by two dosing regimens in patients (pts) with progressing leiomyosarcomas or liposarcomas (L-sarcomas)

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Background: The efficacy of 2 trabectedin (T) IV regimens: 1.5 mg/m² 24h q3 wk (q3wk 24h) or 0.58 mg/m² 3h weekly for 3 of 4 wk (qwk 3h) was studied in an international trial of pts with L-sarcoma progressing despite prior therapy with at least anthracyclines and ifosfamide. Primary endpoint, time to progression (TTP), was assessed by study investigators (IA) and also by independent review (IR) which was the primary study analysis. Pts were restaged symmetrically every 8 wks in both arms.

Methods: To assess the impact of IR on TTP in this trial, a comprehensive comparison of IR vs IA assessments was conducted. IR was performed by an independent team using a predefined charter blinded to study arm: two radiologists independently evaluated images; if any discrepancy was noted, a 3rd radiologist adjudicated. Then a medical oncologist reviewed all assessments with predefined relevant clinical data to provide a final TTP date (event or censored) for each pt.

Results: 270 pts were randomised. In the protocol-specified primary analysis, TTP was significantly better for the q3wk 24h regime by both IA and IR. The reduction in the risk of progression was more profound per IA [HR: 0.668; p=0.005] vs IR [HR: 0.734; p=0.030]. There were slightly fewer TTP events per IR (206; 24% censored) vs IA (216; 20% censored). Overall the IR-IA concordance (event/censored) was 85%. TTP length (regardless of event/censored) was judged identical by IA and IR in 60% of pts, shorter per IR in 25% and longer per IR in 15% of pts. Full concordance (event/censored and TTP length) was reached in 53% of pts. Common discrepancies were: shorter TTP (event) by IR in 19%, longer TTP (censored) by IR in 10%; other discrepancies accounted for ≤5% each. TTP curves were superimposable in the qwk 3h arm despite IA-IR discrepancies. However, in the more efficacious q3wk 24h arm, TTP per IR was not significantly shorter than TTP per IA. Similar findings were seen for PFS.

Conclusions: Overall consistent TTP outcomes were observed with both T regimens between IA and IR. IR resulted in fewer TTP events and a slightly less profound reduction in risk of progression. The impact of IR on TTP reduction was only evident in the more efficacious q3wk 24h regime but did not result in loss of statistical significance for the benefit in TTP associated with T q3wk 24h. IR adds methodological strength and should be performed in large-scale clinical trials of sarcomas when TTP or PFS is the primary endpoint.

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ORAL

Continuous daily dosing (CDD) study of sunitinib malate (SU) in patients (pts) with advanced GIST compares favorably with intermittent dosing

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Background: SU is an oral, multitargeted tyrosine kinase inhibitor of KIT, PDGFRs, VEGFRs, RET, CSF-1R, and FLT3, approved multinationally for the treatment of imatinib-resistant/intolerant GIST. SU safety and efficacy has been demonstrated in a phase III trial using a regimen of 50 mg/d delivered in 6 wk cycles (4 wks on, followed by 2 wks off treatment; 4/2 schedule). This study evaluates the safety and efficacy of CDD of SU (37.5 mg) in pts with GIST after failure of imatinib.

Materials and Methods: 61 pts with imatinib-resistant/intolerant GIST were randomized to receive SU 37.5 mg once daily either in the morning (AM) or evening (PM) in this open-label, multicenter, phase II trial. The primary endpoint was clinical benefit rate (CBR), defined as percentage of patients with CR, PR, or SD ≥ 24 weeks per RECIST. Secondary endpoints included ORR, PFS, safety/tolerability measures and PK parameters. Investigator-assessed efficacy and safety data obtained from this study and the earlier phase III trial were compared informally.

