A Phase 2 Study of Pracinostat and Azacitidine in Elderly Patients with Acute Myeloid Leukemia (AML) Not Eligible for Induction Chemotherapy: Response and Long-Term Survival Benefit

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Abstract #100

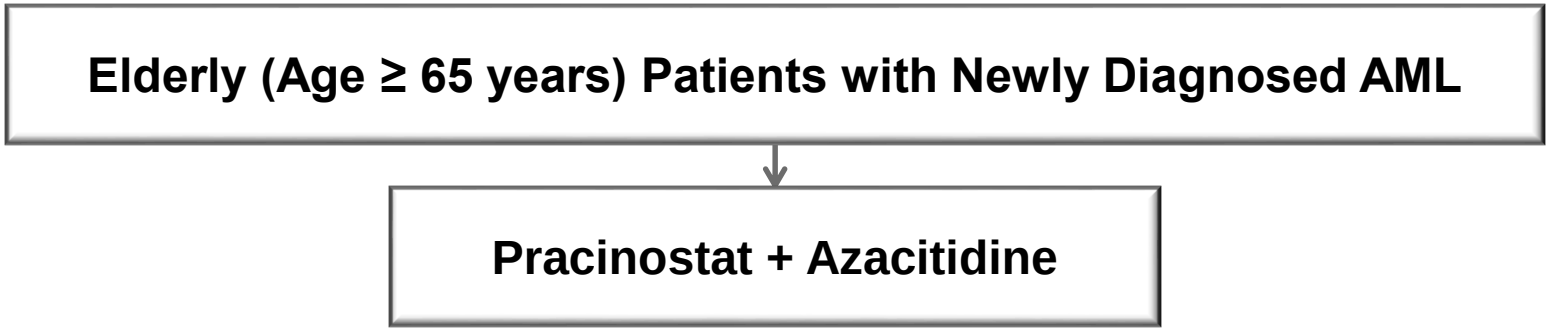
Pracinostat + Azacitidine Introduction

- AML patients deemed unsuitable for intensive induction therapy (age and/or co-morbidities) have limited treatment options
- Pracinostat is a potent hydroxamic acid based oral HDAC inhibitor selective for class I, II and IV isoforms
- In a Phase I study, pracinostat resulted in 1 CR, 1 PR, and 10 SD in 15 patients with AML evaluable for response‡
- In the Phase III study in AML patients ≥ 65 years, azacitidine resulted in a CR rate of 19.5%, median survival of 10.4 months, and 1-year survival of 46.5%
- HDAC inhibitors and azacitidine synergistic *in vitro**
- This study was the first to evaluate the combination of pracinostat and azacitidine in AML

‡ *Garcia-Manero et al. ASH 2010;abstract #3292*

* *Schneider-Stock et al. Idrugs 2007;10:557-561*

Pracinostat + Azacitidine in AML: Study Design



- 50 patients enrolled at 15 sites in the U.S.
- Primary endpoint: CR + CRi + MLFS
  - Response assessments at end of Cycle 1 and 2, then every other cycle until CR achieved or as indicated
- Secondary endpoints
  - Overall response rate (ORR), cytogenetic CR, duration of response
  - Overall survival (OS)
  - Safety & tolerability

CRi = Complete remission with incomplete blood count recovery
MLFS = Morphologic leukemia-free state (i.e., marrow CR)

Main Eligibility Criteria

- Key Inclusion
  - Age ≥65 years
  - Newly diagnosed *de novo*, secondary, or treatment-related AML
  - Intermediate or unfavorable-risk cytogenetics by SWOG classification*
  - ≥ 20% bone marrow blasts
  - ECOG performance 0-2
- Key Exclusion
  - Acute promyelocytic leukemia (FAB M3); t(15;17), t(8;21), t(16;16), del(16q), or inv(16) karyotype
  - Candidate for intensive chemotherapy within the next 4 months
  - Active CNS disease

** Slovak et al. Blood 2000:96;4075-4083*

Treatment Regimen

- Azacitidine 75 mg/m^2 IV/SC daily x 7 days
- Pracinostat 60 mg orally 3 days/week (e.g., M, W, F) x 3 weeks
- Cycles repeated every 28 days
- Dose Modifications
  - Dose reductions
    - Azacitidine for myelosuppression (↓ by 25% from starting dose)
    - Pracinostat for non-hematologic toxicity (↓ by 25% from starting dose)
  - Dose delays (between or within cycles)
    - ≥Grade 3 hematologic toxicity in the absence of disease
    - ≥Grade 3 non-hematologic toxicity despite supportive medical treatment

