A Multicenter, Open-Label, Phase 2 Study of nab-Sirolimus (HB1901) + Endocrine Therapy in HR+/HER2- Advanced Breast Cancer Following Standard Therapy Failure

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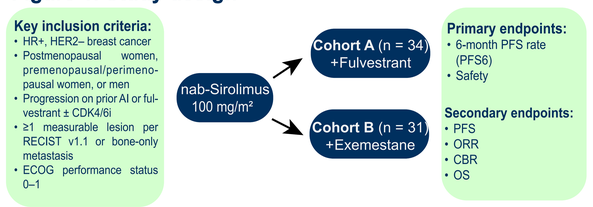
Introduction

- The hyperactivation of the PI3K/AKT/mTOR signaling pathway is regarded as an important mechanism for endocrine therapy and CDK4/6 inhibitor (CDK4/6i) resistance in HR+/HER2- advanced breast cancer.
- nab-Sirolimus (HB1901), a targeted mTOR inhibitor formulated as sirolimus albumin-bound nanoparticles, enhances the solubility of the poorly water-soluble drug and improves its bioavailability compared to conventional sirolimus.
- This trial aimed to investigate its anti-tumor efficacy and safety combined with endocrine therapy in patients following progression on/after CDK4/6i based regimen.
- This poster primarily presents updates on the impact of PI3K/AKT/mTOR pathway mutations on the efficacy of nab-Sirolimus + fulvestrant treatment.

Methods and Materials

- This phase 2 trial enrolled patients with HR+/HER2- advanced BC who had failed aromatase inhibitor (AI)/fulvestrant ± CDK4/6i.
- Patients failing prior AI ± CDK4/6i received nab-Sirolimus + fulvestrant, while those failing fulvestrant ± CDK4/6i received nab-Sirolimus + Exemestane (Figure 1).

Figure 1. Study design



Results

- At data cut-off (May 31, 2025), 65 patients were enrolled (Table 1), of whom 60 patients were efficacy-evaluable，with a median follow-up time of 9.1 months,.
- Among 60 efficacy-evaluable patients, the ORR was 20% (Table 2).
- In the nab-Sirolimus + fulvestrant cohort, 11 efficacy-evaluable patients with PIK3CA/AKT1/PTEN alteration showed improved activity: a median PFS of 9.1 months (Figure 2), and ORR of 27.3% (Table 3).

Table 1. Baseline demographics and clinical characteristics

	nab-Sirolimus + Fulvestrant (N=34)	nab-Sirolimus + Exemestane (N=31)	In Total (N=65)
Age (years)	53.5 (39, 72)	54.0 (31, 71)	54.0 (31, 72)
Female	34 (100)	30 (96.8)	64 (98.5)
Pre- or Peri- menopausal	15 (44.1)	7 (22.6)	22 (33.8)
Postmenopausal	19 (55.9)	23 (74.2)	42 (64.6)
Prior Systemic Therapy			
1 line	9 (26.5)	2 (6.5)	11 (16.9)
2 line	18 (52.9)	12 (38.7)	30 (46.2)
≥3 lines	7 (20.6)	17 (54.8)	24 (36.9)
PIK3CA/AKT1/PTEN Mutant	11 (32.3)	13(41.9)	24(36.9)
ECOG Score ≥1	18 (52.9)	21 (67.7)	39 (60.0)
Prior CDK4/6i Treatment	34 (100)	30 (96.8)	64 (98.5)
CDK4/6i ≥12 months	24 (70.6)	16 (51.6)	40 (61.5)
CDK4/6i <12 months	10 (29.4)	14 (45.2)	24 (36.9)
No	0	1 (3.2)	1 (1.5)
Visceral Metastasis	27 (79.4)	24 (77.4)	51 (78.5)
Liver Metastasis	11 (32.4)	15 (48.4)	26 (40.0)

Table 2. Tumor response of whole efficac-evaluable patients

	nab-Sirolimus + Fulvestrant (N=31)	nab-Sirolimus + Exemestane (N=29)	In Total (N=60)
Best overall response			
Complete response	0	0	0
Partial reponse	9 (29%)	3 (10.3%)	12 (20%)
Stable disease	20 (64.5%)	21 (72.4%)	41 (68.3%)
Progressive disease	1 (3.2%)	4 (13.8%)	5 (8.3%)
Overall response rate	9 (29%)	3 (10.3%)	12 (20%)
Disease control rate	29 (93.5%)	24 (82.8%)	53 (88.3%)
Clinical benefit rate	14 (45.2%)	6 (20.7%)	20 (33.3%)
Duration of response	3.3 (2.40, -)	5.4 (-, -)	3.6 (2.53, -)

Table 3. Tumor response in nab-Sirolimus + fulvestrant cohort

	nab-Sirolimus + Fulvestrant	
	Mutant (N=11)	Wild-type (N=20)
Best overall response		
Complete response	0	0
Partial reponse	3 (27.3)	6 (30.0)
Stable disease	8 (72.7)	12 (60.0)
Progressive disease	0	1 (5.0)
Overall response rate	3 (27.3)	6 (30.0)
Disease control rate	11 (100.0)	18 (90.0)
Clinical benefit rate	8 (72.7)	13 (65.0)

Data are presented as median (range) or n (%).

