# DISCLOSURE

## REDACTED PROTOCOL

## ABI-007-PST-001

## A PHASE 1/2, MULTICENTER, OPEN-LABEL, DOSE-FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF WEEKLY *nab*®- PACLITAXEL IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

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# A PHASE 1/2, MULTICENTER, OPEN-LABEL, DOSE-FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF WEEKLY *nab*®-PACLITAXEL IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

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# PROTOCOL SUMMARY

## Study Title

A Phase 1/2, multicenter, open-label, dose-finding study to assess the safety, tolerability, and preliminary efficacy of weekly *nab*®-paclitaxel in pediatric patients with recurrent or refractory solid tumors.

## Indication

**Phase 1 Portion:** Pediatric patients with recurrent or refractory solid tumors (excluding brain tumors).

**Phase 2 Portion:** Pediatric patients with recurrent or refractory neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma.

## Objectives

### *Primary Objective*

- Phase 1 portion: To determine the pediatric maximum tolerated dose (MTD)/ pediatric recommended Phase 2 dose (RP2D), safety and tolerability
- Phase 2 portion: To characterize antitumor activity at RP2D assessed by overall response rate (ORR)

### *Secondary Objectives*

- Phase 1 portion: To evaluate pharmacokinetics (PK) and characterize ORR
- Phase 2 portion: To characterize duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), 1-year survival. To confirm safety and to evaluate PK

## Study Design

The Phase 1 portion of the study will be a rolling-6 dose escalation design to determine the MTD/RP2D. A safety monitoring committee (SMC) will be formed to make dose escalation decisions. Approximately 64 patients are planned to be enrolled in this portion of the study; approximately 44 into the Dose Determining Sets (DDS), and about 20 additional patients at dose levels evaluated as safe by the SMC.

The Phase 2 portion of the study will enroll additional patients at the RP2D (240 mg/m$^2$ in patients weighing > 10 kg, and 11.5 mg/kg in patients weighing ≤ 10 kg) into one of three solid tumor groups using a Simon two-stage minimax design for each group:

- Neuroblastoma (≤ 23 patients)
- Rhabdomyosarcoma (≤ 23 patients)
- Ewing's sarcoma (≤ 23 patients)

Both phases of the study will be open-label and conducted at multiple centers. The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

**Study Population**

The Phase 1 portion of the study will be conducted in patients ≥ 6 months and < 18 years of age with recurrent or refractory solid tumors (excluding primary or metastatic brain tumors).

The Phase 2 portion of the study will be conducted in patients ≥ 6 months and ≤ 24 years of age with radiologically documented measurable disease by RECIST 1.1 (for neuroblastoma, evaluable disease by $^{123}$I-metaiodobenzylguanidine (MIBG)/Curie score is also acceptable) in several discrete recurrent or refractory solid tumor types (neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma).

**Length of Study**

In both the Phase 1 and 2 portions of the study, patients will enter a 14 day screening period, and if eligible (and the cohort/group is open for recruitment) will proceed to the treatment phase. Patients may remain on treatment until disease progression, unacceptable toxicity, until they begin a new anticancer therapy, withdrawal of consent, parent/guardian/patient refusal, physician decision or death.

All patients in both portions of the study will be followed for 28 days after the last study treatment for safety, monitoring of adverse events and for response until progression (if applicable). Patients will be followed for 1 year after the last dose of *nab*-paclitaxel for survival and new anticancer therapies.

The Phase 1 portion of the study is expected to last up to approximately 18 months. The Phase 2 portion of the study is expected to last for approximately 54 months.

The End of Trial is defined as either the date of the last visit of the last patient to complete the study, or the date of receipt of the last data point from the last patient that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

**Study Treatments**

In both the Phase 1 and 2 portions of the study, patients will receive the investigational product (IP) *nab*-paclitaxel, administered intravenously over approximately 30 minutes, on Days 1, 8, and 15 of a 28-day cycle until disease progression or as described above. The starting dose for the Phase 1 portion will be 120 mg/m$^2$. The dose will be escalated in subsequent cohorts until the MTD/RP2D has been identified. The Phase 2 portion will treat patients at the RP2D identified during the Phase 1 portion. In January 2016, the RP2D was identified as 240 mg/m$^2$ in patients weighing > 10 kg and 11.5 mg/kg in patients weighing ≤ 10 kg.

**Overview of Efficacy Assessments**

All patients will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 at screening and every 8 weeks from Cycle 1 Day 1 until disease progression, the start of a new anticancer therapy or withdrawal of consent. In patients with neuroblastoma, a MIBG scan will be performed according to the same schedule to assess MIBG response.

Response assessments include CT scan or MRI of the chest, abdomen, and pelvis, MIBG scan (for neuroblastoma), any other studies required for tumor imaging, and (for neuroblastoma) bone marrow biopsy for verification of confirmed complete response.

**Overview of Safety Assessments**

All patients will be monitored for adverse events, starting from the time the parent/guardian/patient signs the informed consent/assent form until 28 days after the last dose of IP and at the end of treatment (EOT) visit. A thorough evaluation of medical conditions will be conducted during screening for eligibility. Physical examination (source documented only), vital signs, laboratory assessments (eg, serum chemistry, hematology), 12-lead electrocardiogram (ECG), left ventricular shortening fraction (LVSF) assessment by echocardiogram/multi-gated acquisition (MUGA) scan/ other medically approved method, and Lansky/ Karnofsky performance status will be monitored regularly. The full schedule of assessments is described in Table 4 and Section 6.

**Overview of Statistical Methods**

The Phase 1 portion uses a rolling-6 patient dose escalation design to establish the MTD/RP2D and the Phase 2 portion uses a Simon two-stage minimax design to monitor patient enrollment for each group separately.

**Sample Size**

During the Phase 1 portion of the study, up to approximately 64 patients will be enrolled, depending on the number of dose level cohorts evaluated and the number of additional patients enrolled at dose levels evaluated as safe by the SMC. In the Phase 2 portion, up to 69 efficacy evaluable patients ($\leq 23$ with neuroblastoma, $\leq 23$ with rhabdomyosarcoma, and $\leq 23$ with Ewing's sarcoma) will be enrolled at the RP2D determined in the Phase 1 portion of the study, with at least 14 patients per group. A Simon two-stage minimax design will be used to monitor patient enrollment for each of the 3 groups separately.

For each of the 3 groups, in the first stage, 14 efficacy evaluable patients will be enrolled. If $< 2$ of the 14 patients within a group has a response, the enrollment for this group will be stopped upon determination of the number of responders. If $\geq 2$ of the 14 patients have a response, the enrollment will continue until 23 efficacy evaluable patients are enrolled. At the final analysis, the regimen will be concluded with more than 5% true response rate if $\geq 5$ of 23 patients have a response according to the maximum likelihood estimator. The sample size is based on an 80% power and 10% significance having fixed the lower and upper boundaries to 10% and 28%, respectively.

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**Table 1: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase (SGPT) |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase (SGOT) |
| AUC | Area under the curve |
| β-hCG | β-subunit of human chorionic gonadotropin |
| BSA | Body surface area |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CL | Clearance |
| $C_{max}$ | Maximum plasma concentration of drug |
| CNS | Central nervous system |
| CR | Complete response |
| CRO | Contract research organization |
| CRF | Case report form |
| CRP | Clinical Research Physician |
| CRS | Clinical Research Scientist |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCR | Disease control rate |
| DDS | Dose Determining Set |
| DEHP | di (2-ethylhexyl) phthalate |
| DLT | Dose-limiting toxicity |
| DMSO | Dimethyl sulfoxide |
| DOR | Duration of response |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| EE | Efficacy evaluable |

**Table 1: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| EEA | European Economic Area |
| EOT | End of treatment |
| ESMO | European Society for Medical Oncology |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIV | Human immunodeficiency virus |
| HSCT | Hematopoietic stem cell transplantation |
| HVA | Homovanillic acid |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IND | Investigational New Drug |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| IRT | Integrated Response Technology |
| IV | Intravenous |
| LDH | Lactate dehydrogenase |
| LVSF | Left ventricular shortening fraction |
| MCR | Maintained complete response |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIBG | $^{123}$I-metaiodobenzylguanidine |
| MR | Minor response |
| MRI | Magnetic resonance imaging |
| MTD | Maximum tolerated dose |
| MUGA | Multi-gated acquisition |
| NCI | National Cancer Institute |
| NE | Inevaluable |
| NRSTS | Nonrhabdomyosarcoma soft tissue sarcoma |
| NSCLC | Non-small cell lung cancer |
| ORR | Overall response rate |
| OS | Overall survival |

**Table 1: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| PFS | Progression-free survival |
| PNET | Primitive neuroendocrine tumors |
| PK | Pharmacokinetics |
| PR | Partial response |
| PVC | Polyvinyl chloride |
| RBC | Red blood cell count |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | Recommended Phase 2 dose |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SCLC | Small cell lung cancer |
| SD | Stable disease |
| SEER | Surveillance, Epidemiology, and End Results |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SIOPE | European Society of Pediatric Oncology |
| SMC | Safety monitoring committee |
| SOP | Standard operating procedure |
| SPARC | Secreted protein acidic and rich in cysteine |
| SUSAR | Suspected unexpected serious adverse reaction |
| $t_{1/2}$ | Half-life |
| TEAE | Treatment-emergent adverse event |
| TTP | Time to tumor progression |
| ULN | Upper limit of normal |
| USA | United States of America |
| USP | United States Pharmacopeia |
| VMA | Vanillylmandelic acid |
| Vss | Volume of distribution |
| WBC | White blood cell count |

# 1. INTRODUCTION

## 1.1. Pediatric Indication Background

Sixty percent of all pediatric malignant neoplasms are solid tumors (Dome, 2008). Although brain tumors such as gliomas and medulloblastomas frequently occur in the pediatric population, patients with brain tumors will not be enrolled in this study as there are no data to-date that would indicate that Abraxane has any efficacy in primary or metastatic brain tumors. Therefore, brain tumors are not further discussed in this protocol. The most common non-central nervous system (CNS) solid tumors in the pediatric population (age 0 – 19 years, in the USA) are comprised of the following tumor types: neuroblastoma (7%), Wilms' tumor (5%), rhabdomyosarcoma (3%), retinoblastoma (3%), osteosarcoma (3%), and Ewing's sarcoma (1%) (ACS, Cancer Facts and Figures, 2012).

Although childhood cancer is rare and the 5-year survival rate in non-CNS solid tumors is relatively high in the 0- to 19-years-old pediatric population (68% to 88%), childhood cancer is the leading cause of death by disease in the USA (ACS, Cancer Facts and Figures, 2012). The main reason for cancer death in the pediatric population is refractory and relapsed disease, and improved therapeutic options are needed in this population.

### 1.1.1. Neuroblastoma

Neuroblastoma is a malignant embryonal tumor of the neural crest cells. In children < 1 year old worldwide it is the most common tumor (Heck, 2009). The 5-year survival rates for children aged 0 to 19 years are in the range of 75% in the USA (SEER Table 29.6).

The treatment options for neuroblastoma include surgery, particularly for low-risk tumors, multiagent chemotherapy, and radiation therapy (Ullrich, 2012). For high risk patients, standard treatment generally consists of induction chemotherapy to achieve remission, surgery, and radiotherapy for local control, high-dose chemotherapy with autologous hematopoietic stem-cell rescue and oral 13-cis-retinoic acid for consolidation and immunotherapy (Modak, 2010). The risk of local relapse has decreased with modern surgery and radiotherapy practices along with induction chemotherapy; however, in high-risk neuroblastoma refractory or recurrent disease in bone and bone marrow occurs in most patients (Modak, 2010).

Various combinations of cyclophosphamide, doxorubicin, cisplatin, carboplatin, etoposide, topotecan, vincristine, temozolomide, and irinotecan have been used with response rates of 50% to 60%. Preclinical and clinical pediatric studies showed potential utility of chemotherapy with paclitaxel and docetaxel in neuroblastomas (Izbicka, 2006; Table 2 and Table 3).

### 1.1.2. Rhabdomyosarcoma

Rhabdomyosarcoma is a malignant childhood soft-tissue sarcoma of mesenchymal origin with a 5-year survival rate of 70%. The prognosis depends on the location and disease stage (Dasgupta, 2012).

Treatment is also driven by the primary tumor location and disease stage, which defines the clinical group, and generally includes some combination of pre-operative chemotherapy, surgery, irradiation, and systemic chemotherapy. Standard chemotherapeutic agents include vincristine,

dactinomycin, and cyclophosphamide. In the most high-risk disease, more intensive use of multiagent chemotherapy with other agents is being evaluated in clinical trials (Arndt, 2011).

Although rhabdomyosarcoma is sensitive to first line therapy with a complete response (CR) achieved in the majority of patients, local recurrences still occur in a substantial number of patients (Dantonello, 2008). The prognosis of patients who recur or progress after first line therapy is poor. However, patients who remain disease free after 5 years have a good prognosis and relapses are uncommon, and at 10 years only 9% of patients have late events. However, patients who have gross residual disease following initial surgery in unfavorable sites and those who initially present with metastatic disease more commonly experience relapse (Sung, 2004). The prognosis has not improved significantly in the last 15 years for the more than 15% of children who present with metastatic rhabdomyosarcoma, and the overall cure rate remains below 30% despite the development of more intensive therapies (Oberlin, 2008).

Both docetaxel and paclitaxel have antitumor activity in pediatric rhabdomyosarcoma solid tumor models (Izbicka, 2006), as well as in Phase 1 and 2 clinical studies; however, hypersensitivity and neurological reactions, among others, were dose-limiting with paclitaxel, and clinical activity with taxanes was short-lived (Table 2 and Table 3). The central neurotoxicity of conventional solvent-based paclitaxel has been attributed to the large amount of alcohol and Cremophor contained in the formulation (see Section 1.2.2).

### 1.1.3. Other Pediatric Solid Tumors

#### 1.1.3.1. Nonrhabdomyosarcoma Soft Tissue Sarcoma

Among pediatric nonrhabdomyosarcoma soft tissue sarcomas (NRSTSs), the most common include dermatofibrosarcoma protuberans, malignant fibrous histiocytoma, synovial sarcoma, malignant peripheral nerve sheath tumor, and fibrosarcoma. Other NRSTS that occur in children but not adults (except in rare cases) are infantile fibrosarcoma, infantile rhabdomyofibrosarcoma, and infantile malignant rhabdoid tumor (Spunt, 2008).

The likelihood of local invasion and distant metastases of NRSTSs is dependent on histological grade, dividing into low-grade and high-grade. The outcome of the initial surgical resection is the prognostic variable with the highest importance for nonmetastatic tumors. Overall survival nearly reaches 90 % if tumors are completely resected (generally low-grade). However, 5 year survival is 55% and event free survival is 33% in unresected tumors (generally high grade and invasive). The poorest prognosis among NRSTS is in metastatic tumors, where 5-year survival is only 15% (Levy, 2011).

Accordingly, complete surgical resection is the standard treatment for NRSTS with or without adjuvant radiotherapy for prevention of local recurrence (Agarwala, 2006). Combinations of ifosfamide, cyclophosphamide, vincristine, doxorubicin and etoposide seem to be the most active chemotherapy agents (Chui, 2007).

#### 1.1.3.2. Ewing's Sarcoma

After osteosarcoma, the second most common bone tumor in the pediatric population is Ewing's sarcoma (Dome, 2008). Patients who develop recurrent disease within the initial 2 years have 5-year survival rates of 7%, as compared to 30% if recurrent disease occurs after 2 years

(Jain, 2010). The 5-year survival rate in patients with bone metastases (< 20%) is lower than those with lung/pleura metastases (20% to 40%) (Paulussen, 2009).

Treatment of Ewing's sarcoma combines both neoadjuvant and adjuvant chemotherapy along with local control measures such as surgery and/or radiation. In patients with localized disease, this approach has improved 5-year survival to ≥ 60% (Paulussen, 2009). Commonly used therapeutic agents either as single-agent or primarily in combination include vincristine, dactinomycin, cyclophosphamide, doxorubicin, etoposide, topotecan, irinotecan and ifosfamide (Paulussen, 2009), while clinical activity has also been observed with paclitaxel and docetaxel (Table 2 and Table 3).

#### 1.1.3.3. Melanoma

There has been a rise in the incidence of both adult and pediatric melanoma and it now occurs 7 times more frequently in pediatric patients > 10 years old compared to those < 10 years old (Mills, 2009; Morelli, 2011).The incidence of the disease in children and adolescents younger than 19 years is approximately 4.9 per 1,000,000 (SEER Table 29.1). Although in children with melanoma the overall mortality has declined steadily from 1968 to 2004 in the USA, the overall mortality rate in both children and adults remains at about 40% (Lewis, 2008; Morelli, 2011). The 5-year survival in pediatric patients with malignant melanoma is 96% (SEER Table 29.6), but is only 57% for patients with distant metastasis (Strouse, 2005).

Despite recent advances in treatment, the most effective approach for melanoma is prevention and early detection (Morelli, 2011). The treatment of melanoma in the pediatric populations is at present extrapolated from the adult population. Surgery is the primary course of treatment with adjuvant therapy mainly given only for advanced disease (Brenn, 2007) including chemotherapy, immunotherapy and to a limited extent radiation (Jen, 2009). Dacarbazine has been the standard chemotherapeutic treatment for metastatic melanoma for the past 3 decades. In 2011 two new agents, ipilimumab and vemurafenib, were approved for the treatment of metastatic melanoma. Vemurafenib's benefit is limited to patients with BRAF V600E mutations, which is approximately 40-45% of treatable patients. The efficacy of *nab*-paclitaxel in adult melanoma is described in Section 1.2.1.

### 1.1.4. Conclusion

In the last decades, the prognosis of children with cancer has been improved and 70% of children can now be cured. However, some cancers display a 5-year survival rate of less than 50% and there is a clear unmet medical need in these patient populations.

## 1.2. Taxanes

Microtubule-stabilizing agents such as taxanes and epothilones are powerful antitumor agents and commonly have been used in adults as anticancer agents. Taxanes specifically alone or in combination are approved in breast, prostate, non-small cell lung cancer (NSCLC), ovarian, gastric, and head and neck cancer. They have been investigated and have shown to be active in other refractory malignancies such as previously treated lymphomas, small cell lung cancer (SCLC), oesophageal, endometrial, and bladder cancer (André, 2006).

### 1.2.1. *nab*-Paclitaxel

*nab*-Paclitaxel (ABI-007, ABRAXANE® for Injectable Suspension [Celgene Corporation, Summit, New Jersey, United States, the Sponsor]) is a human serum albumin bound nanoparticle formulation of paclitaxel with a mean particle size of approximately 130 nanometers. *nab*-Paclitaxel has been developed to improve the therapeutic index of paclitaxel; the chemotherapeutic effect is enhanced by exploiting endogenous transport pathways to deliver higher doses of paclitaxel to the tumor (Desai, 2006), while at the same time the toxicities associated with conventional solvent-based paclitaxel formulations using a Cremophor® EL CCI and ethanol vehicle are reduced.