Demographics and Disease Characteristics

	N = 50
Age	
Median (range), years	75 (66-84)
No. (%) age ≥ 75 years	26 (52%)
Bone Marrow Blasts	
Median (range)	40% (20-89%)
Gender, Male	29 (58%)
ECOG Performance Status 0-1	42 (84%)
AML Presentation	
De novo	33 (66%)
Secondary to MDS, MPN, or prior chemo/radiotherapy	17 (34%)
Cytogenetic risk group	
Intermediate	27 (54%)
Cytogenetically normal Cytogenetically abnormal	21 (42%) 6 (12%)
Poor*	21 (42%)
Not classified	2 (4%)

**Poor risk defined using SWOG definition, and included: Del(5q)/-5, -7/del(7q), abnormal 3q, 9q, 20q, 17p, t(6;9), t(9;22) and complex karyotypes (≥ 3 unrelated abnormalities)*

Patient Disposition

- Enrollment from December 2013 to November 2014
- Analysis as of October 15, 2016
- Minimum follow-up: 22 months

	N=50
Number of patients alive	16 (32%)
Number of patients continuing on study therapy	5 (10%)
Number of patients discontinued	45 (90%)
Reasons for discontinuation:	
Progressive Disease	21 (42%)
Adverse Event	14 (28%)
Patient decision	7 (14%)
Investigator decision	3 (6%)

Treatment Emergent Adverse Events in ≥25% of Patients

	All Grades (%)	Grades 3-4 (%)
Hematologic		
Febrile Neutropenia	24 (48)	22 (44)
Thrombocytopenia	23 (46)	23 (46)
Neutropenia	19 (38)	19 (38)
Anemia	19 (38)	15 (30)
Non-Hematologic		
Nausea	39 (78)	3 (6)
Constipation	35 (70)	0
Fatigue	31 (62)	17 (34)
Decreased Appetite	28 (56)	6 (12)
Diarrhea	25 (50)	2 (4)
Vomiting	20 (40)	1 (2)
Cough	18 (36)	0
Dyspnea	17 (34)	1 (2)
Hypokalemia	17 (34)	1 (2)
Edema Peripheral	17 (34)	0
Pyrexia	17 (34)	0
Dizziness	16 (32)	0
Back Pain	14 (28)	3 (6)
Insomnia	14 (28)	0

