Abstract 10551

Phase 1/2 Study of Weekly *nab*-Paclitaxel in Pediatric Patients With Recurrent/Refractory Solid Tumors: Dose Finding and Pharmacokinetics

Lucas Moreno,[1] Michela Casanova,[2] Julia C. Chisholm,[3] Pablo Berlanga,[4] Pascal B. Chastagner,[5] Sylvain Baruchel,[6] Carla Manzitti,[7] Soledad Gallego Mélcon,[8] Nicolas U. Gerber,[9] Gianni Bisogno,[10] Franca Fagioli,[11] Birgit Geoerger,[12] Julia Glade Bender,[13] Isabelle Aerts,[14] Christophe Bergeron,[15] Pooja Hingorani,[16] Ileana Elias,[17] Mathew Simcock,[18] Ruta Slepetis,[19] Nianhang Chen,[19] Gilles Vassal[20]

[1]Hospital Infantil Universitario Niño Jesús, Madrid, Spain; [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Royal Marsden Hospital, Sutton, United Kingdom; [4]Unidad de Oncologia Pediatrica, Hospital Universitario la Fe, Valencia, Spain; [5]Hôpital d'Enfants, Nancy, France; [6]The Hospital for Sick Children, Toronto, ON, Canada; [7]IRCCS Istituto Giannina Gaslini, Genova, Italy; [8]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [9]University Children's Hospital, Zurich, Switzerland; [10]Department of Pediatrics, Hematology/Oncology Division, Padova, Italy; [11]Azienda Ospedaliera Regina Margherita, Torino, Italy; [12]Gustave Roussy, Villejuif, France; [13]Columbia University, New York, NY, USA; [14]Institut Curie, Paris, France; [15]Department of Pediatrics, Centre Leon Berard, Lyon, France; [16]Phoenix Childrens Hosp, Phoenix, AZ, USA; [17]Celgene Corporation, Toronto, ON, Canada; [18]Celgene International, Boudry, Switzerland; [19]Celgene Corporation, Summit, NJ, USA; [20]Institut Gustave Roussy, Paris, France

INTRODUCTION

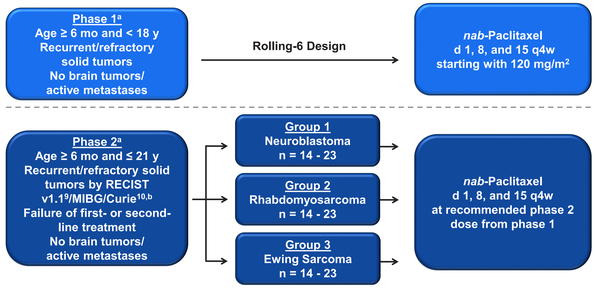
- Although solvent-based paclitaxel has demonstrated activity in children with refractory solid tumors, hypersensitivity and neurological reactions have been dose limiting and thereby compromise efficacy[1,2]
- *nab*®-Paclitaxel is an albumin-bound, solvent-free formulation of paclitaxel that has demonstrated efficacy and safety in adults with various solid tumors[3-7]
  - In preclinical pediatric solid tumor models, *nab*-paclitaxel has demonstrated cytotoxicity in vitro and antitumor activity in vivo
- *nab*-Paclitaxel monotherapy is approved at a dose of 260 mg/m^2 every 3 weeks for treatment of metastatic breast cancer, and has demonstrated efficacy in adults with early-stage breast cancer at a dose of 125 mg/m^2 weekly for the first 3 of 4 weeks[3,8]
- This phase 1/2, multicenter, dose-finding study (in collaboration with Innovative Therapies for Children with Cancer) is currently assessing the safety, tolerability, and preliminary efficacy of weekly *nab*-paclitaxel in pediatric patients with recurrent or refractory solid tumors

OBJECTIVES

- Phase 1: to describe the *nab*-paclitaxel maximum tolerated dose/recommended phase 2 dose, safety, and pharmacokinetic profile as well as preliminary clinical activity in pediatric patients with recurrent/refractory solid tumors

STUDY DESIGN

Figure 1. Study Design



[a] Full Inclusion/Exclusion criteria described on clinicaltrials.gov (NCT01962103). [b] Acceptable for patient with neuroblastoma.