*nab*-Paclitaxel is bound to albumin in amorphous state and, unlike conventional solvent-based paclitaxel formulations where micellar entrapment is observed (Ibrahim, 2002; Sparreboom, 1999; ten Tije, 2003), has linear pharmacokinetic (PK) characteristics. Based on these pharmacokinetic properties, the dose and short infusion time, an increase of the maximum concentration ($C_{max}$) of free paclitaxel up to 10-fold greater than with conventional solvent-based paclitaxel has been reported in the literature (Gardner, 2008). The transport of paclitaxel across the endothelium is enhanced through albumin receptor mediated transcytosis, and the delivery of paclitaxel to tumors may be enhanced by binding of the albumin-bound paclitaxel to interstitial albumin binding proteins, such as secreted protein acidic and rich in cysteine (SPARC; also known as osteonectin) (Desai, 2006). *nab*-Paclitaxel is not known to cross the blood-brain-barrier.

Although it has been hypothesized that SPARC expression may result in an increased concentration of *nab*-paclitaxel in tumors due to its albumin-binding ability, and may play a role in the enhanced antitumor activity, clinical studies remains conflicting (Alvarez-Gallego, 2012; Blackwell, 2010; Desai, 2009; Yardley, 2009) and therefore there is not sufficient data supporting the relationship of SPARC expression to clinical outcomes of *nab*-paclitaxel treatment.

Type of solid tumors had no significant effect on paclitaxel pharmacokinetics in patients who received *nab*-paclitaxel. Ethnic origin had no discernible effect upon PK parameters according to the studies conducted in Western countries, Japan and China.

The novel *nab*-paclitaxel nanoparticles conferred the ability to achieve a higher maximum tolerated dose (MTD) based on every 3-weeks dosing: 300 mg/m$^2$ for *nab*-paclitaxel (DM97-123) versus 175 mg/m$^2$ for conventional solvent-based paclitaxel (Nyman, 2004). The use of albumin also enables *nab*-paclitaxel to be given in a shorter, more convenient infusion time of 30 minutes compared with 3 hours to 24 hours with conventional solvent-based paclitaxel. *nab*-Paclitaxel is given without steroid and antihistamine premedication, which is required for conventional solvent-based paclitaxel to prevent solvent-related hypersensitivity reactions (Taxol Label). Cremophor EL has been shown to leach plasticizers, specifically di (2-ethylhexyl) phthalate (DEHP), from polyvinyl chloride (PVC) bags and polyethylene-lined tubing (Allwood, 1996; Gelderblom, 2001; Pfeifer, 1993; Song, 1996; Venkataramanan, 1986; Xu, 1998). Although no controlled epidemiologic toxicity studies have been conducted in humans exposed to DEHP, severe effects (eg, carcinogenicity, cardiopulmonary toxicity, hepatotoxicity, and nephrotoxicity) have been observed in experimental models. The Taxol product information instructs users to prepare, store, and administer solutions in glass, polypropylene, or polyolefin containers; non-PVC-containing infusion sets (eg, those with polyethylene lining) should be used

(Taxol Label). By comparison, standard tubing and intravenous (IV) bags may be used for the IV administration of *nab*-paclitaxel (Ibrahim, 2002; Nyman, 2004).

Clinical studies of *nab*-paclitaxel conducted in patients with breast cancer have demonstrated:

1. The ability to achieve a higher MTD of *nab*-paclitaxel at 300 mg/m$^2$ vs 175 mg/m$^2$ for conventional solvent-based paclitaxel.
2. Elimination of the need for premedication, which is required with conventional solvent-based paclitaxel to prevent solvent-related hypersensitivity reactions.
3. Shortened infusion times (infusion time of 30 minutes with *nab*-paclitaxel vs 3 hours for conventional solvent-based paclitaxel).
4. Elimination of the need for specialized infusion set apparatus (standard infusion sets suffice whereas non-DEHP [diethylhexylphthalate] sets are required for conventional solvent-based paclitaxel).

A Phase 3 comparison study (Study CA012-0) conducted in patients with metastatic breast cancer compared *nab*-paclitaxel (260 mg/m$^2$) with conventional solvent-based paclitaxel (175 mg/m$^2$). *nab*-Paclitaxel demonstrated greater efficacy (higher response rates, longer times to tumor progression [TTP], longer progression-free survival [PFS], and a 2.3 months overall survival advantage in patients previously treated for metastatic disease) with toxicity similar to that of conventional solvent-based paclitaxel, despite the higher dose of active agent achieved with *nab*-paclitaxel. Grade 4 neutropenia occurred less frequently in the *nab*-paclitaxel group, and did not appear to be related to cumulative dose. Instances of neutropenia were clinically asymptomatic and transient. Grade 3 sensory neuropathies occurred more frequently in the *nab*-paclitaxel group but improved in a median of 22 days.

A Phase 3 comparison study (Study CA031) conducted in patients with advanced NSCLC compared weekly *nab*-paclitaxel (100 mg/m$^2$) and once every three weeks carboplatin (area under the curve [AUC] = 6) against once every three weeks conventional solvent-based paclitaxel (200 mg/m$^2$) and carboplatin (AUC = 6) as first-line therapy. *nab*-Paclitaxel demonstrated significantly greater efficacy by overall response rate (ORR), with a trend toward greater response in PFS and overall survival (OS). There were significantly more ≥ Grade 3 events of sensory neuropathy, neutropenia, arthralgia, and myalgia in the conventional solvent-based paclitaxel arm, but more events of thrombocytopenia and anemia in the *nab*-paclitaxel arm (Socinski, 2012).

A Phase 3 comparison study conducted in patients with metastatic malignant melanoma compared *nab*-paclitaxel (150 mg/m$^2$) on days 1, 8 and 15 with one week rest (28 day cycle) against once every three weeks dacarbazine (1000 mg/m$^2$) as first line therapy. *nab*-Paclitaxel demonstrated significantly greater efficacy by PFS (median PFS 4.8 vs 2.5 months) with a trend towards improvement in OS (interim OS 12.8 vs 10.7 months). Neuropathy and neutropenia occurred significantly more often in the *nab*-paclitaxel arm (Hersh, 2012).

A Phase 3 comparison study conducted in patients with metastatic adenocarcinoma of the pancreas compared *nab*-paclitaxel (125 mg/m$^2$) with gemcitabine 1000 mg/m$^2$ on Days 1, 8, and 15 every 28 days against gemcitabine 1000 mg/m$^2$ alone weekly for seven weeks with one week rest, then weekly for three weeks with one week rest as first line therapy. *nab*-Paclitaxel with gemcitabine demonstrated statistically significant improvement in OS (8.5 versus 6.7 months

respectively) and all efficacy endpoints overall and across subgroups when compared to gemcitabine alone. The most common ≥ grade 3 adverse events reported in the *nab*-paclitaxel and gemcitabine combination arm included neutropenia, fatigue and neuropathy (Von Hoff, 2013).

In Phase 1 studies conducted in the adult population with advanced solid tumors designed to determine the MTD of *nab*-paclitaxel, the following dose-limiting toxicities were observed: keratitis, blurred vision, sensory neuropathy, stomatitis, and Grade 4 neutropenia. In general, hematologic toxicities were not important dose-limiting events; no life-threatening neutropenic infections and no Grade 4 anemia or thrombocytopenia were reported. The most frequently (> 50%) reported toxicities were all expected for this therapeutic drug class, namely fatigue, myalgia, nausea, alopecia, and stomatitis.

*nab*-Paclitaxel is approved globally for the treatment of metastatic breast cancer at a dosage of 260 mg/m² administered IV over 30 minutes once every 3 weeks, in the USA for the treatment of locally advanced or metastatic NSCLC at a dosage of 100 mg/m$^2$ on Days 1, 8, and 15 in combination with carboplatin (AUC = 6) on Day 1, every 21 days, and in the USA and EU for the treatment of first-line metastatic pancreatic adenocarcinoma at a dosage of 125 mg/m$^2$ (followed immediately by gemcitabine) on Days 1, 8, and 15 of each 28-day cycle.

Please refer to the Investigator Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies and adverse event (AE) profile of the IP.

### 1.2.2. Taxanes in Pediatrics

In children, taxanes have been studied in nine Phase 1 and five Phase 2 studies which are represented in Table 2 and Table 3, respectively. Although the efficacy and safety of *nab*-paclitaxel have been evaluated in adult patients with various cancers, there have been no human studies thus far on the effects of *nab*-paclitaxel in the pediatric age group.

In general, taxanes have demonstrated modest activity in children, mainly because of dose-limiting toxicities that limit efficacious dose delivery (Table 2 and Table 3). Standard taxanes, conventional solvent-based paclitaxel and docetaxel, have shown antitumor activity, but have also produced dose-limiting toxicities such as severe hypersensitivity requiring prophylactic medication and/or neutropenia (Blaney, 1997; Geller, 2009). It is also notable that the alcohol in Cremophor EL (polyoxyethylated castor oil) produces central nervous system toxicity in pediatric patients receiving IV infusion of conventional solvent-based paclitaxel over 3 hours (Doz, 2001).

**Table 2: Phase 1 Trials of Taxanes in Children**

| Reference | Agent | N | Age (eligible/ enrolled) | Schedule | Maximum Tolerated Dose | Dose-Limiting Toxicity | Response[a] |
|---|---|---|---|---|---|---|---|
| Hurwitz, 1993 | paclitaxel | 31 | ≤ 22 years / 2-22 years | 24-h infusion/ 21 days | 350 mg/m$^2$ | Neurological | 1 CR (papillary serous carcinoma)<br>2 PR (rhabdomyosarcoma, hepatocellular carcinoma)<br>9 SD (3 Ewing tumors, 2 osteosarcomas, 2 synovialosarcoma, 1 glioma, 1 intrathoracic chordoma) |
| Doz, 2001 | Paclitaxel | 17 | 6 months to 20years/ 1.6 - 19 years | 3-h infusion/ 21 days | No | Neurological, allergic | 0 CR<br>1 PR (rhabdomyosarcoma)<br>1 SD (rhabdomyosarcoma) |
| Woo, 1999 | Paclitaxel | 7 | ≤ 21 years / 6 – 18 years | 24-h infusion/ 21 days | Target AUC 31 to < 45 mM h | Mucositis | 1 patient (leukaemia) responded sufficiently (response or SD) to receive a second cycle |
| Liu, 2001 | Paclitaxel and radiotherapy | 11 | 3-18 years/ 4 – 16 years | 24-h infusion times 7 days | 4 mg/m$^2$/day | Obstipation | 2 PR: glioma |
| Hayashi, 2003 | Paclitaxel | 16 | ≤ 21 years / 7 – 15 years | 3-h infusion twice weekly ×6/28 days | 50 mg/m$_2$ /dose | Hematologic | 0 CR<br>0 PR<br>3 SD (2 osteosarcomas, 1 ependymoma) |
| Horton, 2008 | Paclitaxel | 63 | ≤ 21 years at diagnosis / 0.8 – 23 years | 24 h infusion/ 21 days or weekly for 3 weeks every 28 days | 430 mg/m2 every 21 day, 182 mg/m2 weekly | Hypertension, coagulopathy, metabolic, hepatic, neurological, stomatitis, typhitis | 1 CR (ALL)<br>3 PR (ALL)<br>4 SD |
| Blaney, 1997 | Pocetaxel | 44 | 1 – 21 years/ 1 – 22 years | 1-h infusion/ 21 days | 125 mg/m$^2$ /dose | Hematologic, general | 1 CR (rhabdomyosarcoma)<br>1 PR (PNET)<br>4 SD (3 PNET, 1 colon carcinoma) |
| Seibel, 1999 | Docetaxel and filgrastim | 17 | 1 – 21 years/ 2 – 20 years | 1-h infusion/ 21 days 5µg/kg/ day | 185 mg/m$^2$ /dose | Dermatologic, myalgias | 0 CR<br>1 MR (colon carcinoma)<br>SD: not mentioned |

**Table 2: Phase 1 Trials of Taxanes in Children (Continued)**

| Reference | Agent | N | Age (eligible/ enrolled) | Schedule | Maximum Tolerated Dose | Dose-Limiting Toxicity | Response |
|---|---|---|---|---|---|---|---|
| Geller, 2009 | Paclitaxel and ifosfamide | 15 | ≤ 21 years/ 2 – 18.8 years | Pac 6-h infusion D1/ ifos 2 g/m$^2$ over 1 hour w/ mesna D1-3, q3-4 wk | 425 mg/m$^2$ | Hypersensitivity, neurologic, | 3 MR<br>5 SD |

Table adapted from André, 2006.
ALL = acute lymphocytic leukemia, AUC = area under the curve, CR = complete response, D = Day, DLT = dose-limiting toxicity, h = hour(s), ifos = ifosfamide, mesna = 2-mercaptoethane sulfonate sodium, MTD = maximum tolerated dose, MR = minor response, PNET = primitive neuroendocrine tumors, PR = partial response, SD = stable disease.

**Table 3: Phase 2 Trials of Taxanes in Children**

| Reference | Agent | N | Age | Dose/Schedule | Results[a] |
|---|---|---|---|---|---|
| Hurwitz, 2001 | Paclitaxel | 73 | ≤ 21 years at diagnosis/ 4 months – 19 years | 350 mg/m$^2$ 24-h infusion/ 21 days | Toxicities: mild nausea, central nervous system toxicity, myelosuppression, and febrile neutropenia, including one septic death. One Grade 2 and two Grade 3 allergic reactions. No cardiac toxicities or arthralgias reported.<br>CR: 1 (meduloblastoma), PR: 3 (astrocytoma, glioma, and primitive neuroectodermal)<br>SD (> 2 months): 20 |
| Kretschmar, 2004 | Paclitaxel, topotecan, topotecan-cyclophosphamide | 100 total, 33 paclitaxel | 1 – 21 years/ 13 months – 17 years 8 months | 33 patients: 350 mg/m2 intravenously for 24 h every 14–21 days | Grade 3/4 allergic reactions to paclitaxel in 4 patients. Grade 3/4 neutropenia in 16 patients, Grade 3/4 thrombocytopenia in 6 patients.<br>CR= 1; PR = 5; MR=2, PD = 12, Objective responses (defined as complete responses + partial responses + mixed responses) documented in 25% patients treated with paclitaxel. |
| Zwerdling, 2006 | Docetaxel | 160 | ≤ 21 years old at diagnosis/ 1-27 years | 125 mg/m$^2$, 1-h infusion/ 21 days | Hematologic toxicity most common during therapy. Dermatologic, neurologic, pulmonary, infectious side effects, and edema were significant.<br>CR: 2 (1 patient with osteosarcoma and 1 patient with rhabdomyosarcoma)<br>PR: 6 (3 patients with Ewing sarcoma, 1 patient with osteosarcoma, 1 patient with squamous cell carcinoma, 1 patient with medulloblastoma)<br>SD: 17 patients<br>The 1-year and 5-year overall survival rates for the 160 evaluable patients were 24% (standard error = 4%) and 6% (standard error = 2%). |

**Table 3: Phase 2 Trials of Taxanes in Children (Continued)**

| Reference | Agent | N | Age | Dose/Schedule | Results |
|---|---|---|---|---|---|
| Taxotere® prescribing information | Docetaxel, cisplatin, 5-fluorouracil (5-FU) | 75 (50 docetaxel combination arm) | Not reported/ 1 – 22 years | Docetaxel 75 mg/m2, cisplatin 75 mg/m2, 5-FU 750 mg/m2 | Safety data not reported<br>CR: 1 (out of 50) in docetaxel/cisplatin/ 5-FU arm<br>0 (out of 25) in cisplatin/5-FU arm |
| Harris, 1999 | Paclitaxel | 186 | ≤ 21 years\ not reported | 350 mg/m$^2$, 24-h infusion every 3 weeks | (Safety presented by number of courses associated with event)<br>Neutropenia Grade 3/4: 297 courses<br>Neurotoxicity Grade 3/4: 2 courses<br>Hypersensitivity Grade 4: 1 courses<br>Cardiac toxicity Grade 3: 1 courses<br>CR+PR =11 (1 neuroblastoma, 1 Ewing's sarcoma, 3 rhabdomyosarcoma, 2 nonrhabdo soft-tissue sarcoma, 2 Wilms' tumor, 1 Merkels tumor)<br>MR+SD = 56<br>PD= 99 |

[a] CR = complete response, MR = minor response, PD = progressive disease, PR = partial response, SD = stable disease.

### 1.2.3. *nab*-Paclitaxel Preclinical Studies

In preclinical studies of neuroblastoma models, *nab*-paclitaxel inhibited cell proliferation in vitro and reduced tumor growth in xenograft models, and increased survival in metastatic neuroblastoma mouse models with intratumoral concentration of *nab*-paclitaxel 40 times higher compared to paclitaxel (data on file). In vitro, inhibition of cell proliferation was observed in all rhabdomyosarcoma cell lines studied (RH4, RH30, and RD) and a modest response was seen in the osteosarcoma cell line used in the study (KHOS).

In Study S758, seven neuroblastoma cell lines (CHLA-20, CHLA-15, CHLA-90, LAN-5, SK-N-BE(2), BE(2)C, and SH-SY5Y), three rhabdomyosarcoma (RH4, RH30, and RD), and one osteosarcoma cell line (KHOS) were exposed to increasing concentrations of *nab*-paclitaxel in vitro for 72 hours.

For the seven neuroblastoma cell lines, *nab*-paclitaxel exhibited dose-dependent cytotoxicity in vitro, as measured by cell viability with variable sensitivity. In addition, all three rhabdomyosarcoma cell lines were responsive to *nab*-paclitaxel treatment in a dose-dependent manner as measured by cell viability, while limited response was observed in the osteosarcoma cell line. *nab*-Paclitaxel was also more effective than an equivalent dose of paclitaxel dissolved in dimethyl sulfoxide (DMSO) after 72-hour treatment in all neuroblastoma cell lines tested.

In a separate experiment, athymic nude mice bearing CHLA-20 human neuroblastoma xenografts were treated with *nab*-paclitaxel (10 mg/kg/day IV for 5 consecutive days, or 50 mg/kg IV weekly), or DMSO-paclitaxel (20 mg/kg IV weekly). *nab*-Paclitaxel treatment resulted in significant tumor inhibition. *nab*-Paclitaxel at 50 mg/kg IV weekly also demonstrated significantly greater antitumor activity compared with DMSO-paclitaxel at 20 mg/kg IV weekly.

In athymic mice bearing RH4 rhabdomyosarcoma xenografts, *nab*-paclitaxel dosed at 50 mg/kg IV weekly for 3 weeks was better tolerated than DMSO-paclitaxel at 30 mg/kg IV weekly for 3 weeks as shown by animal body weight. Animals treated with DMSO-paclitaxel had earlier

tumor relapses, which could be suppressed by rechallenging with *nab*-paclitaxel but not with DMSO-paclitaxel.