- **30-day mortality: 2%**
- **60-day mortality: 10%**

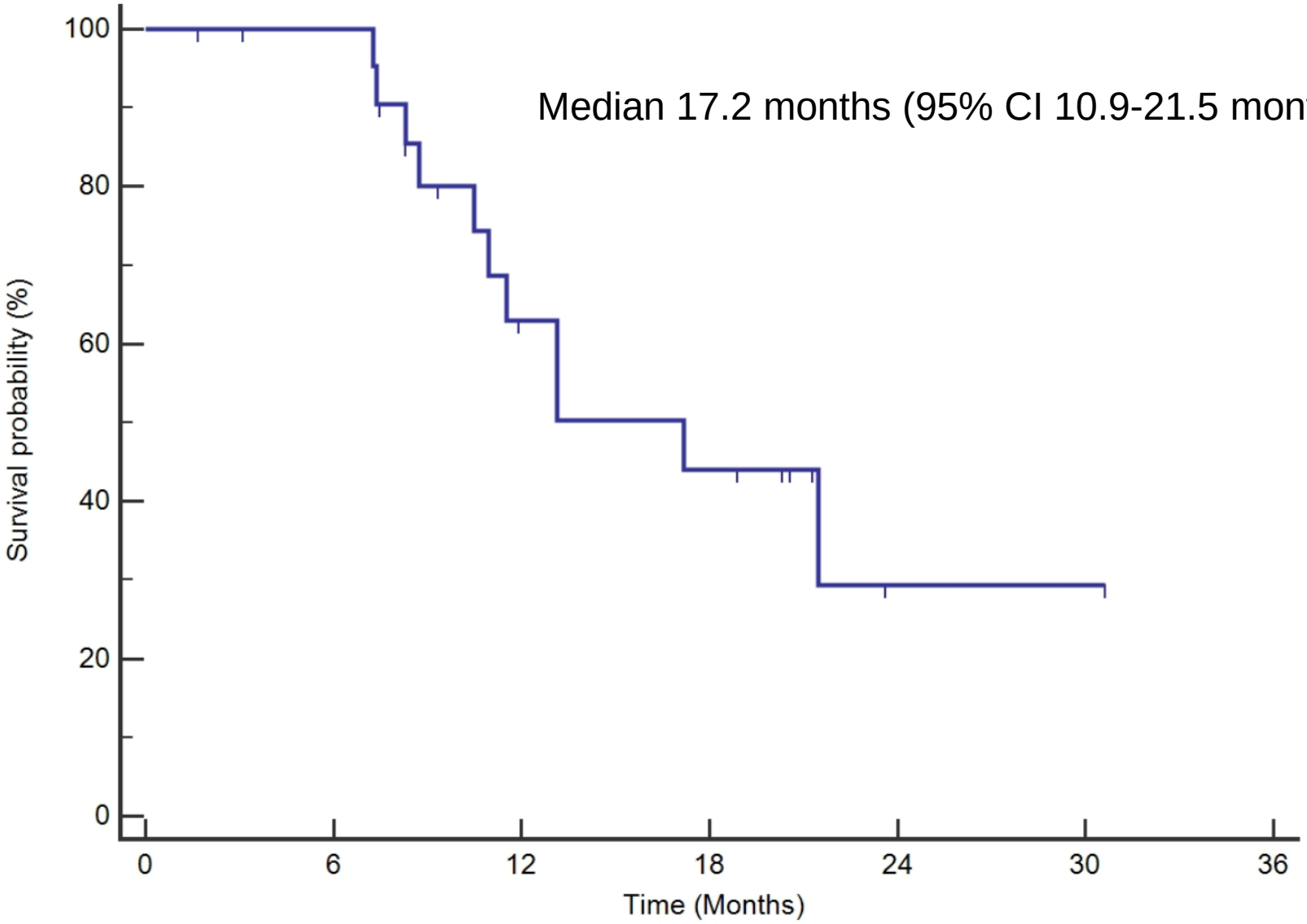
Adverse Events Leading to Drug Discontinuation (n=14)

Adverse Event Leading to Discontinuation	Grade	Cycle
Cycles 1-3 (n = 7)		
Sepsis	5	1
Sepsis	5	1
Sepsis	5	2
Prolonged QTcF/Atrillal fibrillation	3	2
Parainfluenza infection	3	3
Acute kidney injury	1	3
Acute axonal neuropathy	3	3
Cycles 4-6 (n = 2)		
Intermittent fatigue	1	4
Intermittent fatigue	3	4
Cycles >6 (n = 5)		
Diverticulitis	3	7
Supraglotic ulcer	3	7
Fatigue	3	9
Upper respiratory infection	2	12
Fatigue	3	19

Overall Response

Response Assessment	
Primary Endpoint = CR + CRi + MLFS	26 (52%)
Complete response (CR)	21 (42%)
CR with incomplete blood count recovery (CRi)	2 (4%)
Morphologic leukemia free state (MLFS)	3 (6%)
Duration of CR+CRi+MLFS, Median	13.2 months
Time to Marrow CR (<5% blasts)	
Median	57 days
Range	25 – 243 days
No. (%) of patients requiring >6 cycles	3/26 (12%)