- PFS6 in the nab-Sirolimus + fulvestrant cohort: 58.3%
- PFS6 in the nab-Sirolimus + exemestane cohort: 39.9%
- PFS6 of patients with PI3K/AKT/mTOR mutant in the nab-Sirolimus + fulvestrant cohort: 70.1% (Figure 2)
- PFS6 of patients with PI3K/AKT/mTOR wild-type in the nab-Sirolimus + fulvestrant cohort: 52.6% (Figure 2)

Figure 2. Kaplan-Meier plots of progression-free surviavl in nab-Sirolimus + fulvestrant cohort

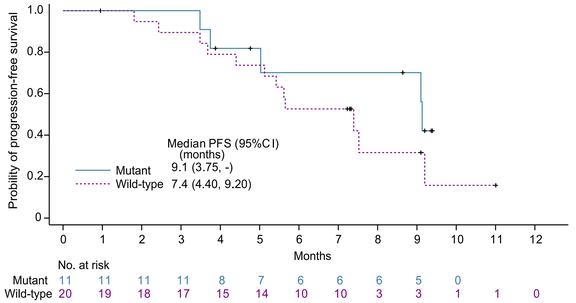
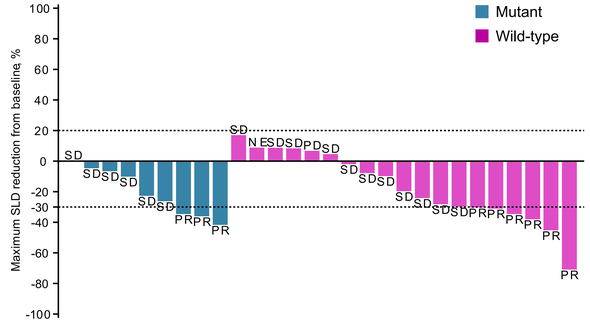


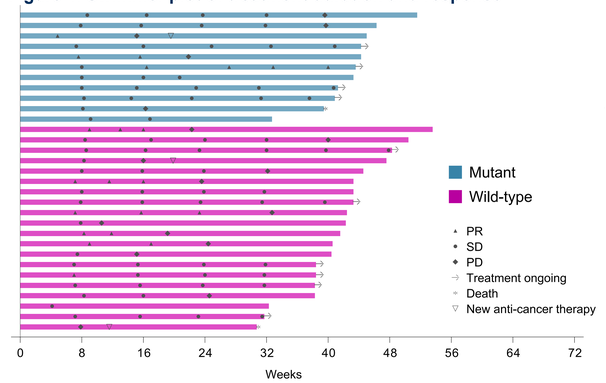
Figure 3. Waterfall plot of best change from baseline in nab-Sirolimus + fulvestrant cohort



Note: Five subjects were not included in the analysis due to the absence of post-baseline tumor assessments by the analysis cut-off date.

- Duration of exposure in the PI3K/AKT/mTOR mutant or wild-type population in the nab-Sirolimus + fulvestrant cohort is shown in Figure 4.

Figure 4. Swimmer plot of treatment duration and response



- Treatment related adverse events (TRAEs) of any grade occur in 64 (98.5%) of 65 patients, in which 26 (40%) were ≥ grade 3 (Table 3).
- One patient in the nab-Sirolimus + fulvestrant cohort occured adverse event in permanent treatment discontinuation.
- No drug-related events leading to death occurred.

Table 4. At least one CTCAE Grade ≥3 sirolimus treatment-related adverse event (incidence >5%).

Event,n(%)	nab-Sirolimus + Fulvestrant (N=34)	nab-Sirolimus + Exemestane (N=31)	In Total (N=65)
Any	13 (38.2)	13 (41.9)	26 (40.0)
Hypokalemia	8 (23.5)	3 (9.7)	11 (16.9)
Hypertriglyceridemia	5 (14.7)	2 (6.5)	7 (10.8)
Hyperglycemia	0	2 (6.5)	2 (3.1)
Decreased neutrophil count	1 (2.9)	2 (6.5)	3 (4.6)

Results

- Nab-sirolimus exhibited manageable toxicity and promising antitumor activity, particularly when combined with fulvestrant (achieving an ORR of 29% and a median PFS of 7.5 months).
- Nab-sirolimus + fulvestrant showed good efficacy in both PIK3CA/AKT1/PTEN altered and wild-type HR+ breast cancer patients.
- This novel mTOR inhibitor-based regimen may address the unmet need in CDK4/6i-failed HR+/HER2- advanced breast cancer.

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