In athymic mice bearing RD rhabdomyosarcoma xenografts, *nab*-paclitaxel (50 mg/kg) and DMSO-paclitaxel (30 mg/kg) dosed IV weekly showed similar body weight change. However, *nab*-paclitaxel was significantly more effective than DMSO-paclitaxel in suppressing RD tumor growth. Further, *nab*-paclitaxel inhibited growth of tumors that continued to progress with DMSO-paclitaxel treatment.

In a separate study with osteosarcoma xenograft nude mice models, *nab*-paclitaxel demonstrated a significantly greater tumor inhibitory rate when compared to adriamycin and conventional solvent-based paclitaxel (99 vs 46% and 41% respectively) (Yang, 2012).

The Pediatric Preclinical Testing Program at National Cancer Institute evaluated *nab*-paclitaxel against a group of pediatric solid tumor xenografts. Results showed that *nab*-paclitaxel administered IV at 50 mg/kg, every 4 days repeated 3 total times was well tolerated in non-tumored and xenograft-bearing SCID mice. Two Ewing's sarcoma xenografts tested (SK-NEP-1 and EW8) and the rhabdomyosarcoma xenograft Rh65 showed maintained complete responses (MCR) following *nab*-paclitaxel treatment. Osteosarcoma xenografts OS-9 and OS-17, and neuroblastoma xenografts NB-1643 and NB-1691 did not show tumor regression to *nab*-paclitaxel, and only showed minimal tumor growth delay.

In summary, recent nonclinical study results have demonstrated that *nab*-paclitaxel displayed dose-dependent cytotoxicity and was also more effective than an equivalent dose of solvent-based paclitaxel in the majority of pediatric solid tumor cell lines tested. Higher doses of *nab*-paclitaxel administered resulted in increased intratumor paclitaxel levels in vivo in mice bearing pediatric tumor xenografts. Further, *nab*-paclitaxel displayed antitumor activity in vivo against pediatric solid tumor models in a dose-dependent fashion and demonstrated increased efficacy compared to solvent-based paclitaxel. Taken together, these nonclinical results suggest that *nab*-paclitaxel, delivered at higher dose than conventional paclitaxel, potentially may achieve clinical benefits in pediatric diseases where conventional paclitaxel is not effective (Zhang, 2013).

## 1.3. Study Rationale

### 1.3.1. Role of *nab*-Paclitaxel in Fulfilling the Unmet Medical Need

The prognosis of pediatric patients with metastatic disease continues to be poor. Survival rates for patients with localized disease are approximately 50% to 70% with the current treatment modalities for neuroblastoma, rhabdomyosarcoma, osteosarcoma, and Ewing's sarcoma. Thus, a great unmet medical need remains for patients with metastatic disease or relapsed localized disease. In the light of therapies currently available for pediatric solid tumors, *nab*-paclitaxel may be a potentially superior alternative treatment option, due to its unique mechanism of action, safety profile (including absence of Cremophor EL), and pharmacodynamics/PK, which distinguish it from conventional solvent-based paclitaxel or docetaxel.

*nab*-Paclitaxel may offer in children, similarly to the adult population, improved efficacy, with lower levels of toxicities as compared to conventional solvent-based paclitaxel due to:

- Enhanced binding of paclitaxel to albumin, microtubules, and cells and increased tissue bioavailability of paclitaxel when compared to conventional solvent-based

paclitaxel, since the paclitaxel is not trapped in the plasma compartment by Cremophor EL micelles

- Increased transendothelial transport by albumin specifically binding to a 60-kDa glycoprotein receptor on the endothelial cell surface, which leads to the formation of caveolae and transcytosis across endothelial cells
- Increased accumulation of the drug at the tumor level
- Linear pharmacokinetic profile
- Absence of Cremophor EL and alcohol in the formulation of *nab*-paclitaxel, reducing the incidence of hypersensitivity reactions, sensory neuropathy, and central nervous system toxicity in children.

### 1.3.2. Rationale for Study Design

This study will consist of two parts: a Phase 1 dose-escalation portion and a Phase 2 expansion portion.

In the Phase 1 portion of this pediatric study, the dose will be escalated using the rolling-6 design, in which cohorts of up to 6 patients will be enrolled, starting with a dose of 120 mg/m² weekly, 80% of the maximum weekly dose investigated in adult patients (150 mg/m²). This strategy presumes that children may have a similar or higher threshold for toxicity in comparison to adults. The rolling-6 design allows a sufficient number of patients to be evaluated for safety and PK at each dose level, while limiting the duration of the study (Skolnik, 2008).

In the Phase 2 portion of this study, patients will be treated at the recommended Phase 2 dose (RP2D), determined during the Phase 1 portion of the study to be 240 mg/m$^2$ in patients weighing > 10 kg (11.5 mg/kg in patients weighing ≤ 10 kg), in order to assess antitumor activity in neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma. Antitumor activity in the neuroblastoma group will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria or $^{123}$I-metaiodobenzylguanidine (MIBG)/Curie score, or both, without crossover between assessment types over time. If both assessment types have been performed on a given subject across the assessment time points, to be considered as a partial response for the ORR analysis, both methodologies should show no worse than stable disease and at least one method should indicate complete response (CR) or partial response (PR). A response is only considered complete if both methodologies indicate CR. This analysis takes into account the fact that both methodologies are used in the assessment of response in neuroblastoma patients, and a partial response obtained by only one method is nevertheless clinically important for determining subsequent treatment options. Studies have shown that high-risk neuroblastoma patients with a Curie score > 2 following induction chemotherapy have extremely poor outcomes, leading to alternative therapies as subsequent options (Yanik, 2013). A Simon two-stage minimax design (Simon, 1989) will be used to limit *nab*-paclitaxel exposure to 14 patients in each group without confirmation of some activity (≥ 2 patients) before moving forward with 9 additional patients in each group. The Simon two-stage design was chosen to minimize the number of patients exposed to *nab*-paclitaxel if the true ORR is less than 10% and yet to allow the trial to establish that an ORR greater than 10% is efficacious.

#### 1.3.2.1. Rationale for Patient Population

In the Phase 1 dose escalation portion, the study will be conducted in patients ≥ 6 months and < 18 years old with recurrent and refractory solid tumors, except brain tumors, that have progressed on standard therapy or for which no standard anticancer therapy exists. The broad eligibility will allow the most rapid identification of the MTD/RP2D.

In the Phase 2 portion, the study will focus on patients with recurrent/refractory neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma. These types of tumors have been selected since they are most likely to be sensitive to *nab*-paclitaxel based on preclinical data. The age range is extended to ≤ 24 years old (young adults) in the Phase 2 portion of the study to increase the likelihood of including patients with recurrent and refractory solid tumors. Patients 15 to 24 years of age are now commonly referred to as "teenagers and young adults"; the European Society for Medical Oncology (ESMO) is collaborating with the European Society of Pediatric Oncology (SIOPE) to target the unmet medical needs of adolescents and young adults, due in part to the varied interfaces between adult and children's services in different healthcare systems (Vassal, 2014). Many patients diagnosed with neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma are followed in pediatric clinics up to 24 years of age, particularly in the recurrent and relapsed setting. For example, an analysis of data from 1973 to 2007 from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database shows that the median age at diagnosis of Ewing's sarcoma is mid-to-late teens (Applebaum, 2011), so many patients with recurrent disease who have undergone several lines of treatment will be in their early twenties. In addition, it will be important to capture instances of confirmed PR as well as CR in order to have a proper chance to evaluate treatment effect and ORR (the primary Phase 2 endpoint) using the Simon two-stage minimax design; therefore, the patients will be required to have radiologically documented measurable disease (for neuroblastoma, evaluable disease by MIBG/Curie score is also acceptable). Patients with these types of tumors may have compromised bone marrow function. In order to prevent their exclusion in the Phase 2 portion of this study, patients with known bone marrow involvement may be enrolled with a platelet level ≥ $50 \times 10^9$ cells/L.

Patients younger than 6 months old have been excluded from this study. Spontaneous regressions of cancers have been reported, especially in neuroblastoma and renal cell carcinoma (Fritsch, 2004; Oluwole, 2009), and may occur in the proposed patient population. The current practice is to adopt a conservative observation (wait-and-see) strategy for patients identified at 6 months of age with limited-stage disease. Furthermore, for more advanced pediatric tumors, surgical treatment (in the case of resectable tumors), radiotherapy, or combination of chemotherapy provide good results as first-line treatment (Berg, 1991; Kim, 2006). Therefore, it would be highly unlikely that patients 0 to 6 months old could be enrolled in the study while a wait-and-see strategy is recommended for limited-stage diseases, and as effective treatment options are currently available for more advanced tumors; consequently, enrollment in a clinical study would not be the preferred treatment option.

#### 1.3.2.2. Rationale for Pharmacokinetics

The *nab*-paclitaxel PK in adult patients has not differed among different tumor types, and is not expected to differ among tumor types in pediatric patients. From this perspective, PK results

obtained from pediatric patients with various types of solid tumors can be extended to any particular type of tumor.

### 1.3.3. Rationale for Dosing

The starting dose in the Phase 1 portion of the study is 120mg/m² weekly on days 1, 8, and 15 of a 28-day cycle, which represents 80% of the maximum weekly dose investigated in adult patients (150 mg/m²) (see Section 1.2.1). Preliminary evaluation of the relationship between paclitaxel clearance and body surface area (BSA) or weight suggests that BSA or weight has minimal impact on paclitaxel clearance in adults patients treated with *nab*-paclitaxel. However, it is unknown if this observation can be extrapolated from adults to children. Since the BSA-based dosing is more conservative and is the approved dosing approach for adult patients, the *nab*-paclitaxel dose will be based on BSA in the pediatric study.

As it is impractical to accurately calculate BSA in children weighing ≤ 10 kg, the BSA-based dose will be converted to mg per kg of weight in these children. The weight-based dose in each cohort is calculated by dividing the total dose at the median BSA (0.41 m²) with the median weight (8.7 kg) for children with weight ≤ 10 kg and aged ≥ 6 months. Additionally, in order to ensure safety in these small children, patients ≤ 10 kg will receive treatment at one dose level lower during the first cycle. The dose-limiting toxicity (DLT) assessment period in these patients will last until the end of Cycle 2.

In three recent adult *nab*-paclitaxel Phase 3 Celgene sponsored studies (NSCLC, melanoma, pancreatic cancer), *nab*-paclitaxel was administered weekly alone (melanoma: 150 mg/m$^2$ weekly on days 1, 8, and 15 of a 28-day cycle) or in combination (NSCLC: 100 mg/m$^2$ continuous weekly dosing; pancreatic cancer: 125 mg/m$^2$ weekly on days 1, 8, and 15 of a 28-day cycle). As a single agent, the weekly dose of 150 mg/m$^2$ used in the melanoma Phase 3 trial and other Phase 1 and 2 studies, the proposed dose level 2 in this trial (See Table 7), was safe and well tolerated and with manageable toxicities.

# 2. STUDY OBJECTIVES

## 2.1. Primary Objective

The primary objective of the Phase 1 portion of the study is to determine the pediatric MTD/RP2D and characterize the safety and tolerability of *nab*-paclitaxel administered intravenously over approximately 30 minutes on Days 1, 8, and 15 of a 28-day cycle in patients ≥ 6 months and < 18 years old with recurrent or refractory solid tumors.

The primary objective of the Phase 2 portion of the study is to determine the antitumor activity assessed by the overall response rate (ORR) of *nab*-paclitaxel given at the RP2D in patients ≥ 6 months and ≤ 24 years old with several discrete recurrent or refractory solid tumor types including neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma.

## 2.2. Secondary Objectives

The secondary objectives of the Phase 1 portion are:

- To evaluate pharmacokinetics (PK).
- To characterize the ORR.

The secondary objectives of the Phase 2 portion are:

- To characterize duration of response (DOR).
- To characterize the disease control rate (DCR).
- To characterize progression-free survival (PFS).
- To characterize 1-year survival.
- To confirm safety.
- To evaluate PK.

## 2.3. Exploratory Objectives

The exploratory objectives of the entire study are:

- In the Phase 1 portion, to assess $^{123}$I-metaiodobenzylguanidine (MIBG) response in patients with neuroblastoma.
- To explore the potential utility of biomarkers of response and resistance in this study population. The most recent available tumor tissue sample will be optionally collected at the time of study entry. Biomarkers will be prioritized for analysis in these samples after study completion, as informed by emerging data.

# 3. STUDY ENDPOINTS

## 3.1. Primary Endpoint(s)

The primary endpoint of the Phase 1 portion of the study is the incidence of DLTs (defined in Section 8.2.1.1) and the incidence of treatment-emergent adverse events (TEAEs).

The primary endpoint of the Phase 2 portion of the study is the ORR, which is the combined incidence of CR and PR, confirmed no less than 4 weeks after the criteria for response are first met, based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. In the neuroblastoma group the ORR will be determined by RECIST and/or the Curie scale (MIBG response), as specified in Section 6.3.

## 3.2. Secondary Endpoint(s)

The secondary endpoints for the Phase 1 portion of the study are:

- Pharmacokinetic parameters including the maximum observed concentration in blood ($C_{max}$), area under the blood concentration-time curve (AUC), clearance and volume of distribution (Vss).
- ORR.

The secondary endpoints for the Phase 2 portion of the study are:

- DOR in patients with a confirmed objective complete response (CR) or partial response (PR).
- DCR is the percentage of patients with a confirmed objective CR or PR, or stable disease for at least 16 weeks.
- PFS based on investigator assessment of response using RECIST 1.1 guidelines. In the neuroblastoma group the PFS will be determined by RECIST and/or the Curie scale (MIBG response), as specified in Section 6.3.
- Survival at 1 year.
- The incidence of TEAEs.
- Population PK parameters (eg, clearance and volume of distribution). Data from the Phase 1 and 2 portions will be analyzed together for this endpoint.

## 3.3. Exploratory Endpoints

The exploratory endpoints for the entire study are:

- In the Phase 1 portion only, MIBG response using Curie score.
- Biomarker analysis prioritized after study completion, as informed by emerging data.
- In the Phase 2 portion only, bone marrow biopsy verification of confirmed complete response in patients with neuroblastoma.

# 4. OVERALL STUDY DESIGN

## 4.1. Study Design

This is a Phase 1/2 multicenter, open-label, dose-finding study to assess the safety, tolerability, PK, and efficacy of *nab*-paclitaxel administered intravenously to patients ≥ 6 months and < 18 years old in the Phase 1 portion and patients ≥ 6 months and ≤ 24 years old in the Phase 2 portion with recurrent and refractory solid tumors.

The Phase 1 portion will be a dose-finding study (rolling-6 design, see section 8.2.1.3) to determine the MTD/RP2D, safety, tolerability, and PK parameters of *nab*-paclitaxel in pediatric patients with recurrent and refractory solid tumors who have progressed on standard therapy or for whom no standard therapy exists. The decision to dose-escalate or to declare an MTD/RP2D will be determined by the safety monitoring committee (SMC) each time clinical and laboratory safety data for a given cohort are available for review. The SMC will also determine the dose(s) appropriate for the Phase 2 portion of the study (or the RP2D).

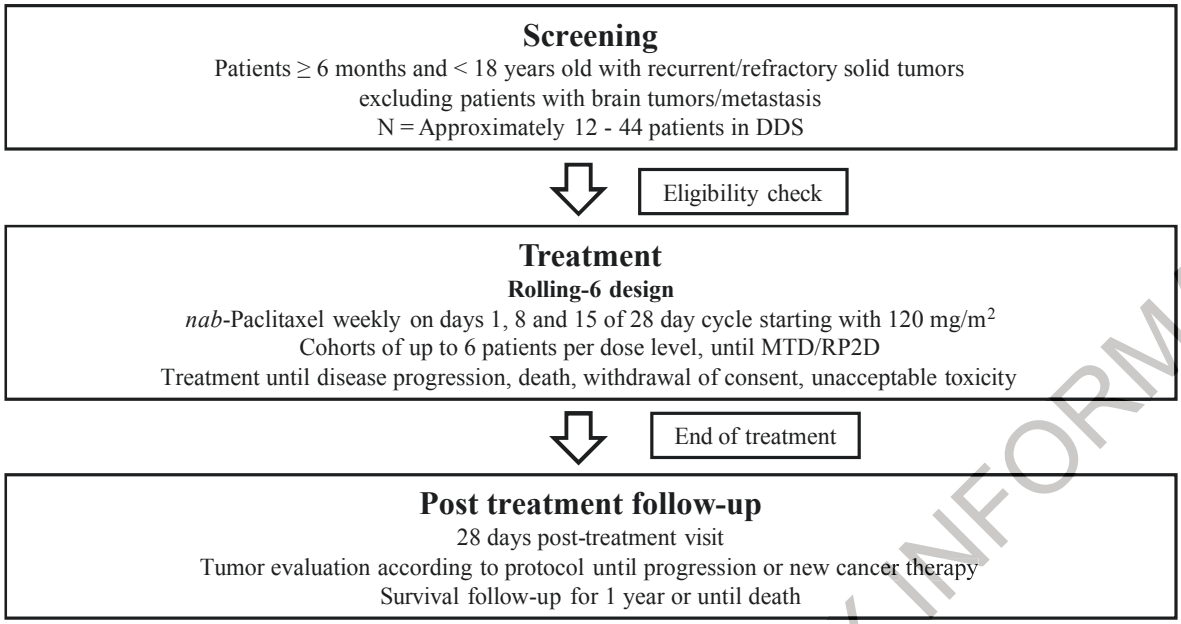
The Phase 2 portion of the study will be conducted at the RP2D, 240 mg/m$^2$ in patients weighing > 10 kg and 11.5 mg/kg in patients weighing ≤ 10 kg, to determine:

1. The antitumor activity of *nab*-paclitaxel in several solid tumor types (three groups: neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma).
2. The safety profile and pharmacokinetics of *nab*-paclitaxel administered at the RP2D.

During the Phase 2 portion, the SMC will continue to review safety data regularly and make recommendations about the study continuation, as appropriate (see Section 8.2.1.2).

