NUC-3373, a targeted inhibitor of thymidylate synthase, in patients with advanced colorectal cancer

BACKGROUND

• CSCs: stem cell cancer
• Incidence: 1.8 million
• Annual deaths: 880,000
• 5-FU remains the cornerstone of treatment for CRC, despite having several limitations:
  - ProTide transformation of FUDR-MP4,5, the active anti-cancer metabolite of 5-FU:
    - NUC-3373: A targeted inhibitor of TS
  - MTD established (2,500 mg/m²)
  - Able to enter cells independently of nucleoside transporters
  - Resistant to breakdown by DPD

• RP2D
  - Heavily pre-treated patient population: 4 prior lines of therapy (range: 2-13)
  - Encouraging efficacy signals observed in heavily pretreated patient with BRCAF mutation (5 prior lines)
  - 28% reduction in fluoropyrimidine refractory patient (CAPOX: PD +35% in 2 months. FOLFIRI: PD in 1.5 months. NUC-3373: -28%; 5.1 months)

NuTide:302 Study

NuTide:302 Study

NuTide:302-A targeted inhibitor of TS

Patient characteristics (n=38)

- Age, years, median (range) 67 (23-91)
- ECOG (0/1) 19/19
- Female, n (%) 21 (55)
- Prior chemotherapy
  - S-FU, n (%) 38/100
  - Oxaliplatin, n (%) 38/100
  - Irinotecan, n (%) 38/100
  - Prior anti-angiogenic, n (%) 22 (58)
  - Prior EGFR inhibitor, n (%) 19 (50)

RESULTS (Part 1)

Patient characteristics (n=38)

- Maln, n (%) 21 (55)
- Female, n (%) 17 (42)
- ECOG (0/1) 19/19
- Age, years, median (range) 58 (23-70)
- Prior lines of therapy, median (range) 4.0 (1-5)
- No of metastatic sites, median (range) 2 (0-6)
- Liver involvement, n (%) 28 (74)
- Prior chemotherapy
  - S-FU, n (%) 38/100
  - Oxaliplatin, n (%) 38/100
  - Irinotecan, n (%) 38/100
- Prior anti-angiogenic, n (%) 22 (58)
- Prior EGFR inhibitor, n (%) 19 (50)

NUC-3373 has a favorable safety profile

- NUC-3373 is currently being investigated in combination with LV and either oxaliplatin or irinotecan in Part 2 of NuTide:302

CONCLUSION

• NUC-3373 is a targeted inhibitor of TS designed to overcome the key cancer resistance mechanisms associated with 5-FU
• NUC-3373 has a favorable safety profile with no FBAL (hand-foot syndrome) or FUTP (L or hepatic) toxicity associated Grade 3 or 4 AE's
• NUC-3373 has an attractive PK profile: long plasma half-life and high intracellular levels of FUDR-MP (active metabolite) compared to 5-FU
• Encouraging efficacy signals observed in heavily pre-treated CRC patients with NUC-3373
• NUC-3373 has the potential to offer enhanced efficacy, an improved safety profile and a more convenient dosing regimen compared to 5-FU
• NUC-3373 is currently being investigated in combination with LV and either oxaliplatin or irinotecan in Part 2 of NuTide:302
• A registrational study of NUC-3373 in 2L CRC patients (NuTide:323) is planned