- Treatment until disease progression, death, withdrawal of consent, or unacceptable toxicity
- Phase 1 DLT assessment during cycle 1 (including cycle 2 d 1 predose evaluations)
- Safety population: all patients receiving ≥ 1 *nab*-paclitaxel dose
- Efficacy population: all eligible treated patients who completed ≥ 2 doses of *nab*-paclitaxel and had baseline and ≥ 1 postbaseline efficacy assessment

Phase 1 Endpoints

- Primary
  - Phase 1: incidence of DLTs and treatment-emergent adverse events
- Secondary
  - Phase 1: pharmacokinetics, overall response rate
- Exploratory
  - Phase 1: MIBG response using Curie score and biomarker analysis

AE, adverse event; AUC, area under the curve; CL, clearance; C_{max}, peak plasma concentration; DLT, dose-limiting toxicity; MIBG, ^{123}I-metaiodobenzylguanidine; PS, performance status; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

METHODS

Phase 1 Dose Escalation

- A rolling-6 dose-escalation design to establish the *nab*-paclitaxel maximum tolerated dose/recommended phase 2 dose[11]
  - Dose-determining set: all patients who experienced a DLT or received 3 weekly *nab*-paclitaxel doses during cycle 1
  - DLT: treatment-related AE leading to treatment discontinuation or
    - Grade 3 or 4 nonhematologic toxicity (excluding transient transaminitis)
    - Grade 3 or 4 nausea or vomiting > 5d despite maximal anti-emetic treatment
    - Grade 4 thrombocytopenia or anemia persisting > 7d or requiring transfusion > 7d
    - Grade 3 thrombocytopenia with bleeding
    - Grade 4 uncomplicated neutropenia > 7d
    - Febrile neutropenia with confirmed bacterial infection
    - Hematologic toxicity delaying treatment > 21d
- If there is no availability for enrollment within the current dose level, patients could enroll at the last dose level evaluated as safe
- Dose-escalation or maximum tolerated dose/recommended phase 2 dose decisions were determined by the Safety Monitoring Committee, which included the principal investigator and all investigators who enrolled patients, the Celgene Clinical Research Physician and Research Scientist, and the product Safety Physician

RESULTS

Patients

- Sixty-five patients were enrolled; 1 was ineligible for treatment and 64 were treated

Table 1. Selected Patient Characteristics

Characteristic	*nab*-Paclitaxel dose 120 mg/m^2 n = 16	150 mg/m^2 n = 8	180 mg/m^2 n = 14	210 mg/m^2 n = 11	240 mg/m^2 n = 8	270 mg/m^2 n = 7	Total N = 64
Dose determining set, n	6	6	6	6	6	7	37
Age, median, years	12.5	14.0	11.0	9.0	12.0	13.0	12.0
≥ 12 years, n (%)	10 (63)	6 (75)	7 (50)	5 (45)	5 (63)	4 (57)	37 (58)
Male, n (%)	7 (44)	4 (50)	5 (36)	4 (36)	7 (88)	4 (57)	31 (48)
Lansky/Karnofsky PS, n (%)							
90 - 100	12 (75)	5 (63)	9 (64)	9 (82)	5 (63)	4 (57)	44 (69)
70 - 80	4 (25)	3 (38)	5 (36)	2 (18)	3 (38)	3 (43)	20 (31)
Solid tumor type, n (%)							
Neuroblastoma	2 (13)	0	2 (14)	4 (36)	2 (25)	0	10 (16)
Rhabdomyosarcoma	3 (19)	1 (13)	7 (50)	2 (18)	1 (13)	0	14 (22)
Ewing Sarcoma	3 (19)	2 (25)	2 (14)	1 (9)	1 (13)	4 (57)	13 (20)
Osteosarcoma	4 (25)	1 (13)	0	1 (9)	1 (13)	1 (14)	8 (13)
Other	4 (25)	4 (50)	3 (21)	3 (27)	3 (38)	2 (29)	19 (30)
Prior treatment lines, median (range), n	3 (1 - 8)	3 (1 - 7)	3 (1 - 7)	3 (1 - 10)	3 (1 - 5)	3 (2 - 4)	3 (1 - 10)