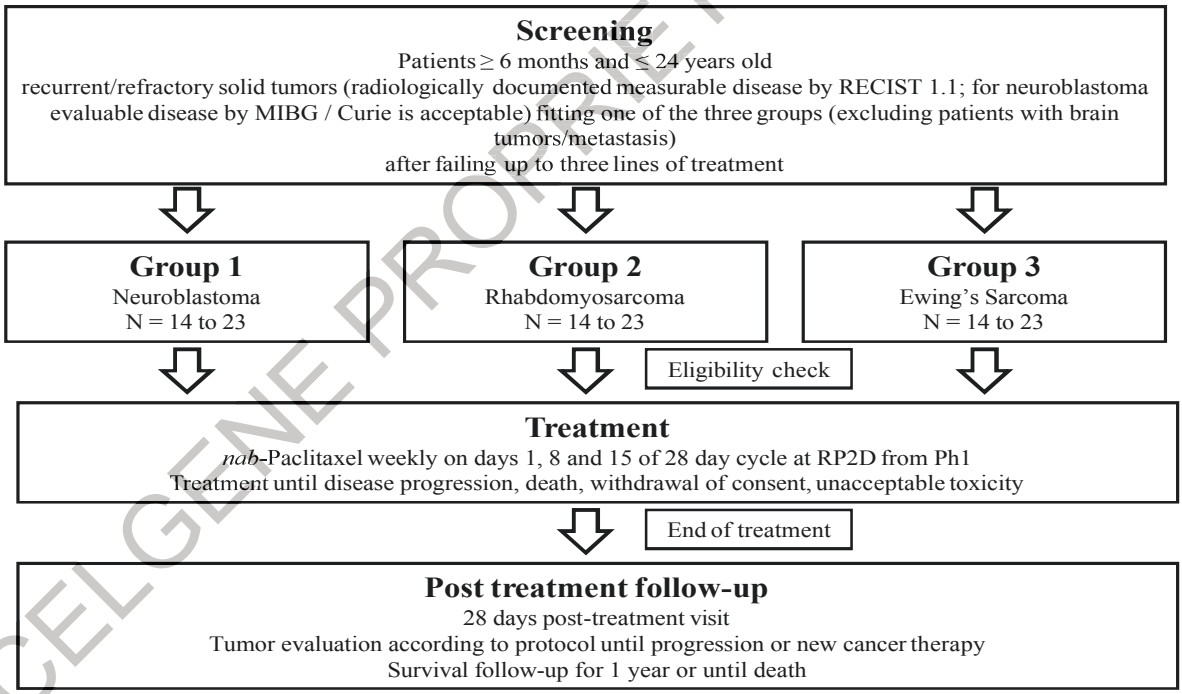
The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

**Figure 1: Phase 1 Study Design**




Refer to Table 7 for dose levels.

**Figure 2: Phase 2 Study Design**



## 4.2. Study Duration

In both the Phase 1 and 2 portions of the study, patients will enter a 14-day screening period, and if eligible (and the cohort/group is open for recruitment) will proceed to the treatment phase. Patients may remain on treatment at the discretion of the investigator until disease progression, unacceptable toxicity, until he/she begins a new anticancer therapy, withdrawal of parent/guardian/patient consent/assent, parent/guardian/patient refusal, physician decision, or death. At the discretion of the investigator, treatment may continue beyond radiologic progression if the patient is benefiting based on other response criteria.

All patients in both portions of the study will be followed for 28 days after discontinuing treatment for safety and monitoring of adverse events, until progression (if applicable) for response, and for 1 year after the last dose of *nab*-paclitaxel for survival and new anticancer therapies.

The Phase 2 portion of the study will begin when the RP2D has been declared in the Phase 1 portion.

## 4.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last patient to complete the study, or the date of receipt of the last data point from the last patient that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

# 5. TABLE OF EVENTS

The Table of Events is applicable to both the Phase 1 and Phase 2 portions of the study.

**Table 4: Table of Events**

| Events | Screening Period | Treatment Period | | | | | | | | | | Follow-up Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Cycle 1 | | | | | | Subsequent Cycles | | | | | |
| Day[a] | -14 to -1 | 1 | 2 | 3 | 4 | 8 | 15 | 1 | 8 | 15 | EOT | 28 Day Safety Visit[b] | Disease Progression/ Survival |
| **STUDY ENTRY** | | | | | | | | | | | | | |
| Informed consent and if applicable assent | X | | | | | | | | | | | | |
| Prior cancer history | X | | | | | | | | | | | | |
| Prior cancer therapies[c] | X | | | | | | | | | | | | |
| Complete medical history | X | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | |
| Prior/ concomitant medication evaluation | X (-28 from screening) | Continuous, until 28 days after treatment discontinuation | | | | | | | | | | | |
| Prior/ concomitant procedures evaluation | X (-28 from screening) | Continuous, until 28 days after treatment discontinuation | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | | | | | |
| IRT registration | X | | | | | | | | | | | | |
| Archival tumor tissue collection (optional) | X, after eligibility confirmation | | | | | | | | | | | | |
| **SAFETY ASSESSMENTS** | | | | | | | | | | | | | |
| Adverse event evaluation | Continuous starting after informed consent/assent signature, until 28 days after treatment discontinuation (and as noted in Section 6.2.1.1) | | | | | | | | | | | | |

**Table 4: Table of Events (Continued)**

| Events | Screening Period | Treatment Period | | | | | | | | | | Follow-up Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Cycle 1 | | | | | | Subsequent Cycles | | | | | |
| Day[a] | -14 to -1 | 1 | 2 | 3 | 4 | 8 | 15 | 1 | 8 | 15 | EOT | 28 Day Safety[g] Visit | Disease Progression/ Survival |
| Physical examination (source documented only) | X | X | | | | X | X | X | X | X | X | X | |
| Weight | X | X | | | | X | X | X | X | X | X | X | |
| Height | X | X | | | | X | X | X | X | X | X | X | |
| Body surface area calculation | | X | | | | X | X | X | X | X | | | |
| Vital signs[d] | X | X | | | | X | X | X | X | X | X | X | |
| Hematology laboratory | X | X | | | | X | X | X | X | X | X | X | |
| Chemistry laboratory[e] | X | X | | | | | | X | | | X | X | |
| Urine homovanillic acid and vanillylmandelic acid (for neuroblastoma only) | X | | | | | | | Every other cycle, starting in Cycle 2 | | | X | X | |
| LVSF assessment by echocardiogram/ MUGA/ other medically appropriate method | X | | | | | | | Every other cycle starting in Cycle 3 | | | X | | |
| 12-lead electrocardiogram | X | | | | | | | Every other cycle starting in Cycle 3 | | | X | | |
| Serum β-hCG (if indicated)[f] | X | As clinically indicated | | | | | | | | | | | |
| Urine β-hCG (if indicated)[f] | X | As clinically indicated | | | | | | | | | X | | |

**Table 4: Table of Events (Continued)**

| Events | Screening Period | Treatment Period | | | | | | | | | | Follow-up Period | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | Cycle 1 | | | | | | Subsequent Cycles | | | | | |
| Day[a] | -14 to -1 | 1 | 2 | 3 | 4 | 8 | 15 | 1 | 8 | 15 | EOT | 28 Day Safety Visit[g] | Disease Progression/ Survival |
| Pharmacokinetic samples[g] | | X | X | X | X | | | | | | | | |
| **EFFICACY ASSESSMENTS** | | | | | | | | | | | | | |
| Tumor evaluation (CT/MRI, see Section 6.3) | X (-28 to -1) | Every 8 weeks (± 5 days) from Cycle 1 Day 1, until progression or new anticancer treatment | | | | | | | | | | | |
| MIBG scan (in patients with neuroblastoma) | X (-28 to -1) | If assessable by MIBG scan at screening, every 8 weeks (± 5 days) from Cycle 1 Day 1, until disease progression or new anticancer treatment. If not assessable by MIBG scan, at screening and suspected progression only. | | | | | | | | | | | |
| Bone marrow biopsy (in patients with neuroblastoma) | | Only at confirmation of complete response | | | | | | | | | | | |
| Lansky performance status (in patients < 12 years old) | X | X | | | | | | X | | | X | X | |
| Karnofsky performance status (in patients ≥ 12 years old) | X | X | | | | | | X | | | X | X | |
| **INVESTIGATIONAL PRODUCT (IP)** | | | | | | | | | | | | | |
| Administer *nab*-paclitaxel | | X | | | | X | X | X | X | X | | | |
| **FOLLOW-UP** | | | | | | | | | | | | | |
| Survival follow-up | | | | | | | | | | | | | Every 1 month for 1 year |
| Anticancer therapy since *nab*-paclitaxel discontinuation | | | | | | | | | | | | X | At every survival follow-up visit for 1 year |

β-hCG = β human chorionic gonadotropin, C#D# = Cycle number Day number, CR= complete response, CT = computed tomography scan, EOT = end of treatment visit, IRT = Integrated Response Technology, LVSF = left ventricular shortening fraction, MIBG = $^{123}$I- metaiodobenzylguanidine scan, MRI= magnetic resonance imaging, MUGA = multi-gated acquisition scan.

[a] An administrative window of ± 2 days is permitted for all visits except C1D1.

[b] If the EOT visit occurs within 7 days of the 28 day safety visit, laboratory evaluations only need to be repeated for abnormal parameters at the EOT visit.

[c] Prior cancer therapies includes surgery, radiation, stem cell transplant, systemic or any other therapy for the patient's cancer.

[d] Vital sign measurements must be recorded in the database at screening and EOT only, and kept in the source documents at all other visits. However, if an abnormal (out of range) value is reported at a given visit, that parameter should be collected in the case report form (CRF) at every subsequent scheduled visit until it returns to normal.

[e] In patients with neuroblastoma ferritin will be analyzed.

[f] For all female patients of childbearing potential (see Inclusion 8), a serum pregnancy test will be done at screening. A urine pregnancy test will be repeated within 72 hours before first treatment if the serum pregnancy test occurred > 72 hours before dosing, and at EOT. Pregnancy tests conducted after screening will be recorded in the source documentation only.

[g] All patients will have pharmacokinetic samples taken on C1D1. A subset of patients will have samples taken on C1D2, C1D3, and C1D4 as described in Section 6.4.

# 6. PROCEDURES

Screening evaluations will be performed for all patients to determine study eligibility. These evaluations must be completed within 14 days of first dosing unless noted below.

Any questions regarding patient eligibility should be directed to the Celgene medical monitor or designee. Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Safety laboratory analyses and all assessments (with the exception of PK and biomarker analyses) will be performed locally. Laboratory normal ranges must be submitted to the Celgene or designated contract research organization (CRO) data manager. Screening laboratory values must demonstrate patient eligibility, but may be repeated within the screening window if necessary.

The following will be performed at screening as specified in the Table of Events, after informed consent/assent has been obtained:

- Cancer history (including specific information regarding diagnosis, staging, and histology)
- Demographics (initials, date of birth, sex, race, and ethnicity-if allowed by local regulations)
- Prior cancer therapies: includes surgery, radiation, stem cell transplant, systemic or any other therapy for the patient's cancer
- Complete medical history (all relevant medical conditions occurring more than 28 days before screening should also be included)
- Prior and concomitant procedures (including all procedures occurring ≤ 28 days before screening)
- Prior and concomitant medication evaluation (including those taken ≤ 28 days before screening, except for those taken for cancer)
- Archival tumor sample collection (optional): If available and consented, the sample should be retrieved and sent after patient eligibility is confirmed. It is recommended that this be sent before the end of Cycle 1
- Physical examination (source documented only), height, weight
- Vital signs (including blood pressure, temperature, and heart rate)
- Performance status
  - Lansky performance status recommended in patients < 12 years old at the time of informed consent/assent
  - Karnofsky performance status recommended in patients ≥ 12 years old at the time of informed consent/assent

  - An individual patient should be evaluated by the same performance status method or scale for the duration of the study

- Left ventricular shortening fraction (LVSF) assessment by echocardiogram, multi-gated acquisition (MUGA) scan, or other medically appropriate method (eg, magnetic resonance imaging, MRI). Patients with a historical LVSF assessment performed ≤ 14 days before the first dose need not repeat the assessment for the purposes of screening.
- 12-lead electrocardiogram (ECG). Patients with a historical ECG performed ≤ 14 days before the first dose need not repeat the ECG for the purposes of screening.
- Response assessment/ tumor evaluation (see Section 6.3). Patients with historical tumor scans evaluable per RECIST 1.1 (and MIBG scan for neuroblastoma) performed ≤ 28 days before the first dose need not repeat scans for the purposes of screening
  - Patients who are symptomatic for brain metastases must have a brain scan at screening to confirm eligibility
- Complete blood count (CBC) with differential, including but not limited to red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count, absolute neutrophil count (ANC), and platelet count. ANC should be measured with automated count where available
- Chemistry panel including, but not limited to, sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase (ALT/SGPT), lactate dehydrogenase/serum glutamic pyruvic transaminase (LDH), and uric acid
- For neuroblastoma the following will also be assessed:
  - Urine homovanillic acid (HVA) and vanillylmandelic acid (VMA)
  - Blood ferritin
- Pregnancy test is required for all female patients of childbearing potential defined as being ≥ 12 years of age or who have reached menarche, whichever occurs first. Serum β-hCG pregnancy test will be performed at screening. Urine pregnancy test will be performed to assess patient eligibility within 72 hours prior to the first administration of IP, if the serum pregnancy test did not already occur with 72 hours of dosing
- Adverse event assessment begins when the parent/guardian/patient signs the informed consent/assent form
- IRT registration: If the patient meets all eligibility criteria, registration in IRT should be performed as described in Section 8.3

## 6.1. Treatment Period

The patient will begin treatment at the assigned dose upon confirmation of eligibility and authorization from the sponsor that there is a spot available in the current cohort/group(s) (see Section 8.3). The patient must start treatment within 14 days of signing the informed consent form (ICF). For all subsequent visits, an administrative window of ± 2 days is permitted.

Treatment cycles are 28 days in duration.

The following evaluations will be performed at the frequency specified in the Table of Events, Table 4. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified:

- Concomitant medications evaluation
- Concomitant procedures evaluation
- Physical examination (source documented only)
- Vital signs: In general, on-treatment vital sign measurements will be source documented only. However, if an abnormal (out of range) value is reported at any given visit, that parameter should be collected in the case report form (CRF) at every subsequent scheduled visit until it returns to normal
- Weight
- Height
- Complete blood count with differential
- Chemistry panel (with ferritin for neuroblastoma)
- Urine HVA and VMA for neuroblastoma: every other cycle starting in Cycle 2
- Performance status
- LVSF assessment
    - Every other cycle starting in Cycle 3
    - If the results are abnormal, the assessment should be repeated as clinically indicated
- 12- lead ECG: every other cycle starting in Cycle 3
- Adverse event evaluation (continuously)
- Response assessment/ tumor evaluation (see Section 6.3)
- Pharmacokinetic sampling (see Section 6.4)

### 6.1.1. End of Treatment

An end of treatment (EOT) evaluation should be performed for patients who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in the Table of Events:

- Physical examination (source documented only), height, and weight
- Vital signs
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Performance status
- LVSF assessment
- 12-lead ECG
- Adverse event evaluation
- Complete blood count with differential
- Chemistry panel (with ferritin for neuroblastoma)
- Urine HVA and VMA for neuroblastoma
- Urine β-hCG (for females of childbearing potential)
- Response assessment/ tumor evaluation will be continued at the schedule defined in the Table of Events, and does not need to be performed specifically for the EOT visit except as specified in Section 6.3.1.1.1

## 6.2. Follow-up Period

### 6.2.1. 28-Day Follow-up

All patients will be monitored for reporting of new or follow-up of existing AEs for 28 days after the last dose of IP, as well as SAEs made known to the investigator at any time thereafter that are suspected of being related to IP, as described in Section 11.1. If the 28-day Follow-up visit occurs within 7 days of the EOT visit and EOT laboratory values are not of clinical significance, laboratory collection is not required at the 28-day Follow-up visit. The 28-day Follow-up assessments include:

- Physical examination (source documented only), height, and weight
- Vital signs
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Performance status
- Adverse event evaluation
- Complete blood count with differential
- Chemistry panel (with ferritin for neuroblastoma)
- Urine HVA and VMA for neuroblastoma

#### 6.2.1.1. Special Monitoring

Neuropathy (eg, motor neuropathy, sensory neuropathy, peripheral neuropathy) AEs present at the time of treatment discontinuation should be followed until 1 of the following are met, but no less than the minimum 28 days required in Section 6.2.1 and Section 11.1:

- Improvement to ≤ Grade 1
- At least 3 months have elapsed without improvement or worsening
- The patient initiates any other anticancer therapy during the follow-up

### 6.2.2. Efficacy Follow-up

All patients who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will be followed for response and new anticancer therapies as specified in Section 6.3.

### 6.2.3. Survival Follow-up

After the EOT visit, all patients will be followed for survival until death, lost to follow-up, or one year after EOT, whichever occurs first. This evaluation should be conducted monthly for 1 year from the last dose of IP. New anticancer therapies should be collected at the same schedule for 1 year from the last dose of IP.

Survival follow-up may be conducted by record review (including public records) and/or telephone contact with the patient, family, or the patient's treating physician.

## 6.3. Response Assessments

Response assessments (tumor evaluations) should be performed at screening (up to 28 days before the start of IP) and every 8 weeks (± 5 days) from Cycle 1 Day 1 until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study. Evaluation of response should be performed using RECIST 1.1 guidelines. In the Phase 2 portion of the study, patients with neuroblastoma will also be assessed at screening for response using MIBG evaluation and the Curie score, as described in Section 6.3.1.1.1, and then (if evaluable by MIBG scan at screening) every 8 weeks (± 5 days) from Cycle 1 Day 1 until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study. Patients without MIBG evaluable lesions at screening should have a subsequent MIBG scan at suspected progression only.

New anticancer therapies will also be collected at the same schedule. New anticancer therapy includes (but is not limited to) any systemic or local-regional medication, surgery, radiation, or any other therapy intended to treat the patient's cancer.

If necessary, an independent (central) assessment of response may be conducted by the sponsor after study completion.

### 6.3.1. Assessment of Response According to RECIST 1.1

Response will be assessed using RECIST 1.1. Response assessments include computed tomography (CT) scan or MRI. The regions to be imaged are the chest and abdomen/pelvis, as well as any other studies required for tumor imaging. The same mode of imaging for lesion evaluation at screening must be used consistently throughout the study.

The CT imaging should include contrast unless medically contraindicated. Conventional CT should be performed with contiguous cuts of 5 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm.

All patients with evidence of objective tumor response (CR or PR) should have the response confirmed with repeat assessments at the next scheduled scan, but after no less than 4 weeks. Response assessments must have occurred ≥ 6 weeks from Cycle 1 Day 1 to be considered as stable disease (SD) for a best response.

Additional details and definitions of response are found in Appendix A in Section 19.1.

#### 6.3.1.1. Other Assessments

Patients who are symptomatic for brain metastasis at screening must undergo a brain scan to confirm eligibility.

Additional scans, including further brain scans, MRI of the head, or nuclear medicine bone scan, may be performed if clinically indicated (eg, symptoms of brain metastasis) at the discretion of the investigator.

##### 6.3.1.1.1. Other Assessments for Neuroblastoma

Patients with neuroblastoma should be assessed at screening for MIBG response using the Curie score. The Curie score is a semi-quantitative scoring system for the comparison of sequential whole-body MIBG scans in children with neuroblastoma (Ady, 1995).

