Abstract TPS4185:
Phase II study on safety and efficacy of NMS-01940153E, an MPS1 inhibitor with first-in-class potential, in adult patients with unresectable hepatocellular carcinoma (HCC) previously treated with systemic therapy.

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Monopolar spindle 1 kinase (MPS1/TTK) Inhibitor NMS-01940153E (NMS-153) in HCC

MPS1 is overexpressed in HCC

Liu X et al., Oncotarget. 2015.

MPS1 is a selective inhibitor with long residence time

Reig M et al., EASL Liver Cancer Summit. 2023.

NMS-153 is highly active in HCC cell lines

Reig M et al., 34th EORTC-NCI-AACR Symposium. 2022.

High MPS1 expression associated with poor prognosis

Liu X et al., Oncotarget. 2015.
Countries and sites
Italy (2 sites), Spain (1 site)

Patient characteristics
12 patients treated, 11 Male (6 at each Dose Level)
- 50% with metastatic and 50% with locally advanced disease;
- 2 average prior therapies (1-3);
- 66% (8 patients) with increase in alpha-fetoprotein (AFP).

Safety
No G5 Drug related adverse events (DRAE)
- Manageble safety general profile;
- Most frequent any grade drug-related TEAEs was neutropenia (2/6 patients at 100 mg/m2/wk, all G≥3), recovery to G1 was 9.5d;
- MTD = 100 mg/m2/week.

PK
- The PK profiles of parent and metabolite showed an increase in exposure with the dose with approximately 4-day half-life for the parent drug;
- PK at the RP2D was in a meaningful, active range relative to preclinical predictions.

Efficacy
- Of 11 patients evaluable for efficacy, two (one for each dose level, 002 and 004) had confirmed investigator-assessed PRs with duration of 2.5 and 9.3 months; both discontinued treatment due to PD at 6.5 and 11.1 months from treatment start, respectively.
- Two further patients (003 and 007), one for each dose level, had durable SDs, one progressing after 10.9 months from treatment initiation, and one still on treatment 26.5 months after enrollment. Three patients, two with PR and one with SD, showed AFP decrease.

* Reig M et al., 34th EORTC-NCI-AACR Symposium. 2022.
Phase II study on safety and efficacy of NMS-01940153E, an MPS1 inhibitor with first-in-class potential, in adult patients with unresectable HCC previously treated with systemic therapy

**Background**

- MPS1 plays a pivotal role in HCC: MPS1 is overexpressed in HCC and its overexpression correlates with higher tumor grade, large tumor size, lower patient survival and with the presence of the portal vein tumor thrombus (PVTT);
- Cell lines harboring activating mutations in the CTNNB1 gene (present in about 30% of HCC tumors), are highly sensitive to MPS1i;
- NMS-01940153E for anti-proliferation in HCC cell lines relative to standard-of-care TKIs and promising combinability;
- Phase I MPSA-153-001 showed clinical activity in HCC, including two confirmed PRs. Safety features were reasonable, with manageable and reversible neutropenia as the most frequent any grade TRAE.

**Study design**

Reig M et al., J Hepatol. 2022.
Phase II study on safety and efficacy of NMS-01940153E, an MPS1 inhibitor with first-in-class potential, in adult patients with unresectable HCC previously treated with systemic therapy

**Main Objectives**

- The primary objective is to assess the antitumor activity of NMS-153 in adult patients with unresectable HCC previously treated with systemic therapy measured as objective response rate (ORR) by investigator-assessed RECIST 1.1.
- Secondary endpoints are safety, PK, ORR as measured by investigator-assessed mRECIST, DoR, PFS and OS. Exploratory endpoints include biomarkers assessment on cfDNA.

**Main Eligibility Criteria**

- Diagnosis of HCC;
- Measurable disease;
- Disease progression on standard-of-care treatment including an immune checkpoint inhibitor as first line and at least one TKI;
- No more than 3 prior systemic treatment lines.

**General Design**

- Exploratory two-stage study with an interim analysis for futility and safety rules for unacceptable toxicity;
- NMS-01940153E is administered IV at the RP2D of 100 mg/m²/wk, which showed PK in a predicted active range;
- Interim evaluation for futility will be undertaken as soon as the first 10 evaluable patients will be enrolled;
- An independent DSMB will review the interim results and provide recommendation on the study progress.

**Countries**

- Italy, Spain and USA