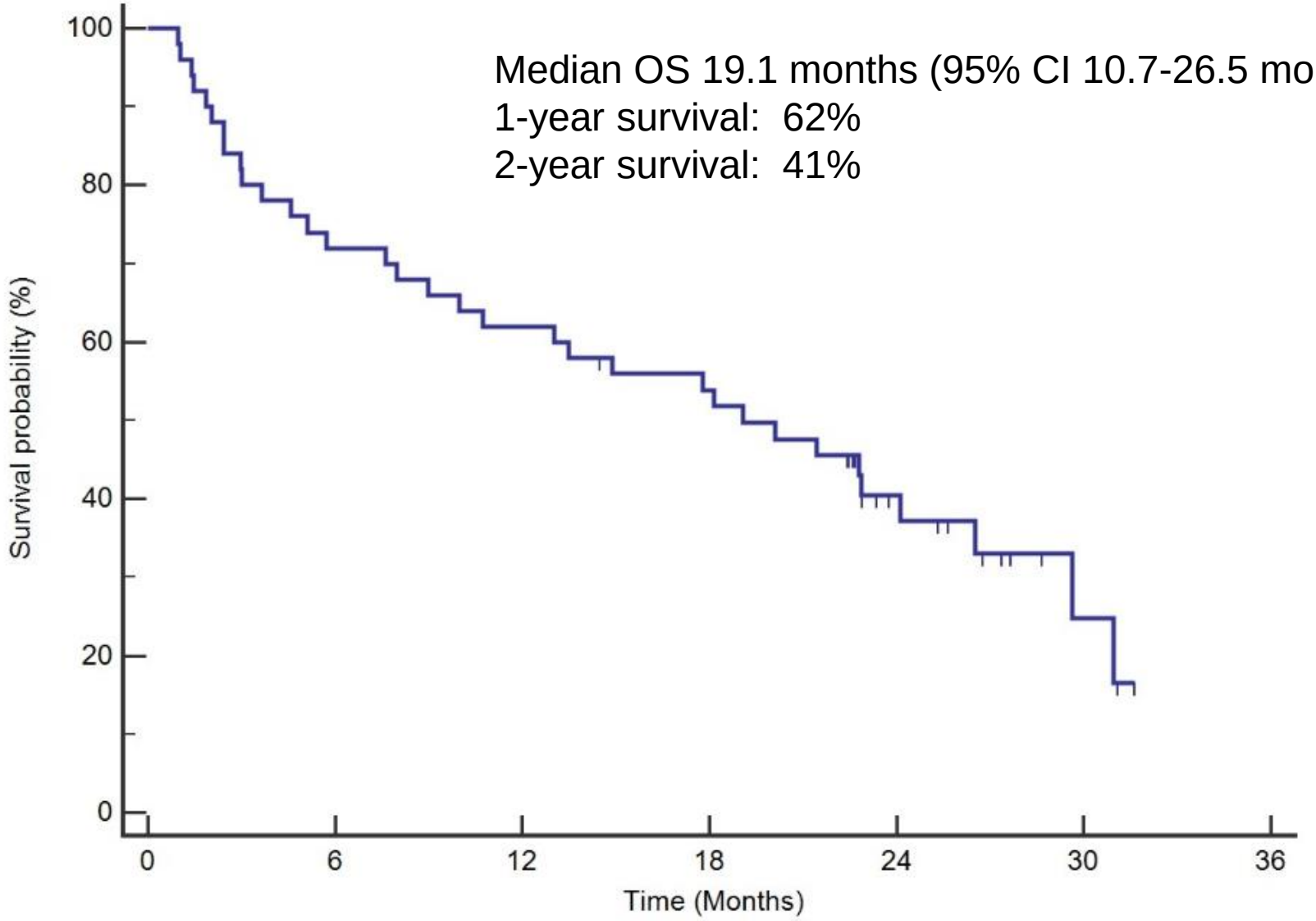
Duration of Response (CR/CRi)