Patients with MIBG-evaluable lesions should be assessed for response using the Curie score (Section 19.2 Appendix B) at screening (up to 28 days before the start of IP) and every 8 weeks (± 5 days) from Cycle 1 Day 1 thereafter until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study. Patients without MIBG evaluable lesions at screening should have a subsequent MIBG scan at suspected progression only.

Patients with confirmed objective CR will be assessed for bone marrow disease through bone marrow biopsy. If the patient was assessed by both RECIST and MIBG/Curie score, both methodologies must show confirmed objective CR.

## 6.4. Pharmacokinetics

Pharmacokinetic blood samples will be collected for the first dose (Cycle 1 Day 1) from all patients in both the Phase 1 and 2 portions of the study to analyze paclitaxel concentrations in blood.

Samples will be collected from all patients enrolled in the Phase 1 portion of the study according to a dense PK sampling strategy as specified in Table 5.

Samples will be collected from all remaining patients enrolled in the study according to a sparse PK sampling strategy as specified in Table 6, or if optionally consented according to a dense PK sampling strategy.

**Table 5: Dense PK Sampling**

| Sample Number | Sample Time (hours) | Patients ≥ 6 Years Old | Patients < 6 Years Old |
|---|---|---|---|
| 1 | 1-2 minutes prior to the end of infusion (no window, must be collected before end of infusion) | X | X |
| 2 | 15 minutes after end of infusion (± 5 minutes) | X | X |
| 3 | 1 hours after end of infusion (± 5 minutes) | X | |
| 4 | 3 hours after end of infusion (± 10 minutes) | X | X |
| 5 | 5 hours after end of infusion (± 10 minutes) | X | X |
| 6 | 8 hours after end of infusion[a] (± 1 hour, recommended) | X | |
| 7 | 24 hours after end of infusion[b] (± 3 hours) | X | X |
| 8 | 48 hours after end of infusion[c] (± 3 hours) | X | |
| 9 | 72 hours after end of infusion[d] (± 3 hours, recommended[e]) | X | |

[a] Recommended sample at 8 hours after infusion should be performed in any center where the patient can remain to have the sample drawn. Patients who are being treated as an out-patient may omit this sample.
[b] 24- hour sample may occur on study Day 2, depending on the timing.
[c] 48-hour sample may occur on study Day 3, depending on the timing.
[d] 72-hour sample may occur on study Day 4, depending on the timing.
[e] Recommended sample at 72 hours after infusion should be performed in patients who live close enough to the center to return on the third day. Patients living far from the center may omit this sample.

**Table 6: Sparse PK Sampling**

| Sample Number | Sample Time (hours) | Patients ≥ 6 Years Old | Patients < 6 Years Old |
|---|---|---|---|
| 1 | 15 minutes after end of infusion (± 5 min) | X | X |
| 2 | 3 hours after end of infusion (± 10 minutes) | X | X |
| 3 | 24 hours after end of infusion (± 3 hours)[a] | X | X |

[a] 24-hour sample may occur on study Day 2 depending on the timing.

The following information must be captured in the CRFs for Cycle 1, Day 1 through Day 4:

- The dose level and total dose administered (Day 1 only)
- The exact time of the start and end of infusion (Day 1 only)
- The exact time of each PK sample collection in addition to the scheduled time point

At each PK sampling time point, approximately 0.5 mL of blood will be drawn and distributed into tubes provided by Celgene or its representative as described in the laboratory manual. For PK samples collected at 1-2 minutes prior to, 15 minutes after, and 1 hour after the end of the infusion, the blood should be drawn from the arm contralateral to the arm used for drug infusion.

Instructions for sample collection, processing, storage, and shipping are included in Section 19.4, Appendix D, and also in a laboratory manual.

## 6.5. Biomarkers

The most recently available tumor tissue sample will be optionally collected at the time of study entry. The study laboratory manual will include procedures for providing these samples, which will be used to study tumor characteristics and their correlation with patient outcomes and treatment response. The specific use of these samples is not being pre-specified and will be determined based on emerging data and methodological advances. A potential use of these samples is to assess in the pediatric patients in this study the value of markers of response to nab-paclitaxel that may be identified in studies of adult patients.

# 7. STUDY POPULATION

## 7.1. Number of Patients

In the Phase 1 portion of the study, at least 12 to approximately 64 patients with various solid tumors will be enrolled, depending on the number of dose escalation cohorts and the number of additional patients enrolled at dose levels evaluated as safe by the SMC.

In the Phase 2 portion of the study, up to 69 efficacy evaluable patients will be enrolled, in 3 different groups (≤ 23 with neuroblastoma, ≤ 23 with rhabdomyosarcoma, and ≤ 23 with Ewing's sarcoma), with at least 14 patients per group.

## 7.2. Inclusion Criteria

Patients must meet all of the following criteria to be enrolled in the study:

1. Patient is male or female, meeting the following age requirements at the time the informed consent document (and assent form, if applicable) is signed.
    a. Phase 1: patient is ≥ 6 months to < 18 years of age
    b. Phase 2: patient is ≥ 6 months to ≤ 24 years of age
2. Patient has a confirmed solid tumor diagnosis according to the following:
    a. Phase 1: patient has a recurrent or refractory solid tumor that has progressed or did not respond to standard therapy, or for which no standard anticancer therapy exists
    b. Phase 2: patient has radiologically documented measurable disease by RECIST 1.1 (for neuroblastoma, evaluable disease by MIBG/Curie score is also acceptable) in one of the following tumor types and has failed up to three lines of treatment
        i. Group 1: neuroblastoma (patients with bone marrow disease only are not permitted)
        ii. Group 2: rhabdomyosarcoma
        iii. Group 3: Ewing's sarcoma
3. The patient has a Lansky/ Karnofsky performance status score of ≥ 70%
4. The patient has adequate serum chemistry levels, evidenced by the following laboratory values
    a. AST (SGOT), ALT (SGPT) ≤ 2.5 × upper limit of normal range (ULN)
    b. Total bilirubin ≤ 1.5 × ULN
    c. Creatinine ≤ 1.5 × ULN
5. The patient has adequate bone marrow function, evidenced by the following:
    a. Absolute neutrophil count ≥ $1.0 \times 10^9$ cells/L

b. Platelets ≥ 80 × $10^9$ cells/L (transfusion independent, defined as not receiving platelet transfusions within 7 days prior to laboratory sample). In the Phase 2 portion, for patients with known bone marrow involvement, platelets ≥ 50 × $10^9$ cells/L

c. Hemoglobin ≥ 8 g/dL (transfusion is permitted to fulfill this criterion)

6. The patient (when applicable) or patient's parent(s) or legal guardian(s) understand(s) and voluntarily signed an informed consent document prior to any study-related assessments/procedures being conducted. Where locally applicable, the patient also understands and voluntarily provides his/her assent prior to any study-related assessments/procedures being conducted.
7. Male patients of childbearing potential must use a condom during sexual intercourse and shall not father a child during the study and for 6 months after the last dose of study medication.
8. Female patients of childbearing potential [defined as all female patients ≥ 12 years old or who have reached menarche, whichever occurs first] must have both of the following:

   a. Agree to the use of two physician-approved contraceptive methods simultaneously or practice complete abstinence while on study medication or for a longer period if required by local regulations

      i. True abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

      ii. Acceptable contraceptive methods include: oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) including at least one barrier method.

   b. Have negative serum pregnancy test result at screening confirmed by negative urine pregnancy dipstick within 72 hours prior to first dose of IP (if serum test occurred > 72 hours from first dose); pregnancy test with sensitivity of at least 25 mIU/mL

## 7.3. Exclusion Criteria

The presence of any of the following will exclude a patient from enrollment:

1. The patient has a primary brain tumor(s) or brain metastasis (unless metastasis is treated and stable for > 28 days). In patients who are symptomatic, a brain scan is required to exclude metastasis.
2. The patient has ≥ Grade 2 peripheral neuropathy by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) at screening.
3. The patient has received therapeutic dose chemotherapy or radiotherapy ≤ 21 days prior to start of IP.

4. The patient has received maintenance dose chemotherapy (eg, low dose cyclophosphamide) ≤ 7 days from the first dose of IP.
5. The patient has received any investigational therapy ≤ 28 days prior to start of IP. Investigational therapy is defined as any medicinal product that is not approved in the country of treatment for any indication, adult or pediatric.
6. The patient has received any biological therapy ≤ 7 days prior to the start of IP, or monoclonal antibody ≤ 3 half-lives or 28 days, whichever is shorter, prior to the first dose of IP.
7. The patient has received allogeneic hematopoietic stem cell transplantation (HSCT) ≤ 3 months or autologous HSCT ≤ 21 days prior to start of IP.
8. The patient has had major surgery or significant trauma ≤ 14 days prior to start of IP.
9. The patient has not recovered from the acute toxic effects of prior chemotherapy, radiation, or major surgery/significant trauma.
10. The patient has had minor surgery ≤ 7 days from the start of study treatment (excluding the placement of central/peripheral lines, skin biopsy).
11. The patient has a known history of stroke, myocardial infarction, peripheral vascular disease, or recent (within 3 months) uncontrolled deep venous thrombosis.
12. The patient has a known history or current diagnosis of HIV infection, regardless of treatment status.
13. The patient has an uncontrolled intercurrent illness including but not limited to ongoing or active infection requiring antibiotic, antifungal, or antiviral therapy, symptomatic heart failure, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
14. The patient has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from participating in the study.
15. The patient has any condition, including the presence of laboratory abnormalities, that places the patient at unacceptable risk if he/she were to participate in the study.
16. The patient has any condition that confounds the ability to interpret data from the study.
17. The patient or parent(s)/guardian(s) is/are unable to comply with the study visit schedule and other protocol requirements, in the opinion of the investigator.

# 8. DESCRIPTION OF STUDY TREATMENTS

## 8.1. Description of Investigational Product(s)

*nab*-Paclitaxel, the IP, will be supplied by the sponsor (Celgene) in single-use vials. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin as a stabilizer.

Unreconstituted *nab*-paclitaxel should be stored in accordance with the product label. Reconstituted *nab*-paclitaxel should be used immediately. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel. Reconstitution and administration should follow local prescribing information and local practice.

Temperature records for *nab*-paclitaxel must be made available to Celgene or other Celgene representatives for verification of proper study drug storage.

To facilitate the administration of small volumes, *nab*-paclitaxel suspension may alternatively be administered using syringe based devices (eg, a syringe pump), provided that a silicone oil-free syringe is used to extract the reconstituted *nab*-paclitaxel suspension from the vial and the reconstituted *nab*-paclitaxel is stored in the syringe at room temperature for no longer than 8 hours.

## 8.2. Treatment Administration and Schedule

In both the Phase 1 and 2 portions of the study, the treatment will be given until disease progression, the patient begins a new anticancer treatment, withdrawal of parent/guardian/patient consent/assent, parent/guardian/patient refusal, physician decision, toxicity that cannot be managed by dose delay or dose reduction alone (reductions are prohibited in Cycle 1 [and Cycle 2 for patients ≤ 10 kg] for the Phase 1 portion only), or the study ends for any reason. *nab*-Paclitaxel will be administered intravenously over approximately 30 minutes, without corticosteroid or antihistamine premedication, weekly on Days 1, 8, and 15 of a 28-day cycle. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.

### 8.2.1. Phase 1 Portion: Dose Escalation

In the Phase 1 portion of the study, up to 6 patients will be assessed at a starting dose of 120 mg/m$^2$ *nab*-paclitaxel (80% of the weekly investigated adult dosage). Dose escalation will occur according to example dose levels described in Table 7, using the rolling-6 design (as described in Section 8.2.1.3). Doses not listed in Table 7, including intermediate doses or doses higher than 210 mg/m$^2$, may be tested based on study data and recommendations from the SMC.

For patients who weigh ≤ 10 kg the dosage will be calculated per kg, and *nab*-paclitaxel will be administered according to the schedule in Table 7. In order to ensure their safety, patients weighing ≤ 10 kg will receive a reduced dose (by one level) in Cycle 1, and if well tolerated (no DLTs) will receive the full dose starting in Cycle 2.

**Table 7: Phase 1 Portion Example Dose Levels**

| Dose Level[a] | Dose | Dose (Patients ≤ 10 kg) | |
|---|---|---|---|
| | All Cycles | Cycle 1 | Subsequent Cycles |
| *-1* | *100 mg/m²* | *4.0 mg/kg*[b] | *4.5 mg/kg* |
| **1 (Starting dose)** | **120 mg/m²** | **4.5 mg/kg** | **5.5 mg/kg** |
| 2 | 150 mg/m² | 5.5 mg/kg | 7.0 mg/kg |
| 3 | 180 mg/m² | 7.0 mg/kg | 8.5 mg/kg |
| 4 | 210 mg/m² | 8.5 mg/kg | 10.0 mg/kg |

[a] Dose levels are also used for dose reductions in both the Phase 1 and 2 portions, as described in Section 8.2.3.4. Dose level -1 may reduce to 80 mg/m² and 60 mg/m², or 3.0/4.0 mg/kg and 2.0/3.0 mg/kg (Cycle 1/Subsequent Cycles).
[b] 4.0 mg/kg is the calculated equivalent of 80 mg/m².

#### 8.2.1.1. Definition of Dose-limiting Toxicity

The DLT assessment period will be as follows:

- For patients > 10 kg: the first cycle including Cycle 2 Day 1 predose evaluations
- For patients ≤ 10 kg: the first two cycles including Cycle 3 Day 1 predose evaluations

A DLT is defined as IP-related AE(s) occurring during the DLT assessment period that lead to treatment discontinuation or meet one of the following criteria:

- Grade 3 or 4 nonhematologic toxicity (excluding transient transaminitis)
- Grade 3 or 4 nausea or vomiting that persists > 5 days despite maximal anti-emetic treatment
- Grade 4 thrombocytopenia or anemia that persists > 7 days or requires transfusion > 7 days
- Grade 3 thrombocytopenia with bleeding
- Grade 4 uncomplicated neutropenia lasting > 7 days
- Febrile neutropenia with confirmed bacterial infection
- Grade 3 hematologic toxicity requiring treatment delay > 21 days

Events that are considered DLTs based on their duration will be considered a DLT if they start during the DLT assessment period.

Events due to disease progression or to current underlying disease cannot be considered DLTs. Events that are not considered related to IP cannot be considered DLTs.

If a patient experiences a DLT, the dose should be delayed until resolution of the AE to CTCAE Grade 1.

#### 8.2.1.2. Safety Monitoring Committee

The SMC will decide whether to dose escalate, dose reduce, or declare an MTD, and will determine the dose(s) appropriate for the Phase 2 portion of the study (RP2D). During the Phase 2 portion, the SMC will continue to review safety data regularly and make recommendations about the study continuation, as appropriate.

The members of the SMC will include the principal investigator, all investigators who recruited patients into the current cohort (or a subinvestigator designee), the Celgene Clinical Research Physician or designee, the Celgene Clinical Research Scientist or designee, and the Product Safety Physician or designee (if applicable). Additional details regarding the composition and responsibilities of the SMC are detailed in the SMC charter.

#### 8.2.1.3. Dose Escalation Procedures

Up to 6 patients will be treated at the first dose level, and subsequent dose escalation will proceed using the rolling-6 design. In each cohort a minimum of 2 patients treated and eligible for the Dose Determining Set (DDS, refer to Section 10.2) are required to make a dose decision.

If zero DLTs are observed in the first 3 patients eligible for the DDS the SMC may decide to escalate the dose for the next cohort. An additional 3 patients (up to a total of 6 per cohort) may be enrolled at the same dose while awaiting the DDS eligibility of 3 patients and SMC decision.

If one DLT occurs prior to an SMC dose escalation decision, the cohort will be required to enroll 6 patients total. If one or fewer patients experience a DLT in these 6 patients, the dose will be escalated in the next cohort, unless there are other safety considerations by the SMC. If more than one DLT occurs within the first dose level, a -1 dose level will be evaluated (100 mg/m$^2$).

If two or more patients in a given cohort experience a DLT at any time during enrollment, the MTD will have been exceeded and the previous lower dose will be declared the MTD.

Patients ineligible for the DDS may be replaced at the discretion of the sponsor.

For each cohort, the decision whether or not to dose-escalate in the next cohort or to declare the MTD/RP2D will be made by the SMC. The SMC will review all available clinical laboratory and safety data for a given cohort and, if applicable, data from previous cohorts.

The SMC decision to escalate to the next dose level will be driven by the incidence of DLTs (as described in Section 8.2.1) and the totality of data.

Additional factors for safety evaluation that may be considered by the SMC include (but are not limited to):

- Incidence of TEAEs and SAEs
- Physical examinations
- Laboratory abnormalities (serum chemistry, hematology, and differentials)
- Dose modifications (skipped doses, reduced doses, dose interruptions, and/or treatment discontinuation)

If other safety considerations are noted, the SMC may take other actions, including expansion of the current dose level or declaration of the RP2D despite not being at the MTD.

#### 8.2.1.4. Recommended Phase 2 Dose

After the MTD has been established, the SMC will determine the dose to be used in the Phase 2 portion of the study (RP2D). This dose may be the MTD determined in Phase 1 (or highest dose tested if no MTD is determined), but it may be a dose less than the MTD if this dose is determined to have a better risk-benefit profile. The RP2D cannot be greater than the MTD.

Once the RP2D has been formally established, recruiting for Phase 2 may begin immediately. In January 2016 the SMC determined that the RP2D is 240 mg/m$^2$ in patients weighing > 10 kg, and 11.5 mg/kg in patients weighing ≤ 10 kg.

### 8.2.2. Phase 2: Dose Expansion

The Phase 2 portion of the study will be conducted at the established RP2D (as described in Section 8.2.1.4) at the same schedule as in the Phase 1 portion.

### 8.2.3. Treatment Modification

Treatment modifications are applicable during the Phase 1 and Phase 2 portions of the study, except that dose reductions during Phase 1 Cycle 1 are not permitted as noted below.

#### 8.2.3.1. Body Surface Area or Weight Changes

If the patient's BSA (or weight for patients ≤ 10 kg) has changed by ≥ 10% from the last value used for dose calculations, then the patient's dose should be recalculated with the new value. Otherwise, dose adjustments should be based on actual body weight/BSA and follow institutional guidelines.

#### 8.2.3.2. Treatment Delay

IP administration should occur within a ± 2 day administrative window of the scheduled day of dosing. IP may be delayed for other reasons based on the guideline below. If Day 8 or Day 15 treatment is delayed ≤ 4 days, the treatment may be administered and the 28 days cycle continues per protocol. If the investigator suspects a drug related toxicity, an unscheduled visit with additional laboratory assessments may be performed. When treatment (either Day 1, 8, or 15) is consecutively delayed for two or more cycles, dose reduction should be considered. Patients experiencing IP-related toxicities that require a delay in scheduled dosing of IP for > 21 days will be discontinued from further participation in this study (except if day 22 falls on a weekend or holiday, in which case IP may be administered the next business day).