Results: 60 of the 61 randomized pts received treatment with SU on the CDD schedule (30 pts per arm). After a median follow-up of 43 weeks (range: 4–66+), 17 pts remain on study, 11 pts have completed, and 33 have discontinued. AEs necessitated dose reduction to 25 mg in 9 pts. The most common non-hematologic AEs of any cause were diarrhea (42%), asthenia (38%), and fatigue (35%). Grade 3 AEs were asthenia (15%), fatigue (8%), and diarrhea (12%); grade 4 abdominal pain was reported in 5% of patients. Grade 3/4 hematologic AEs included neutropenia (13%), anemia (15%), and thrombocytopenia (3%). Toxicities were comparable between AM and PM dosing, and the AE profile from this trial was similar to that seen in the phase III trial. Preliminary PK data indicated no unexpected accumulation with CDD. To date, the median PFS is 34 weeks (CI: 25.1–40.2) with an overall CBR of 31%, including 11% of patients with PRs. Efficacy results from the phase III trial were comparable (PFS: 28 weeks [CI: 14–34]; CBR: 25%; PR: 7%; N=207).

Conclusions: In pts with imatinib-resistant/intolerant GIST, administration of SU at 37.5 mg CDD results in a similar safety/tolerability and efficacy profile as when administered at 50 mg/d on the 4/2 schedule, and appears to be a safe and effective alternative dosing strategy in pts with imatinib-resistant/intolerant GIST.

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ORAL

Assessment of plasma levels of soluble KIT (sKIT) as a potential surrogate marker for TTP in patients (pts) with advanced gastrointestinal stromal tumor (GIST) treated with sunitinib

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Background: A previous analysis from a phase I/II GIST trial suggested that a decline in plasma levels of sKIT may correlate with measures of clinical benefit in pts treated with sunitinib malate (SUTENT[®]; SU). SU is an oral multitargeted tyrosine kinase inhibitor of KIT, PDGFRs, VEGFRs, RET, CSF-1R, and FLT3, approved multinationally for the treatment of imatinib-resistant or -intolerant GIST and advanced renal cell carcinoma. In this study, using samples from of a previously reported phase III trial, changes in plasma levels of sKIT were evaluated as a potential surrogate marker for TTP in GIST pts treated with SU.

Materials and Methods: Pts in the original phase III trial were randomized in a 2:1 ratio to receive SU 50 mg (n=207) or placebo (n=105) daily in 6-wk cycles (4 wks on and 2 wks off treatment). The primary endpoint was TTP using RECIST. Samples for sKIT measurement were taken predose on days 1, 14, and 28 (cycle 1), and days 1 and 28 (cycles 2 and 3). Plasma sKIT levels were analyzed with performance-validated ELISA. Prentice Criteria, Cox models, and the Proportion of Treatment Effect (PTE) were used to analyze the results (PTE=1 is a perfect surrogate).

Results: After 4 wks (cycle 1 day 28) of treatment, 215 pts (SU 138, placebo 77) had matched pairs of baseline and on-study plasma samples for sKIT. At this timepoint, SU treatment was associated with a significant decrease in sKIT levels (P<0.0001). Decreases in sKIT levels were also found to be a significant predictor of longer TTP, compared with increases in sKIT levels (HR=0.53; 95% CI, 0.37–0.75; P=0.0003). The relationships between SU treatment and sKIT levels, and lowered sKIT levels and longer TTP, continued throughout the sampling period, including off-treatment periods. By the end of cycle 2 (161 pts [SU 121, placebo 40]), changes in sKIT levels replaced initial treatment group as a stronger indicator of TTP (PTE=0.62; HR=0.51; 95% CI, 0.38–0.69; P<0.0001), which continued through to the beginning of cycle 3 day 1 (143 pts [SU 102, placebo 41]; PTE=0.64; HR=0.42; 95% CI, 0.29–0.60; P<0.0001).

Conclusions: These preliminary results suggest that, after two cycles of SU treatment, circulating levels of sKIT appear to function as a surrogate marker for TTP in pts with imatinib-resistant GIST. Further studies are