Response Assessment By Patient Subgroup

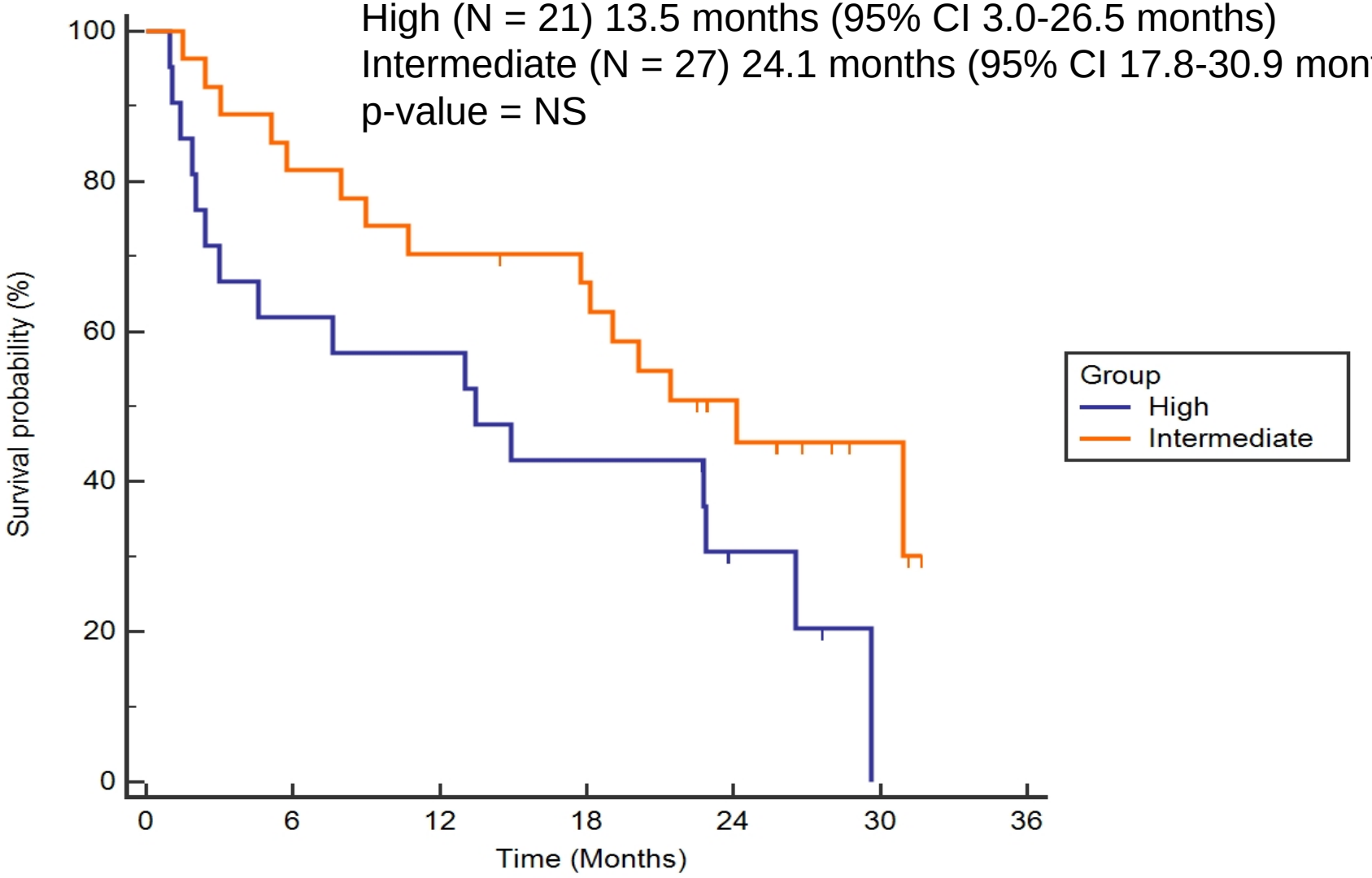
	CR (%)	CR + CRi + MLFS (%)
Overall population (N = 50)	42.0	52.0
Cytogenetic Risk Group		
Intermediate (N = 27)	48.1	59.3
High (N = 21)	38.1	47.6
Age		
≥75 years (N = 26)	42.3	57.7
66-74 (N = 24)	41.7	45.8
Type AML		
De novo (N = 33)	42.4	51.5
Secondary (N = 17)	41.2	52.9
ECOG Performance Status		
0-1 (N = 42)	40.5	50.0
2 (N = 8)	50.0	62.5