**Day 1 Treatment Delay**

If the treatment to be given on Day 1 is delayed, the 28-day cycle will not be considered to start until the day IP is actually administered to the patient.

**Day 8 Treatment Delay**

If the treatment to be given on Day 8 is held for ≤ 4 days, the treatment may be administered and the 28-day cycle continues per protocol. If Day 8 treatment is delayed > 4 days, the treatment will be considered as missed and will not be made up.

**Day 15 Treatment Delay**

If the treatment to be given on Day 15 is held for ≤ 4 days, the treatment may be administered and the 28-day cycle continues per protocol. If Day 15 treatment is delayed > 4 days, that week becomes the week of rest. The next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a 21-day cycle. The subsequent cycle resumes the scheduled 28-day cycle.

#### 8.2.3.3. Missed Treatment

A missed Day 8 or Day 15 treatment is defined as IP not administered within ≤ 4 days of the expected dose day and should be entered in the CRF as a missed dose. If the investigator suspects drug-related toxicity, an unscheduled visit with additional laboratory tests may be performed.

Patients with a missed treatment during the DLT assessment period in the Phase 1 portion of the study are not eligible for the DDS (as defined in Section 10.2) and will be replaced at the discretion of the sponsor.

#### 8.2.3.4. Dose Adjustment

For the Phase 1 portion of the study, dose adjustments are not permitted during Cycle 1 (and during Cycle 2 for patients ≤ 10 kg).

Starting with Cycle 2 in the Phase 1 portion of the study or anytime during the Phase 2 portion of the study, treatment dosing may be reduced for hematologic and other toxicities according to Table 8 and Table 9. Dose adjustments are to be made according to the AE showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE v4.0.

If deemed necessary, a dose should be reduced by one dose level according to Table 7. A maximum of two dose reductions are permitted. If a toxicity requiring dose adjustment occurs after a second dose reduction, further treatment must be discontinued. Once a dose has been reduced, it must not be increased to the previous level. If a patient experiences a severe hypersensitivity reaction, *nab*-paclitaxel should be permanently discontinued and the patient should not be rechallenged.

**Table 8: Hematologic Toxicity: Recommended Dose Reductions**

| Adverse Event/ Criteria | Occurrence | Action[a] |
|---|---|---|
| Neutropenic fever (with confirmed bacterial infection)<br>OR<br>Neutropenia Grade 4<br>OR<br>Delay of next cycle due to persistent neutropenia Grade 3 | 1st occurrence | Dose reduction to the next lower level for subsequent cycles once ANC is ≥ 1000 cells/mm$^3$. |
| | 2nd occurrence | Dose reduction to the next lower level for subsequent cycles once ANC is ≥ 1000 cells/mm$^3$. |
| | 3rd occurrence | Discontinue treatment |
| Thrombocytopenia Grade 4 that persists > 7 days or requires transfusion > 7 days | 1st occurrence | Dose reduction to next lower level; initiation of next cycle is delayed until platelet count is 80,000 cells/mm$^3$.<br>For Phase 2 patients with known bone marrow involvement, initiation of next cycle is delayed until platelet count is 50,000 cells/mm$^3$. |
| | 2nd occurrence | Discontinue treatment |

ANC = absolute neutrophil count.
[a] For the Phase 1 portion of the study, dose adjustments are not permitted during Cycle 1. Patients with bone marrow disease should not be considered for dose reduction if the AE is related to the disease.

**Table 9: Nonhematologic Toxicity: Recommended Dose Reductions**

| Adverse Event | Occurrence | Action[a] |
|---|---|---|
| Grade 3 or 4[b] peripheral neuropathy | 1st occurrence | Interrupt treatment until toxicity improves to ≤ Grade 1. When treatment is resumed, reduce by 1 dose level. |
| | 2nd occurrence | |
| | 3rd occurrence | Discontinue treatment |
| Grade 2[c] or 3 cutaneous toxicity | 1st occurrence | Interrupt treatment until toxicity improves to Grade 0 or 1[c]. When treatment is resumed, reduce by 1 dose level. |
| | 2nd occurrence | Discontinue treatment |
| | 3rd occurrence | Discontinue treatment |
| Grade 4 cutaneous toxicity | 1st occurrence | Discontinue treatment |
| Grade 3 mucositis or diarrhea | 1st occurrence | Interrupt treatment until toxicity improves to Grade 0 or 1. When treatment is resumed, reduce by 1 dose level. |
| | 2nd occurrence | |
| | 3rd occurrence | Discontinue treatment |
| Grade 4 mucositis or diarrhea | 1st occurrence | Discontinue treatment |
| Any other Grade 3 or 4 nonhematologic toxicity, excluding alopecia | 1st occurrence | Interrupt treatment until toxicity improves to Grade 0, 1, or 2[d]. When treatment is resumed, reduce by 1 dose level. |
| | 2nd occurrence | |
| | 3rd occurrence | Discontinue treatment |

[a] For the Phase 1 portion of the study, dose adjustments are not permitted during Cycle 1.
[b] Neuropathy should be followed as described in Section 6.2.1.1.
[c] Cutaneous toxicity should be considered for dose reductions only if clinically indicated, at the discretion of the investigator.
[d] The degree of adverse event resolution depends upon the type of nonhematologic toxicity seen and the course that is chosen to be medically most sound in the judgment of the physician investigator.

#### 8.2.3.5. Intrapatient Dose Escalation

Intrapatient dose escalation beyond the dose initially assigned to a patient is not permitted during Cycle 1 (or anytime in the Phase 2 portion). Once a patient's dose has been reduced, it must not be increased to the previous level.

During the Phase 1 portion of the study, patients receiving treatment beyond Cycle 1 who have not had any dose reductions may, following approval by the SMC, have the dose level increased, providing that the alternative dose level has been shown to be well tolerated by at least one cohort of other patients in this study. In these instances, additional PK evaluation at the higher dose level may be conducted.

### 8.2.4. Overdose

On a per dose basis, an overdose of *nab*-paclitaxel is defined as 10% over the protocol-specified dose of IP assigned to a given patient, regardless of any associated adverse events or sequelae. On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For *nab*-paclitaxel, an infusion completed in less than 25 minutes may increase $C_{max}$ by approximately 20% which is the threshold for clinical relevancy. For infusions completed between 25 and 30 minutes, there is no clinical significance. A *nab*-paclitaxel infusion completed in less than 25 minutes will therefore meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11.1 for the reporting of adverse events associated with overdose.

## 8.3. Method of Treatment Assignment

In the Phase 1 portion of the study, patients will be assigned to a dose level using the Integrated Response Technology (IRT). The investigator or designee (eg, subinvestigator, study coordinator) will register the patient in the IRT system. Upon confirmation of eligibility, the patient will enrolled into the current dose level in the IRT system. If there is no availability within the current cohort, the CRP/CRS will permit enrollment via IRT at the last dose level evaluated as safe by the SMC. The date of the next SMC meeting, after which patients may be screened for the next cohort, will be provided to the investigator.

In the Phase 2 portion of the study, patients will be included in one of three indication-based groups as described in Inclusion criterion 2.b. Patients will be registered in IRT and upon confirmation of eligibility, enrolled to one of the three groups. Enrollment for each group will remain open according to a Simon two-stage design as described in Section 10.3. One or more groups may be closed while one or more groups remain open for enrollment.

## 8.4. Packaging and Labeling

The label(s) for IP will include sponsor name, address, and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

## 8.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs Celgene (or designee).

Only completely unused IP vials should be retained by the site until a representative from Celgene or other Celgene-designated personnel have completed an inventory. Partially used and completely used vials should be destroyed according to local guidelines, and disposition should be recorded on the Investigational Drug Accountability Record Form.

The investigator, or designee, shall record the dispensing of IP to patients in the IP accountability record. The IP record will be made available to Celgene, or other authorized Celgene-designated monitoring personnel, for the purpose of accounting for the IP supply. Inspections of the IP supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Celgene or its designee and a plan for resolution will be documented.

Investigational product will not be loaned or dispensed by the investigator to another investigator or site.

## 8.6. Investigational Product Compliance

Accurate recording of all IP administration will be made in the appropriate section of the patient's CRF and source documents. The investigator or designee is responsible for accounting for all study-specific IP both administered or in their custody during the course of the study.

# 9. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this trial, additional medications may be required to manage aspects of the disease state of the patients, including side effects from trial treatments or disease progression. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the investigator.

All concomitant treatments, including blood and blood products, must be reported on the CRF.

For information regarding other drugs that may interact with *nab*-paclitaxel and affect its metabolism, pharmacokinetics, or excretion, please see the *nab*-paclitaxel (ABRAXANE) local package insert.

## 9.1. Permitted Concomitant Medications and Procedures

Erythropoietin may be administered at the discretion of the investigator, consistent with institutional guidelines. Granulocyte colony-stimulating factors may not be given during the DLT assessment period, but subsequently may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC < 500 cells/µL.

## 9.2. Prohibited Concomitant Medications and Procedures

Granulocyte colony-stimulating factors may not be given during the DLT assessment period.

Radiotherapy is not allowed during the study, except for palliative purposes for nontarget lesions. Surgical intervention as anticancer therapy during Cycle 1 will require the patient to discontinue from study treatment. Minor surgical intervention in subsequent cycles will be assessed on a case by case basis after discussion with the Celgene Clinical Research Physician.

Although patients with neuroblastoma will be assessed for response using $^{123}$I-MIBG scans, administration of $^{131}$I-MIBG therapy (eg, for neuroblastoma treatment) is prohibited.

Administration of other chemotherapy, immunotherapy, antitumor hormonal therapy, investigational therapy, or other anticancer therapy during the study is not allowed.

Administration of Coumadin or coumarin derivatives is not allowed during this study; low-molecular weight heparin should be used instead.

The potential drug-drug interaction precautions contained in the *nab*-paclitaxel prescribing information will be applied to this study (refer to the local prescribing information). Specifically, the metabolism of paclitaxel is catalyzed by cytochrome P450 isozymes CYP2C8 and CYP3A4.

Strong inducers of CYP3A4 and CYP2C8 are prohibited for use from the first dose of IP until permanent discontinuation. Such medications include but are not limited to:

- Strong inducers of CYP3A4: avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort.

Strong inhibitors of CYP3A4 and CYP2C8 should be avoided whenever possible from the first dose of IP until permanent discontinuation. If possible, patients should be switched to other

medications for the comorbidity prior to starting IP. Such medications include but are not limited to:

- Strong inhibitors of CYP2C8: gemfibrozil
- Strong inhibitors of CYP3A4: boceprevir, clarithromycin, conivaptan, grapefruit juice, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, posaconazole, telaprevir, telithromycin, and voriconazole.

Caution is recommended when administering *nab*-paclitaxel concomitantly with any substrates or inhibitors of the cytochrome P450 isozymes CYP2C8 and CYP3A4. Similarly, drugs, herbal preparations, and/or dietary supplements known to influence the expression of CYP3A (eg, garlic supplements) and/or CYP2C8 should be used with caution (see www.drug interactions.com for a regularly updated list of drug interactions with cytochrome P450 isozymes).

Please check the prescribing information of the concomitant medication for full information on the CYP interaction potential.

Patients and parent(s)/guardian(s) must be made aware that the following medications are not allowed to be taken concomitantly with *nab*-paclitaxel: ritonavir, saquinavir, indinavir, nelfinavir, or investigational drug(s) other than described as a treatment regimen in this study.

## 9.3. Required Concomitant Medications and Procedures

Not applicable.

# 10. STATISTICAL ANALYSES

## 10.1. Overview

The Phase 1 portion uses a rolling-6 patient dose escalation design to establish the MTD/RP2D, and the Phase 2 portion uses a Simon two-stage minimax design to monitor patient enrollment for each group separately.

Statistical analyses will be performed by study phase, dose level, and tumor group as needed or applicable.

## 10.2. Study Population Definitions

The study population definitions are as follows:

- **Enrolled Population** – All patients enrolled; ie, all patients who are marked as enrolled in the clinical database regardless of whether they have received IP.
- **Safety Population** – All patients who take at least one dose of IP
- **Efficacy Evaluable (EE) Population** – All treated patients who meet eligibility criteria, complete at least one dose of investigational product, and have baseline and at least one postbaseline efficacy assessment if having not discontinued the investigational product prior to postbaseline efficacy assessment due to disease progression or symptomatic deterioration. Here efficacy assessment means radiological assessment of the tumor or tumor assessment by other appropriate means. Investigational product discontinuation due to disease progression or symptomatic deterioration must be documented as the primary reason for treatment discontinuation in the treatment discontinuation CRF.
- **Dose Determining Set (DDS)** – The primary endpoint for the Phase 1 portion of the study, determination of the MTD/RP2D, will be performed on the DDS. In patients weighing > 10 kg, the DDS includes all patients who experienced a DLT, or received all 3 weekly doses of *nab*-paclitaxel at the cohort planned dose during Cycle 1 and had adequate safety assessments during the DLT assessment period (Cycle 1 including predose assessments on Cycle 2 Day 1). In patients weighing ≤ 10 kg, the DDS includes all patients who experienced a DLT, or received all 6 weekly doses of *nab*-paclitaxel at the cohort planned doses during Cycles 1 and 2 and had adequate safety assessments during the DLT assessment period (Cycle 1 and 2 including predose assessments on Cycle 3 Day 1).
- **Pharmacokinetic Population** – The pharmacokinetic population includes all patients who received at least 1 dose of *nab*-paclitaxel and had evaluable concentration data.

## 10.3. Sample Size and Power Considerations

During the Phase 1 portion, a rolling-6 patient dose escalation design will be used to establish the MTD/RP2D, and up to approximately 24 patients will be enrolled into the DDSs, depending on the number of dose levels evaluated. Patients who are ineligible for the DDS in a given cohort

will be replaced at the discretion of the sponsor, and additional non-DDS patients may be enrolled at dose levels evaluated as safe by the SMC. A minimum of 12 patients will be treated in the Phase 1 portion of the study, regardless of the number of dose levels tested.

In the Phase 2 portion, up to 69 additional efficacy evaluable patients (≤ 23 patients in each of the 3 groups) will be enrolled at the RP2D determined in the Phase 1 portion of the study. A Simon two-stage minimax design will be used to monitor patient enrollment for each of the groups separately.

The ORR is defined using the maximum likelihood estimator.

For each of the 3 groups in the first stage, 14 efficacy evaluable patients will be enrolled. If < 2 of the 14 patients has a response, the enrollment for this group will be stopped upon determination of the number of responders. If ≥ 2 of the 14 patients have a response, the enrollment will continue until 23 efficacy evaluable patients are enrolled. At the final analysis, the regimen will be concluded with more than a 5% true response rate if ≥ 5 of 23 patients have a response. The acceptance rate for the second stage will be 21.74% response rate, at 80% power and 10% significance having fixed the lower and upper boundaries to 10% and 28%, respectively. The response rate in the Phase 2 neuroblastoma group will be determined using both RECIST and the MIBG/Curie score.

A minimum of 14 patients will be treated in each tumor group.

## 10.4. Demographic and Baseline Characteristics

In the Phase 1 portion of the study, the baseline characteristics of patients will be summarized by dose level for the Safety population and the EE population. In the Phase 2 portion of the study, the baseline characteristics of patients will be summarized by tumor group for the Safety population and the EE population. The age, weight, height, and other continuous demographic and baseline variables will be summarized using descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum). Lansky/Karnofsky performance status, gender, race, and other categorical variables will be summarized with frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

## 10.5. Patient Disposition

Patient disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percentage. A listing of patients with protocol violations or protocol deviations will be provided.

## 10.6. Efficacy Analysis

Efficacy endpoints will be analyzed for both the safety population and the efficacy evaluable population. Efficacy will be analyzed by dose cohort and tumor group once all patients have completed the study. The efficacy variable of primary interest is overall response rate (ORR). Tumor response will be based on RECIST 1.1 and will be assessed by the investigator. Patients with neuroblastoma additionally will be assessed for MIBG response using the Curie score (Phase 2 only). For patients in the neuroblastoma group, ORR will be based on either the RECIST criteria or the Curie score, or both, without crossover between assessment types over

time. If both assessment types have been performed on a given subject across the assessment time points, to be considered as a partial response for the ORR analysis, both methodologies should show no worse than stable disease and at least one method should indicate CR or PR. A response is only considered complete if both methodologies indicate CR. The efficacy variable of focus for the Phase 1 portion will be ORR. For the Phase 2 portion, efficacy variables to be analyzed include ORR, duration of response, disease control rate, PFS, and 1-year survival. Ninety-five percent confidence intervals of response rate will be provided. A case-by-case description of all patients who exhibited a confirmed CR or PR using RECIST, and additionally for neuroblastoma using MIBG/Curie score as applicable, will be provided. A descriptive analysis of other evidence of antitumor activity will be provided based on clinical, radiographic, and biologic assessments of efficacy. If there are sufficient data, Kaplan-Meier estimates will be provided for duration of response, PFS, and 1-year survival.

Data listings will be provided for all relevant data collected during the study.

Full details of the efficacy analysis will be given in the statistical analysis plan (SAP).

## 10.7. Safety Analysis

All patients in the Safety population will be included in the safety analyses. Adverse events, vital sign measurements, physical examination findings, clinical laboratory information, ECG, LVSF assessment, Lansky/Karnofsky performance status, and concomitant medications and procedures will be tabulated and summarized by study phase (Phase 1 or 2 portion), dose level, and tumor group, as appropriate.

During the Phase 1 DLT assessment period, DLTs and all available safety data will be reviewed on an ongoing basis by the investigators and sponsor and summarized at the conclusion of each dose level.

Adverse events observed during both Phase 1 and Phase 2 will be coded using the MedDRA classification system. The severity of the AEs will be graded according to the NCI CTCAE version 4.0 whenever possible.

Adverse events will be analyzed in terms of treatment-emergent AEs. Treatment-emergent adverse events (TEAEs) are defined as any AEs that begin or worsen in grade after the start of IP through 28 days after the last dose of IP.

The frequency of AEs will be tabulated by MedDRA System Organ Class and Preferred Term. In the by-patient analysis, a patient reporting the same event more than once will be counted only once. Adverse events will also be summarized by NCI CTCAE grade. If a patient reports the same AE more than once, the event with the maximum grade will be tabulated in "by grade" tables. The incidence of serious adverse events (SAEs) and AEs that lead to dose reduction, drug interruption, or discontinuation of study drug will be summarized. Adverse events of special interest based on the Risk Management Plan will also be summarized. Listings of patients who discontinued study drug due to an AE, patients with SAEs, and deaths will be presented.

Clinical laboratory data will be summarized. Laboratory data will be graded according to NCI CTCAE version 4.0 criteria wherever possible. The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by baseline status.