Treatment Exposure and Safety

- The relative *nab*-paclitaxel dose intensity was > 90% in all cohorts (Table 2)
- DLTs were grade 3 dizziness (120 mg/m^2) and grade 4 neutropenia > 7 days (270 mg/m^2)
- At all dose levels, grade 3/4 AEs were mainly hematologic (Table 3)
- Grade 1/2 peripheral neuropathy and hand-foot-syndrome occurred in 16% and 6% of patients, respectively
  - Grade ≥ 2 peripheral neuropathy by Standardised MedDRA Queries in 9% of patients

Table 2. Treatment Exposure

Parameter	*nab*-Paclitaxel dose 120 mg/m^2 n = 16	150 mg/m^2 n = 8	180 mg/m^2 n = 14	210 mg/m^2 n = 11	240 mg/m^2 n = 8	270 mg/m^2 n = 7
Relative dose intensity, median, %	100.0	99.1	99.5	99.9	95.8	94.8
Cumulative dose, median, mg/kg	715.6	812.4	1074.5	1248.4	1806.0	1536.5
Patients with ≥ 1 treatment-related AE leading to dose reduction, n (%)	0	1 (13)	2 (14)	1 (9)	3 (38)	3 (43)
Patients with ≥ 1 treatment-related AE leading to discontinuation, n (%)	1 (6)	0	0	1 (9)	1 (13)	1 (14)

Table 3. Selected Safety[a]

Grade 3/4 AEs, %	*nab*-Paclitaxel dose 120 mg/m^2 n = 16	150 mg/m^2 n = 8	180 mg/m^2 n = 14	210 mg/m^2 n = 11	240 mg/m^2 n = 8	270 mg/m^2 n = 7
Hematologic						
Neutropenia	31	38	36	73	88	86
Leukopenia	31	0	14	27	50	43
Anemia	25	50	21	18	25	29
Lymphopenia	19	25	7	9	13	29
Nonhematologic						
Hand-foot syndrome	0	0	0	0	0	29
Hyponatraemia	6	38	0	0	0	0
Hypotension	0	25	7	0	0	0

[a] AEs present in ≥ 20% of patients in ≥ 1 dosing cohort are reported.

Selection of Recommended Phase 2 Dose

- At the 270 mg/m^2 dose, 3/5 patients continuing beyond cycle 1 had a dose reduction in cycle 2 due to toxicity
- DLT-based criteria to determine the nontolerable dose were not met; however, 270 mg/m^2 was declared the nontolerable dose based on totality of safety information, including grade ≥ 3 toxicities during the first 2 cycles (neutropenia: n = 5/7; skin toxicity: n = 2/7; peripheral neuropathy: n = 1/7)
- 5/7 patients at 270 mg/m^2 and 3/8 patients at 240 mg/m^2 had grade 4 neutropenia in cycle 1

Efficacy

- Of 44 efficacy-evaluable patients, 1 (2%) and 6 (14%) had complete and partial responses, respectively (Table 4)
  - RECIST responses in 5 pts (complete response in Ewing sarcoma; partial responses in Ewing sarcoma, rhabdomyosarcoma, sarcoma not otherwise specified, and renal tumor)
  - Partial response per MIBG/Curie, an exploratory endpoint, in 2 pts with neuroblastoma
- Of the 7 responders, 3 received *nab*-paclitaxel at 240 mg/m^2; 2 received 210 mg/m^2, and 1 each received 180 mg/m^2 and 270 mg/m^2

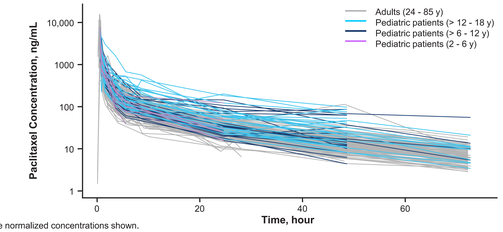
Table 4. Best Response

Response, n (%)	N = 44 Efficacy evaluable (n = 41 RECIST and n = 3 MIBG/Curie)
Complete response	1 (2)
Partial response	6 (15)
Stable disease	10 (24)
≥ 16 weeks	3 (7)
< 16 weeks	7 (17)

Preliminary *nab*-Paclitaxel Pharmacokinetic Profile

- *nab*-Paclitaxel concentration profiles are similar across age groups (Figure 2)

Figure 2. Individual Concentration Profiles by Age Group[a]



[a] Dose normalized concentrations shown.