Overall Survival



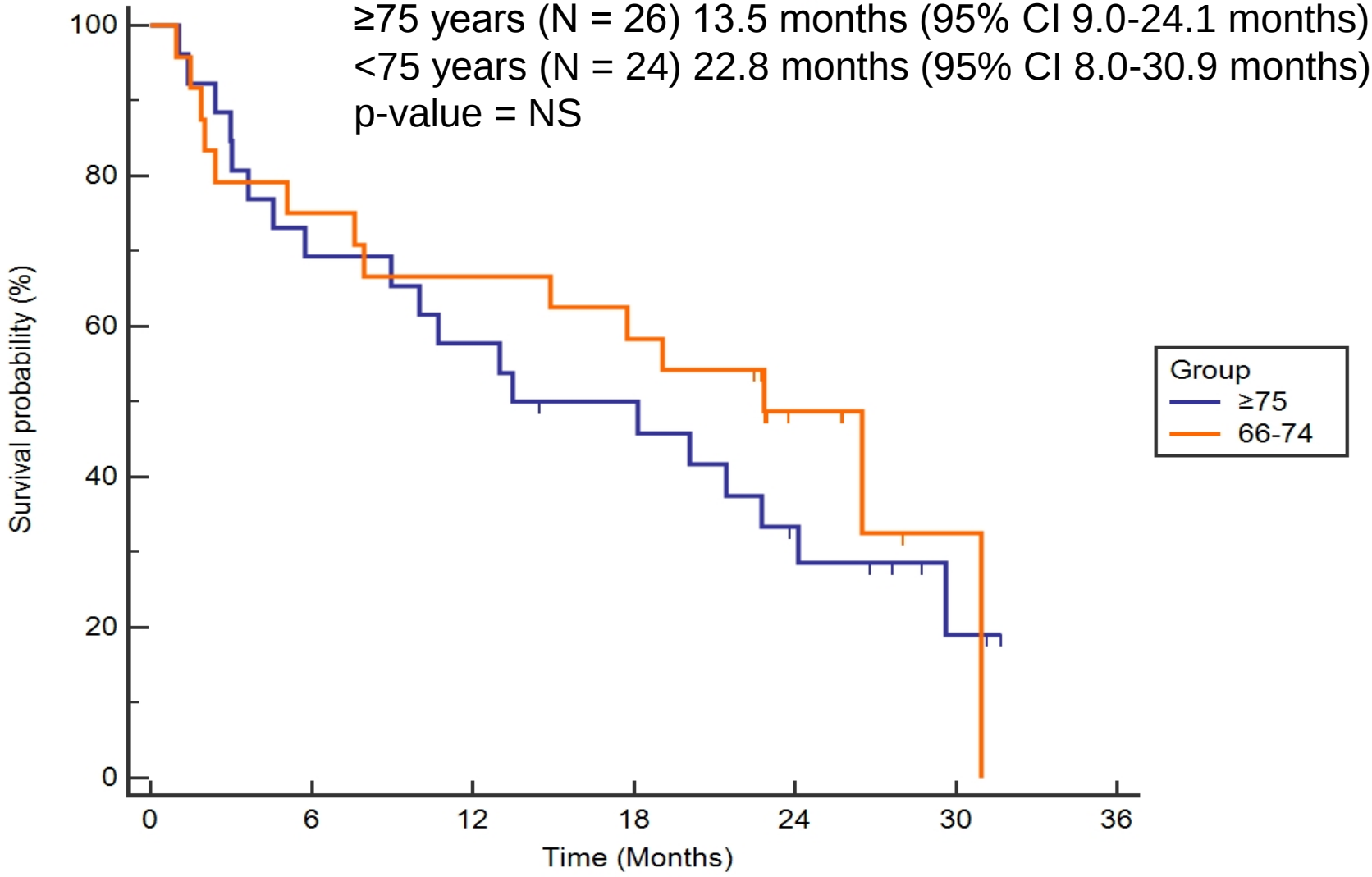
Overall Survival by Cytogenetic Risk Group

High (N = 21) 13.5 months (95% CI 3.0-26.5 months)
Intermediate (N = 27) 24.1 months (95% CI 17.8-30.9 months)
p-value = NS