Vital signs, ECG, and LVSF assessment will be summarized by cross-tabulations presenting normal and abnormal values by number of patients at pre- and post-IP initiation.

Performance status by cycle and change from baseline will be summarized using descriptive statistics.

Graphical displays will be provided where useful in the interpretation of results.

Full details of the safety analysis will be given in the SAP.

## 10.8. Interim Analysis

During the Phase 2 portion of the study, a Simon two-stage minimax design will be used to monitor patient enrollment and tumor response rate for each group separately, as described in Section 10.3.

## 10.9. Other Topics

### 10.9.1. Pharmacokinetic Analysis

Pharmacokinetic data from patients in the Phase 1 and 2 portion of the study will be analyzed together.

Noncompartmental PK analysis will be performed using the blood concentration versus time data obtained from patients participating in dense PK sampling to estimate $C_{max}$, AUC, clearance (CL), volume of distribution at the steady state (Vss), and half-life ($t_{1/2}$). If data allow, main PK parameters (CL and Vss) will be summarized by age group as appropriate (eg, < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to ≤ 24 years).

Population PK analysis will be performed using nonlinear mixed effect modeling. Concentration data obtained from both dense and sparse PK sampling will be combined to develop the population PK model. Effect of age and body size on *nab*-paclitaxel PK will be assessed. Other relevant covariates for the main PK parameters will also be identified. The between-patient variability for PK parameters will be estimated, as appropriate. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored.

# 11. ADVERSE EVENTS

## 11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome, rather than the individual signs or symptoms of the diagnosis or syndrome, should be recorded on the AE page of the CRF.

Clinically significant signs and symptoms associated with disease progression are expected to be reported as AEs; however, study indication progressive disease (PD) that is asymptomatic or solely documented radiographically per RECIST 1.1/MIBG does not require reporting as an AE.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms. See Section 8.2.4 for the definition of overdose. In the event of overdose, the patient should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for nab-paclitaxel overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All patients will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the patient's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs and serious adverse events (SAEs) will be recorded by the investigator from the time the parent/guardian/patient signs the informed consent/assent document (if applicable) to 28 days after the last dose of IP and during the EOT visit. Serious adverse events made known to the investigator at any time thereafter that are suspected of being related to IP will also be recorded. AEs and SAEs will be recorded on the AE page of the CRF and in the patient's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

## 11.2. Evaluation of Adverse Events

A qualified investigator will evaluate all adverse events as to:

### 11.2.1. Seriousness

A SAE is any AE occurring at any dose that:

- Results in death

- Is life-threatening (ie, in the opinion of the investigator, the patient is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay)
- Results in persistent or significant disability/incapacity (a substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE form/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

### 11.2.2. Severity / Intensity

For both AEs and SAEs, the investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the patient's symptoms according to the current active minor version of the NCI CTCAE, Version 4.0.

AEs that are not defined in the NCI CTCAE should be evaluated for severity / intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on patient/event *outcome* or *action* criteria associated with events that pose a threat to a patient's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

### 11.2.3. Causality

The investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

| | |
|---|---|
| Not suspected: | Means a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event |
| Suspected: | Means there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event |

If an event is assessed as suspected of being related to an ancillary treatment that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

### 11.2.4. Duration

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

### 11.2.5. Action Taken

The investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

### 11.2.6. Outcome

The investigator will report the outcome for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the patient's participation in the study must be followed until recovered, recovered with sequelae, not recovered, or death (due to the SAE).

## 11.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

## 11.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female patient or partner of a male patient are immediately reportable events.

### 11.4.1. Females of Childbearing Potential

For the purposes of this study, a female patient is considered of childbearing potential if she is ≥ 12 years old or has reached menarche, whichever occurred first.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on IP, within 28 days of the patient's last dose of IP, or at the EOT visit are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female patient may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The investigator will follow the female patient until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

### 11.4.2. Male Patients

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking IP should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

## 11.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE form/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The investigator is required to ensure that the data on these forms are accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the parent/guardian/patient signs informed consent/assent form (if applicable) to 28 days after the last dose of IP and at the EOT visit), and those made known to the investigator at anytime thereafter that are suspected of being related to IP. SAEs occurring prior to IP administration (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a patient died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the investigator is responsible for informing the Institutional Review Board/ Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

### 11.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

## 11.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to nab-paclitaxel based on the Investigator Brochure.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the investigator of the following information

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to patients.

The investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

**Celgene Drug Safety Contact Information**

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

# 12. DISCONTINUATIONS

## 12.1. Treatment Discontinuation

Patients who are discontinued from IP for any reason are not discontinued from the study, and will continue to be followed as described in Section 6.2 until study discontinuation (Section 12.2).

The following events are considered sufficient reasons for discontinuing a patient from the IP:

- Dose-limiting toxicity
- Adverse event(s)
- Disease progression
- Symptomatic deterioration (global deterioration of health status without objective evidence of disease progression)
- Physician decision
- Withdrawal by patient
- Withdrawal by parent/guardian
- Death
- Lost to follow up
- Protocol violation
- Pregnancy
- Other (to be specified on CRF)

The reason for discontinuation should be recorded in the CRF and in the source documents.

The decision to discontinue a patient from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a patient, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

## 12.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a patient from the study follow-up periods:

- Withdrawal by patient
- Withdrawal by parent/guardian
- Death
- Lost to follow up
- Protocol violation
- Other

The reason for discontinuation should be recorded in the CRF and in the source documents.

# 13. EMERGENCY PROCEDURES

## 13.1. Emergency Contact

In emergency situations, the investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page).This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/CRO Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

## 13.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

# 14. REGULATORY CONSIDERATIONS

## 14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and investigator abide by Good Clinical Practice (GCP), as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

## 14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all investigators, who in turn will select their staff.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all patients/parents/guardians who sign an informed consent/assent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient's source documents.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to patient records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example, on the investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

## 14.3. Patient Information and Informed Consent / Assent

The investigator must obtain informed consent of a patient or legal representative (parent/guardian) prior to any study-related procedures, and where applicable assent from the patient. A patient considered adult by local regulations (eg, patients who are ≥ 18 years old,

emancipated minors, mature minors) must provide informed consent for him/herself. In this section, it is implied that where applicable, the patient must also provide his/her assent for participation at the time of his/her parent/guardian consent.

Documentation that informed consent/assent occurred prior to the study patient's entry into the study and of the informed consent/assent process should be recorded in the study patient's source documents, including the date. The original informed consent/assent document, signed and dated by the study patient's parent/guardian or patient (when applicable) and by the person consenting the study patient prior to the study patient's entry into the study, must be maintained in the investigator's study files and a copy given to the study patient's parent/guardian or to the patient (when applicable). In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study patients participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document, signed and dated by the study patient's parent/guardian/patient (when applicable) and by the person consenting the study patient, must be maintained in the investigator's study files and a copy given to the study patient.

## 14.4. Confidentiality

Celgene affirms the patient's (parents'/guardians') right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the investigator to permit Celgene representatives, and when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the patient's parent/guardian signed informed consent document, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

## 14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the investigator name, protocol number, study title, and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

## 14.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document (assent document if applicable), and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent/assent document should also be revised.

The investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the investigator (or coordinating investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit patients for the study must be reviewed by Celgene and the IRB/EC prior to use.

## 14.7. Ongoing Information for the Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible
- Periodic reports on the progress of the study
- Deviations from the protocol or anything that may involve added risk to patients.

## 14.8. Closure of the Study

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities).

In addition, the investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment
- GCP noncompliance
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the study protocol.

# 15. DATA HANDLING AND RECORDKEEPING

## 15.1. Data / Documents

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed, and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROMs.

## 15.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene standard operating procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

## 15.3. Record Retention

Essential documents must be retained by the investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all patients (and assent documents where applicable)
- Patient identification code list, screening log (if applicable), and enrollment log
- Record of all communications between the investigator and the IRB/EC
- Composition of the IRB/EC
- Record of all communications between the investigator, Celgene, and their authorized representative(s)
- List of subinvestigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures
- Copies of CRFs (if paper) and of documentation of corrections for all patients
- IP accountability records
- Record of any body fluids or tissue samples retained

- All other source documents (patient records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

The investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location, or is unable to retain them for a specified period. The investigator must obtain approval in writing from Celgene prior to destruction of any records. If the investigator is unable to meet this obligation, the investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

# 16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

## 16.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during, and after the study. All aspects of the study are reviewed with the investigator and the staff at a study initiation visit and/or at an investigator meeting. Prior to enrolling patients into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent/assent, record keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, patient's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consents/assents, adherence to inclusion/exclusion criteria, and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

## 16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs, and applicable supporting records of study patient participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, European Medicines Agency, Health Canada) and company authorized representatives. The investigator should make every effort to be available for the audits and/or inspections. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

# 17. PUBLICATIONS

As described in Section 14.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable), and contribution to abstract, presentation, and/or publication development.

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# 19. APPENDICES

## 19.1. Appendix A: RECIST 1.1

The following information is extracted/summarized from Eisenhauer, 2009, New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Please refer to the primary reference for further information.

### 19.1.1. Definitions

At screening, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable.

#### 19.1.1.1. Measurable Disease

**Tumor Lesions.** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20mm by chest X-ray

**Malignant Lymph Nodes.** To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

#### 19.1.1.2. Nonmeasurable Disease

All other lesions are considered nonmeasurable, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥ 10 to < 15mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

#### 19.1.1.3. Special Considerations for Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local (radiation) therapy should be considered measurable or nonmeasurable according to Eisenhauer, 2009.

### 19.1.2. Tumor Response Evaluation

#### 19.1.2.1. Target Lesions

When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be

representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the measurable criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

#### 19.1.2.2. Nontarget Lesions

All nonmeasurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered nontarget lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present," "absent," or "unequivocal progression."

#### 19.1.2.3. Response Criteria

Target and nontarget lesions are evaluated for response separately, and then the tumor burden as a whole is evaluated as the Overall response.

##### 19.1.2.3.1. Target Lesion Response

Target lesions will be assessed as follows:

- **Complete Response (CR).** Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
- **Partial Response (PR).** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD).** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD).** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

##### 19.1.2.3.2. Nontarget Lesion Response

Nontarget lesions will be assessed as follows:

- **Complete Response (CR).** Disappearance of all nontarget lesions and normalisation of tumor marker level. All lymph nodes must be nonpathological in size (<10mm short axis).
- **Non-CR/Non-PD.** Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD).** Unequivocal progression (see comments below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression).

**When the patient also has measurable disease.** In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

**When the patient has only nonmeasurable disease.** This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localised to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so: therefore, the increase must be substantial.

#### 19.1.2.3.3. Overall Response

Overall response should be assessed according to Table 10 for patients with target lesions, and Table 11 for patients with only nontarget lesions.

**Table 10: Time Point Response: Patients With Target (± Nontarget) Disease**

| Target Lesions Response | Nontarget Lesion Response | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/ non-PD | No | PR |
| CR | Not evaluated | No | PR |
| PR | Non-PD or not all evaluated | No | PR |
| SD | Non-PD or not all evaluated | NO | SD |
| Not all evaluated | Non-PD | No | NE |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.

**Table 11: Time Point Response: Patients With Nontarget Disease Only**

| Nontarget Lesions Response | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/ non-PD | No | Non-CR/ non-PD[a] |
| Not all evaluated | No | NE |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

[a] "Non-CR/non-PD" is preferred over "stable disease" for nontarget disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.

#### 19.1.2.4. Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget disease.

## 19.2. Appendix B: Curie Scale for MIBG Response

The Curie score is a semiquantitative scoring system for the comparison of sequential whole-body MIBG scans in children with neuroblastoma. The following information is extracted/summarized from Ady, 1995, and Matthay, 2003. Please refer to the primary references for further information.

### 19.2.1. MIBG Scan Assessable

Patients with neuroblastoma who have positive uptake of $^{123}$I-MIBG will be considered assessable by MIBG scan and will be assessed for response using the Curie score. Patients with neuroblastoma whose disease is also measurable by CT and patients with all other tumor types will be assessed by RECIST 1.1 (Matthay, 2010; Bagatell, 2011).

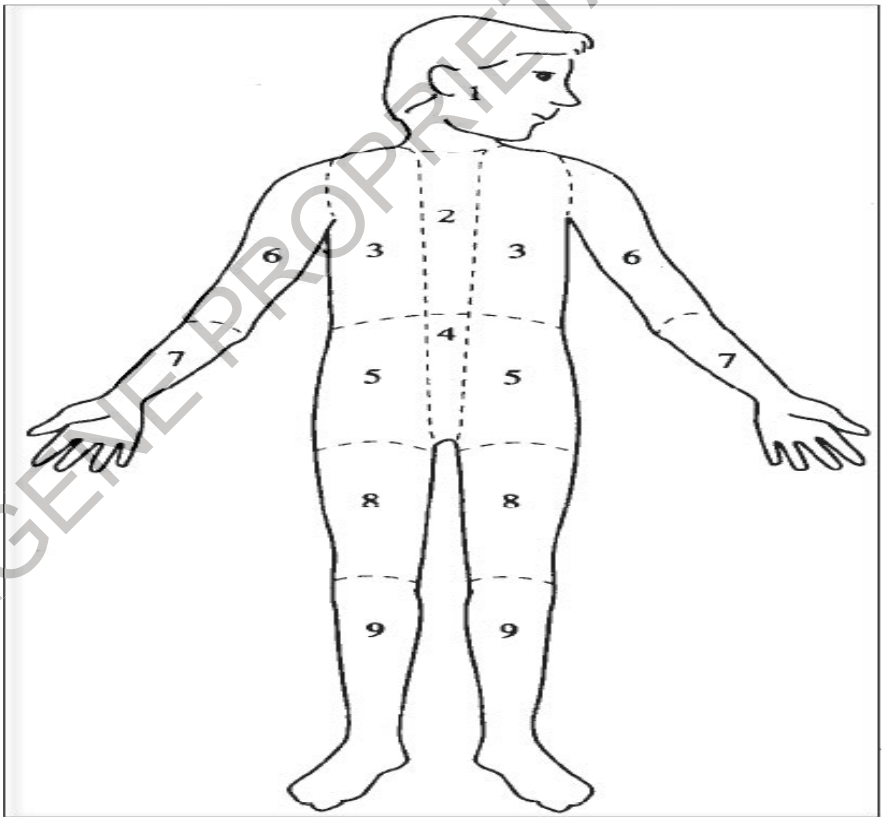
### 19.2.2. Tumor Response Evaluation

The body is divided into nine anatomic sectors for osteomedullary lesions, with a tenth general sector allocated for any extra-osseous lesions. In each region, the absolute extension score of the lesions is graded as:

- 0 = no site per segment
- 1 = one site per segment
- 2 = more than one site per segment
- 3 = massive involvement (> 50% of the segment)

The absolute score is obtained by adding the score of all the segments, as shown in Figure 3 and listed here: (1) head and face; (2) neck and back vertebral column; (3) ribs and sternum; (4) lumbar and sacral column; (5) pelvis; (6) arms; (7) forearms and hands; (8) thighs; (9) legs and feet; and (10) any soft tissue involvement.

**Figure 3: Curie Score Anatomical Regions**




Source: Ady, 1995.

The relative score is calculated by dividing the absolute score at each time point by the corresponding pretreatment overall score.

### 19.2.3. Response Criteria

The relative score of each patient is calculated at each response assessment time point and classified as below:

- **Complete Response:** Postscreening absolute score = 0. All areas of uptake on MIBG scan completely resolved.
- **Partial Response:** Relative score ≥ 0.1 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
- **Stable Disease (nonresponse):** Relative score > 0.5 (lesions weakly but significantly reduced) to < 1 (lesions not reduced).
- **Progressive Disease:** New lesions on MIBG scan, regardless of relative score.

## 19.3. Appendix C: Performance Status

### 19.3.1. Lansky Performance Status

The Lansky performance status is a play-performance scale designed for pediatric cancer patients (Lansky, 1987). The Lansky performance status is recommended in this study for patients < 12 years of age. The parent/caregiver should select the scale that is most representative (average) of the child's activity over the past week according to Table 12.

**Table 12: Lansky Performance Scale**

| Score | Description |
|---|---|
| 100 | Fully active, normal |
| 90 | Minor restrictions in physical strenuous activity |
| 80 | Active, but tires more quickly |
| 70 | Both greater restriction of, and less time spent in, active play |
| 60 | Up and around, but minimal active play; keeps busy with quieter activities |
| 50 | Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities |
| 40 | Mostly in bed; participates in quiet activities |
| 30 | In bed; needs assistance even for quiet activities |
| 20 | Often sleeping; play entirely limited to very passive activities |
| 10 | No play; does not get out of bed |
| 0 | Unresponsive |

### 19.3.2. Karnofsky Performance Status

The Karnofsky performance status is an assessment of the patient's ability to perform normal activity and care for himself/herself. The Karnofsky performance status is recommended in this study for patients ≥ 12 years of age. The research staff should interview the patient and determine the patient's Karnofsky performance status according to Table 13.

**Table 13: Karnofsky Performance Status Scale**

| Condition | Performance Status % | Comments |
|---|---|---|
| A. Able to carry on normal activities and to work. No special care is needed | 100 | Normal. No complaints. No evidence of disease |
| | 90 | Able to carry on normal activity. Minor signs or symptoms of disease |
| | 80 | Normal activity with effort. Some signs or symptoms of disease |
| B. Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed | 70 | Care of self. Unable to carry on normal activity or do active work |
| | 60 | Requires occasional assistance, but is able to care for most of his/her needs |
| | 50 | Requires considerable assistance, but is able to care for most of his/her needs. |
| C. Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly | 40 | Disabled. Requires special care or assistance |
| | 30 | Severely disabled. Hospitalization is indicated although death is not imminent |
| | 20 | Hospitalization necessary, very sick active supportive treatment necessary |
| | 10 | Moribund. Fatal processes progressing rapidly. |
| | 0 | Dead |

Adopted from Karnofsky, 1949.

## 19.4. Appendix D: Pharmacokinetic Sample Handling Instructions

### 19.4.1. Blood Sample Labeling

Labels must contain the following information:

- Protocol No.: **ABI-007-PST-001**
- Patient ID number
- Part: ie, Dense PK or Sparse PK
- Nominal Time: eg, 1 h or 5 h after end of infusion
- Sample Type: **Primary or Back-up**

It is recommended that all blood collection tubes and storage vials should be labeled **prior to** sample collection and processing.