Table 5. Preliminary Phase 1 Pharmacokinetic Parameters[a]

Parameter, geometric mean	*nab*-Paclitaxel dose 120 mg/m^2 n = 12	150 mg/m^2 n = 6	180 mg/m^2 n = 14	210 mg/m^2 n = 11	240 mg/m^2 n = 6	270 mg/m^2 n = 6
AUC_{24}, h•ng/mL	6575	7200	8141	9517	10,306	10,378
C_{max}, ng/mL	4347	4988	5510	5350	8251	9201
CL, L/h	17.4	23.0	21.0	18.8	18.7	26.1

[a] Fewer patients evaluable for pharmacokinetic evaluation.

CONCLUSION

- At doses ≤ 240 mg/m^2, *nab*-paclitaxel demonstrated a manageable safety profile
- The most common grade 3/4 toxicities were hematologic
  - Grade 1/2 skin toxicity and neuropathy were also observed
- The recommended phase 2 *nab*-paclitaxel dose was 240 mg/m^2 d 1, 8, and 15 q4w
- This *nab*-paclitaxel dose is almost twice that used in a recent phase 3 trial in adults with early breast cancer (125 mg/m^2 qw 3/4) and almost equal to the approved dose (260 mg/m^2 q3w) in adults with metastatic breast cancer[3,8]
- *nab*-Paclitaxel 240 mg/m^2 d 1, 8, and 15 q4w demonstrated promising preliminary clinical activity in pediatric patients with solid tumors
- Phase 2, assessing *nab*-paclitaxel at the recommended phase 2 dose in pediatric patients with neuroblastoma, rhabdomyosarcoma, or Ewing sarcoma, is accruing

ACKNOWLEDGMENTS

This study is supported by Celgene Corporation, Summit, NJ. The authors received editorial and production support in the preparation of this poster from MediTech Media, Ltd, funded by Celgene Corporation. The authors are fully responsible for all content and editorial decisions for this poster.

DISCLOSURES

LM: consultant or advisor, Novartis, Bayer, Roche, AstraZeneca; MC: consultant or advisor Roche, Bayer, Loxo Oncology, Boehringer Ingelheim; JCC: consultant or advisor, F. Hoffman La Roche, Merck Sharp and Dohme; PB: nothing to disclose; PBC: nothing to disclose; SB: stock ownership, MetronomX, Inc.; honoraria, Celgene; consultant or advisor, Celgene; research funding, Servier; CM: nothing to disclose; SGM: nothing to disclose; NUG: nothing to disclose; GB: consult or advisor, Loxo Oncology; FF: nothing to disclose; BG: nothing to disclose; JGB: research funding, Celgene, Merck: nothing to disclose; IA: nothing to disclose; CB: nothing to disclose; PH: nothing to disclose; IE, MS, RS, NC: employment and stock ownership, Celgene; GV: research funding, Celgene.

REFERENCES

1. Doz F, et al. *Br J Cancer*. 2001;84:604-610.
2. Geller I, et al. *Pediatr Blood Cancer*. 2009;52:346-350.
3. Abraxane (package insert). Summit, NJ: Celgene Corporation; 2015.
4. Socinski MA, et al. *J Clin Oncol*. 2012;30:2055-2062.
5. Gradishar WF, et al. *J Clin Oncol*. 2005;23:7794-7803.
6. Von Hoff DD, et al. *N Engl J Med*. 2013;369:1691-1703.
7. Zhang L, et al. *Clin Cancer Res*. 2013;19:5972-5983.
8. Untch M, et al. *Lancet Oncol*. 2016;17:345-356.
9. Eisenhauer EA, et al. *Eur J Cancer*. 2009;45:228-247.
10. Ady N, et al. *Eur J Cancer*. 1995;31A:256-261.
11. Skolnik JM, et al. *J Clin Oncol*. 2013;26:190-195.

Correspondence: Lucas Moreno - lmorenom@ext.cnio.es

Poster Presentation at the 52nd ASCO Annual Meeting, June 3 - June 7, 2016; Chicago Illinois