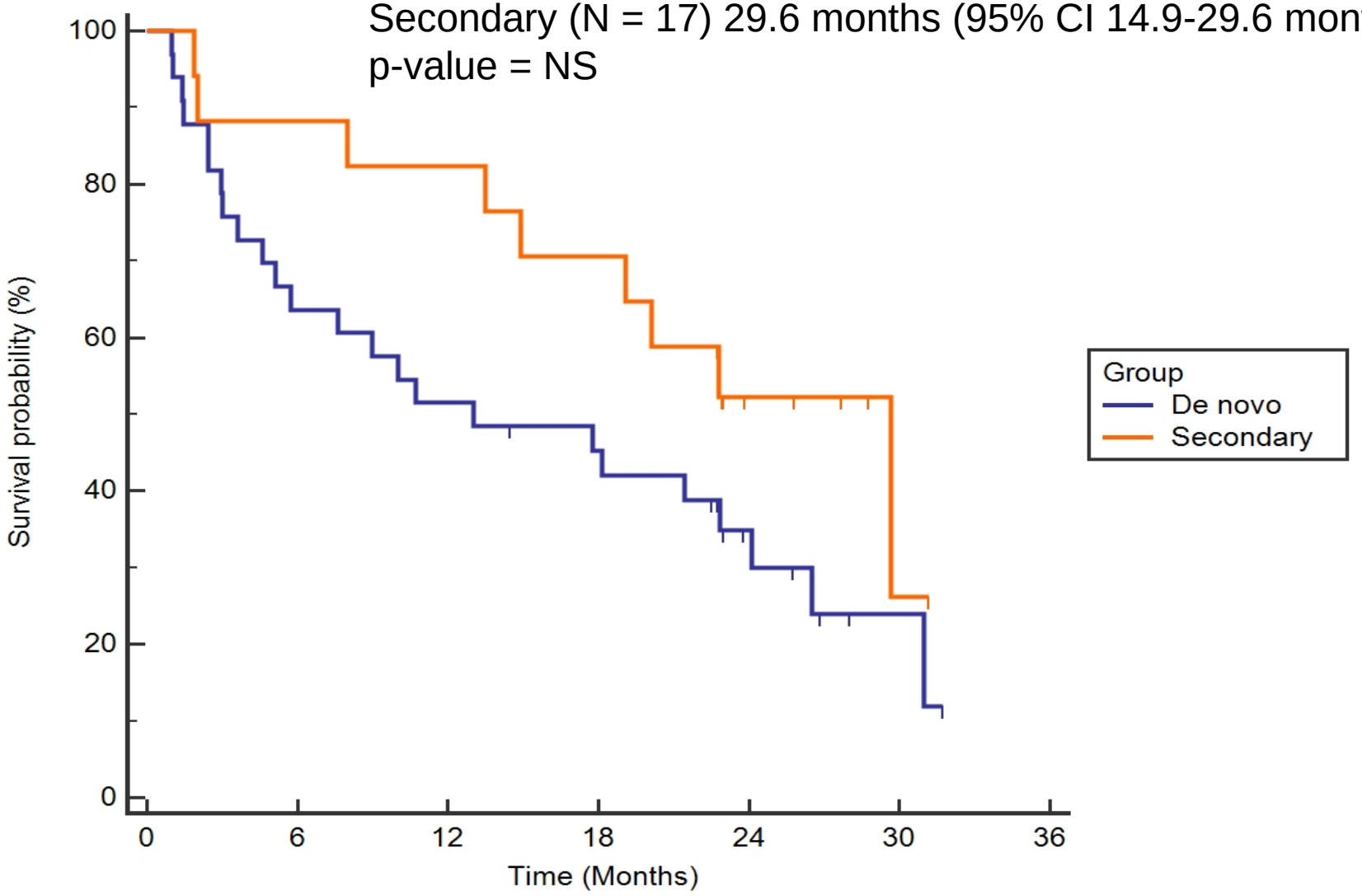
Overall Survival by Age

≥75 years (N = 26) 13.5 months (95% CI 9.0-24.1 months)
<75 years (N = 24) 22.8 months (95% CI 8.0-30.9 months)
p-value = NS



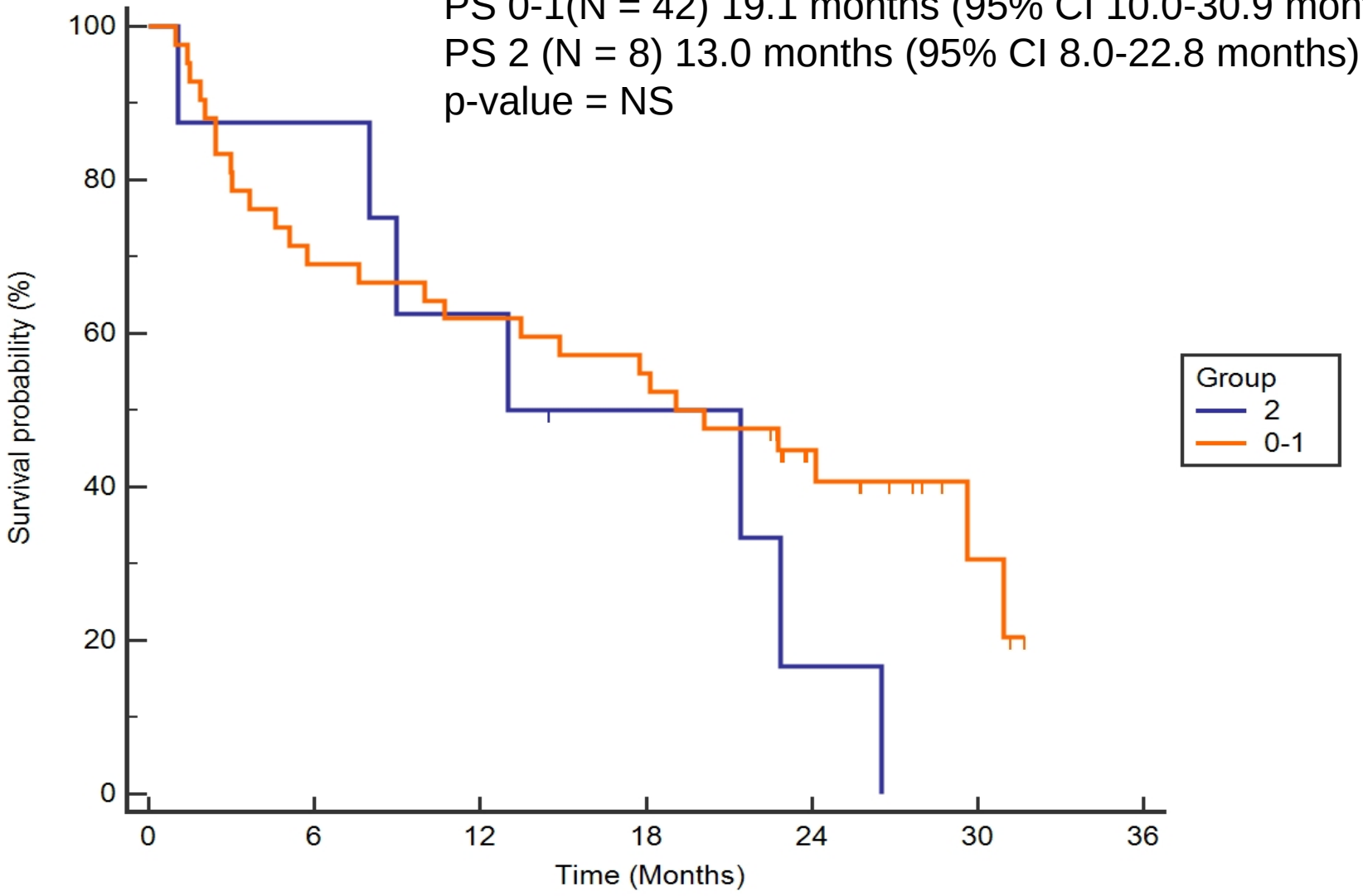
Overall Survival in De Novo vs Secondary AML

De novo (N = 33) 13.0 months (95% CI 5.7-24.1 months)
Secondary (N = 17) 29.6 months (95% CI 14.9-29.6 months)
p-value = NS



Overall Survival by ECOG Performance Status

PS 0-1(N = 42) 19.1 months (95% CI 10.0-30.9 months)
PS 2 (N = 8) 13.0 months (95% CI 8.0-22.8 months)
p-value = NS



Pracinostat + Azacitidine in AML: Conclusions

- Pracinostat + azacitidine is well tolerated in elderly AML
- Prolong survival in the overall population and in patient subsets defined by cytogenetics risk group, *de novo* or secondary AML, age and ECOG performance status
- Results compare favorably to the Phase 3 study of azacitidine in a similar AML patient population
- Marrow remission typically achieved within the first 2 cycles, but prolonged exposure required in some patients to maximize response
- Site recruitment is ongoing for a global Phase 3 study of Pracinostat + Azacitidine in newly diagnosed AML patients unfit for intensive induction chemotherapy

Acknowledgement and COI

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- The study was sponsored by MEI Pharma

- Pracinostat is an investigational agent, not approved for commercial use in the United States