### 19.4.2. Blood Sample Collection:

Blood samples should be collected as follows:

- Collect approximately 0.5 mL of whole blood into a **K3 EDTA** tube. For PK samples collected at 1-2 minutes prior to, and 15 minutes after and 1 hour after the end of infusion, the blood should be drawn from the arm contralateral to the arm used for drug infusion.
- Accurately record the time of blood collection.
- Gently invert the tube 3 to 5 times.
- Transfer approximately 0.25 mL of blood into each of the two prelabeled, prechilled, polypropylene storage tubes (one primary and one back-up). If the blood draw volume is less than 0.5 mL, the first aliquot (primary sample) should be filled with 0.25 mL of blood, and the second aliquot (back-up) with the remaining volume. Keep storage tubes on ice until they are ready to be transferred into a freezer (-20ºC or colder) where they will remain stored until shipping.

### 19.4.3. PK Sample Shipment

All PK sample label information on the storage tubes have to be checked against the requisition form and then the samples must be shipped frozen and on dry ice to the central lab.

#### 19.4.3.1. Sample Collection Documents to Accompany Shipment(s)

A copy of the completed specimen manifest must accompany the shipment, and must list the following information at minimum:

- Sponsor name: Celgene Corp
- Celgene Study Number: ABI-007-PST-001
- Subject ID Numbers
- Group: ie, Dense PK or Sparse PK
- Nominal collection times: eg, 1 h or 5 h after end of infusion
- Sample collection date: eg, 10 Jan 2013
- Sample type: Primary or Backup

# Celgene Signing Page

**This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.**

UserName: PPD
Title: PPD
Date: Wednesday, 13 July 2016, 05:07 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Updated Inclusion Criterion 1b for Phase 2 to Allow Enrollment of Patients ≥ 6 Months to ≤ 24 Years of Age**

In the Phase 2 portion of the study, the original protocol permitted enrollment of patients ≤ 21 years of age. Limitation of the age to 21 years does not represent the entire population of patients seen by pediatric oncologists. Patients 15 to 24 years of age are now commonly referred to as "teenagers and young adults"; the European Society for Medical Oncology (ESMO) is collaborating with the European Society of Pediatric Oncology (SIOPE) to target the unmet medical needs of adolescents and young adults, due in part to the varied interfaces between adult and children's services in different healthcare systems (Vassal, 2014). Many patients diagnosed with neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma are followed in pediatric clinics up to 24 years of age, particularly in the recurrent and relapsed setting. For example, an analysis of data from 1973 to 2007 from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database shows that the median age at diagnosis of extraskeletal Ewing's sarcoma is 19.5 years and that of skeletal Ewing's sarcoma is 16.3 years (Applebaum, 2011). By the time many of these adolescent patients have failed several lines of treatment they are 21 to 24 years old. (Protocol Summary and Sections 1.3.2.1, 2.1, 4.1, 7.2, and 10.9.1)

- **Updated Inclusion Criterion 2b for Phase 2 to Allow Enrollment of Patients Who Have Failed up to Three Lines of Treatment**

In the original protocol, patients were eligible to be enrolled in Phase 2 if they had failed first or second line treatment or if they had evidence of refractory disease. However, current pediatric clinical practice in North America and Europe already includes up to three standard lines of treatment. Limiting eligibility to patients who have failed only first or second line treatment thus prevents the participation of a majority of patients (who have failed three previous lines and for whom new treatment options are limited).

In addition, the phrase "or has evidence of refractory disease" is now removed in order to avoid ambiguity concerning the number of previous lines of treatment. (Figure 2 and Section 7.2)

- **Modification of Exclusion Criterion 7 to Differentiate Between Autologous and Allogeneic Hematopoietic Stem Cell Transplant (HSCT)**

The protocol required that patients should not have received any hematopoietic stem cell transplant (HSCT) ≤ 3 months prior to start of investigational product (IP).

Allogeneic HSCT carries a substantial risk of graft-versus-host disease. Therefore, it is sound clinical practice to delay the start of new chemotherapy for a period of at least 3 months after allogeneic HSCT. Autologous HSCT does not share this risk, and so it is clarified that the exclusion period prior to start of IP is ≤ 21 days for autologous HSCT. (Section 7.3)

- **Updated Assessment of the Primary Endpoint (Overall Response Rate [ORR]) in the Phase 2 Neuroblastoma Group Using Both the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Criteria and the Curie Score**

In Protocol Amendment 4, the ORR for patients in the neuroblastoma group was based on either the RECIST criteria or the Curie score without crossover between assessment types over time; should both assessment types have been performed on a given subject across the assessment time points, the less favorable assessment type (in terms of achievement of response) would be considered for the ORR analysis.

However, response obtained by one of the methods is clinically meaningful even if the other method yields a measurement of stable disease; response in neuroblastoma patients is not adequately assessed by RECIST criteria alone. Studies have shown that high-risk neuroblastoma patients with a Curie score > 2 following induction chemotherapy have extremely poor outcomes, leading to alternative therapies as subsequent options (Yanik, 2013). Even in patients who have received several previous lines of treatment, a response assessed by $^{123}$I-metaiodobenzylguanidine (MIBG)/Curie score is clinically important in determining subsequent treatment options.

With the implementation of Protocol Amendment 5, if both assessment types have been performed on a given subject across the assessment time points, to be considered as a partial response for the ORR analysis, both methodologies should show no worse than stable disease and at least one method should indicate complete response (CR) or partial response (PR). A response is only considered complete if both methodologies indicate CR. (Sections 1.3.2 and 10.6)

- **Clarification of Definition of the Efficacy Evaluable Population**

Per the Phase 2 Simon two-stage design in Section 10.3 (Sample Size and Power Considerations), for each of the 3 groups in the first stage, 14 efficacy evaluable patients will be enrolled. If < 2 of the 14 patients has a response, the enrollment for this group will be stopped upon determination of the number of responders. If ≥ 2 of the 14 patients have a response, the enrollment will continue until 23 efficacy evaluable patients are enrolled.

However, the Efficacy Evaluable Population was defined in Protocol Amendment 4 Section 10.2 (Study Population Definitions) as "All treated patients who meet eligibility criteria, complete at least two doses of investigational product, and have baseline and at least one postbaseline efficacy assessment. Here efficacy assessment means radiological assessment of the tumor or tumor assessment by other appropriate means." Patients may experience symptomatic deterioration (a measure of clinical progression in the absence of objective radiological tumor assessment) prior to a post-baseline efficacy assessment, and may have had only one dose of investigational product.

With the implementation of Protocol Amendment 5 the definition of the Efficacy Evaluable Population is updated as follows to accurately include patients with clinical progression in the analysis of ORR: "All treated patients who meet eligibility criteria, complete at least one dose of investigational product, and have baseline and at least one postbaseline efficacy assessment if having not discontinued the investigational product prior to postbaseline efficacy assessment due to disease progression or symptomatic deterioration. Here efficacy assessment means radiological assessment of the tumor or tumor assessment by other

appropriate means. Investigational product discontinuation due to disease progression or symptomatic deterioration must be documented as the primary reason for treatment discontinuation in the treatment discontinuation CRF." In addition, the definition of symptomatic deterioration in Section 12.1 Treatment Discontinuation is updated from "Symptomatic deterioration (global deterioration of health status)" to "Symptomatic deterioration (global deterioration of health status without objective evidence of disease progression)." (Sections 10.2 and 12.1)

- **Addition of Definition of nab-Paclitaxel Overdose**

Section 8.2.4 has been updated to align with current company standard protocol language concerning *nab*-paclitaxel overdose. (Section 8.2.4)

- **Identification of the Recommended Phase 2 Dose (RP2D)**

During the Phase 1 portion of the study, the Safety Monitoring Committee (SMC) determined that the RP2D is 240 mg/m2 in patients weighing > 10 kg, and 11.5 mg/kg in patients weighing ≤ 10 kg. This information is added to the protocol. (Protocol Summary and Sections 1.3.2, 4.1, and 8.2.1.4)

- **Updated Phase 1 Enrollment Numbers**

During the Phase 1 portion of the study, 6 dose cohorts (a total of 44 patients in the Dose Determining Sets) were evaluated, and about 20 additional patients were enrolled at dose levels evaluated as safe by the SMC. This information is added to the protocol. (Protocol Summary, Figure 1 and Section 7.1)

- **Allowance for the Use of Historical Left Ventricular Shortening Fraction (LVSF) Assessments and Electrocardiograms (ECGs) at Screening**

The protocol required that LVSF assessments and ECGs be performed at screening after informed consent/assent has been obtained. In order to avoid subjecting young patients to repeated stressful procedures during a short time period, with the implementation of Protocol Amendment 5 if a patient has a historic LVSF assessment or ECG that was performed prior to informed consent/assent for non-study reasons, the procedure does not need to be repeated for screening. The procedure must have been performed within 14 days of the first dose of *nab*-paclitaxel. (Section 6)

References:

Applebaum MA, Worch J, Matthay KK, Goldsby R, Neuhaus J, West DC, et al. Clinical features and outcomes in patients with extraskeletal Ewing sarcoma. Cancer. 2011;117(13):3027-32.

Vassal G, Fitzgerald E, Schrappe M, Arnold F, Kowalczyk J, Walker D, et al. Challenges for the Children and Adolescents With Cancer in Europe: The SIOP-Europe Agenda. Pediatr Blood Cancer. 2014;61(9):1551-7.

Yanik GA, Parisi MT, Shulkin BL, Naranjo A, Kreissman SG, London WB, et al. Semiquantitative mIBG scoring as a prognostic indicator in patients with Stage 4 neuroblastoma: a report from the Children's Oncology Group. J Nucl Med. 2013;54(4):541-548.

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Increased Scope of Dense Pharmacokinetic (PK) Sample Collection**

This protocol amendment increases dense PK sampling from the first 18 to 24 patients (regardless of study phase) to all patients enrolled in Phase 1. The PK sampling scheme in the original protocol was based on the assumption that up to approximately 4 dose level cohorts would be enrolled, each with 6 patients. However, it was not taken into account that there were patients who had undergone PK sampling but did not meet all criteria for inclusion in the Dose Determining Sets (DDS); these patients were replaced and PK samples were collected, as per protocol and in agreement with the Safety Monitoring Committee (SMC). In addition, patients were also enrolled at a dose previously determined to be safe during the interim period between the closing of one cohort and an SMC dose escalation decision to open a new cohort; therefore, the number of patients who had PK samples collected is higher than anticipated. In order to permit full noncompartmental PK analysis of all Phase 1 dose levels, and in particular the dose determined to be the Recommended Phase 2 Dose (RP2D), dense PK sampling will be obtained for all patients enrolled in Phase 1 (up to approximately 40 patients).

- **Change of the Third Solid Tumors Group in Phase 2 from Mixed Tumors to Ewing's Sarcoma**

For the Phase 2 portion of the study the original protocol was designed to determine the antitumor activity of *nab*-paclitaxel in patients with several discrete solid tumor types: neuroblastoma, rhabdomyosarcoma, and a mixed solid tumor group (eg, nonrhabdomyosarcoma soft tissue sarcomas, melanoma, or tumors in which the drug showed activity during the Phase 1 part of the study and/or in preclinical studies). Study investigators strongly advised that the third group should be changed to include only one patient category, ie, patients with Ewing's sarcoma. Analysis of a miscellaneous group of tumors would not lead to meaningful Phase 2 results since it may not be possible to accrue enough patients in any of the other indications to signal significant activity. This recommendation by the pediatric investigators was based on consideration of the available preclinical data in Ewing's sarcoma, and occurred following review of the patients enrolled to date in the Phase 1 portion of Study ABI-007-PST-001.

- **Harmonization of Sample Size and Simon Two-Stage Minimax Design for the Three Groups in Phase 2**

Since the third Phase 2 group will include only Ewing's sarcoma patients and not mixed tumor types, a Simon two-stage minimax design will now be used to evaluate treatment effect in this group as well. In addition, based on feedback that in the Phase 2 portion of the study the neuroblastoma group is unnecessarily large and it would be appropriate to have the identical Simon 2-stage design for all 3 groups, the protocol design is now simplified, while maintaining its relevance. The 3 Phase 2 groups will now monitor enrollment using the same Simon 2-stage design already in place for the rhabdomyosarcoma group. For each of the 3 groups, in the first stage, 14 efficacy evaluable patients will be enrolled. If < 2 of the 14

patients within a group has a response, the enrollment for this group will be stopped upon determination of the number of responders. If ≥ 2 of the 14 patients have a response, the enrollment will continue until 23 efficacy evaluable patients are enrolled. At the final analysis, the regimen will be concluded with a greater than 5% true response rate if ≥ 5 of 23 patients have a response according to the maximum likelihood estimator. The sample size is based on an 80% power and 10% significance, having fixed the lower and upper boundaries to 10% and 28%, respectively.

- **Updated Inclusion Criterion 2 for Phase 2 to Require Radiologically Documented Measurable Disease by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (for Neuroblastoma Evaluable Disease by MIBG/Curie Score is also Acceptable)**

The primary endpoint of Phase 2 is Overall Response Rate (ORR); evaluation of instances of confirmed partial response (PR) in addition to complete response (CR) will be necessary in order to have a chance to properly evaluate treatment effect and ORR using the Simon two-stage minimax design. Patients will therefore be required to have radiologically documented measurable disease (for neuroblastoma, evaluable disease by MIBG/Curie score is also acceptable).

- **Updated Assessment of the Primary Endpoint (Overall Response Rate [ORR]) in the Phase 2 Neuroblastoma Group to Use Both the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 Criteria and the Curie Score**

In the original study protocol the response in all Phase 2 patients is assessed by computed tomography (CT) or magnetic resonance imaging (MRI) using RECIST criteria, with an exploratory endpoint of determination of response using $^{123}$I-metaiodobenzylguanidine (MIBG) and Curie score in the neuroblastoma group. Based on investigator feedback that the lack of MIBG assessment would potentially weaken the significance of the study results, and could potentially make it difficult to enroll subjects in the neuroblastoma group, the assessment of ORR in the Phase 2 neuroblastoma group will now use both the RECIST criteria and the Curie score when possible. The Curie score is a semiquantitative scoring system for the comparison of sequential whole-body MIBG scans in children with neuroblastoma (Ady, 1995), and MIBG scans are now considered the most sensitive and specific method of staging and response evaluation in neuroblastoma (Matthay, 2010). Using both methods will allow for a more comprehensive and relevant evaluation of response in neuroblastoma patients who do not have measurable disease by RECIST criteria. With this amendment, the ORR for patients in the neuroblastoma group will be based on either the RECIST criteria or the Curie score without crossover between assessment types over time. Should both assessment types have been performed on a given subject across the assessment time points, the less favorable assessment type (in terms of achievement of response) will be considered for the ORR analysis. In addition, consequently, this assessment of MIBG response in neuroblastoma patients is no longer considered an exploratory objective in Phase 2.

- **Confirmation of Complete Response in Phase 2 Neuroblastoma**

Patients in the Phase 2 neuroblastoma group who exhibit confirmed complete response will have a bone marrow biopsy performed to ensure that disease not assessable by RECIST or by MIBG methodologies is not present. This has been added as an exploratory endpoint in Phase 2.

- **Decreased Minimum Platelet Level in Inclusion Criterion 5 for Phase 2 Patients with Known Bone Marrow Involvement**

Patients with the solid tumor types being studied (particularly neuroblastoma) can have bone marrow involvement resulting in low platelet levels due to their disease and to previous treatment regimens. In order to allow their enrollment, Inclusion Criterion 5 is updated to allow platelets $\geq 50 \times 10^9$ cells/L for patients with known bone marrow involvement; these levels are considered acceptable for treatment in clinical practice and will not increase the risk to patients.

**The amendment also includes several other minor clarifications and updates:**

- Addition of guidance on flushing of the intravenous line following administration of *nab*-paclitaxel (Section 8.2)
- Addition of statements regarding study conduct in compliance with International Conference on Harmonisation (ICH) Good Clinical Practices (GCPs) to align with updated company standard protocol language (Study Summary and Overall Study Design)
- Clarification of Phase 1 sample size to include additional patients enrolled at dose levels evaluated as safe by the SMC (Protocol Summary)
- Update to length of Phase 1 (from 12 months to up to 18 months) (Protocol Summary)
- Clarification of SAE reporting during the 28-day follow-up period to align with updated company standard protocol language (Section 6.2.1)
- Update to the description of response assessments to include that the sponsor may conduct an independent assessment of response after study completion (Section 6.3)
- Update to Inclusion Criterion 8 to align with current Celgene Standard Risk Language (Section 7.2)
- Clarification that the safety analysis will include summarization of adverse events of special interest (Section 10.7)
- Update to treatment discontinuation information concerning the treating physician's responsibilities (Section 12.1)
- Update to Section 14.2 to align with current company standard protocol language concerning investigator responsibilities for handling of confidential information
- Update to Section 17 to align with current company standard protocol language concerning publication
- Addition of references (Section 18)
- Clarification that the MIBG tumor response assessment includes a 10th segment for any soft tissue involvement (Section 19.2.2)

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Update to the new IND number for *nab*-paclitaxel for the pediatric solid tumors indication.

CCI

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- In the Phase 2 portion of the study, a change to the sample size for the Phase 2 neuroblastoma arm, and modifications of the Simon two-stage minimax design to implement acceptance rates of approximately 20% response rates for the neuroblastoma and rhabdomyosarcoma arms.
- The addition of ≥ Grade 2 peripheral neuropathy to the exclusion criteria.
- The addition of information concerning the use of syringe-based devices for administration of small volumes of *nab*-paclitaxel suspension.
- A change from cautionary use to prohibition of concomitant medications classified as strong inducers of cytochrome P450 isozymes CYP2C8 and CYP3A4, and additional guidance on the use of strong inhibitiors of the same isozymes.

Other minor changes included in this amendment are summarized below:

- An administrative change to the Medical Monitor title and contact information.
- An administrative change to include the approval of *nab*-paclitaxel in the USA and EU for the treatment of first-line metastatic pancreatic adenocarcinoma.
- Clarification and updates to the description of the rolling-6 design for the Phase 1 portion of the study.
- The addition of the use of "other medically appropriate method" for left ventricular shortening fraction (LVSF) assessment.
- The addition of company standard language for the description of investigational product.
- Clarification of permitted dose reductions from dose level -1 in the Phase 1 portion of the study.
- Clarification of recommendation concerning labeling of pharmacokinetic (PK) samples.
- Administrative changes to clarify protocol language and provide one additional literature reference.
- Administrative changes to correct minor formatting errors

# 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- A global administrative change of Sponsor name from'Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation' to 'Celgene Corporation' to reflect the retirement of the legacy entity 'Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation' as Sponsor Name.
- The addition of echocardiogram/multi-gated acquisition (MUGA) scans for increased cardiotoxicity monitoring.
- Modification of the schedule of events to increase the frequency of 12-lead electrocardiogram (ECG) testing.
- The addition of a 3-month washout period for hematopoietic stem cell transplantation (HSCT) to the exclusion criteria.
- A decrease in the volume of blood drawn for pharmacokinetic (PK) sampling.
- An administrative change to clarify the PK sampling requirements for samples collected up to 1 hour after the end of study drug infusion.
- Removal of Cycle 1 Day 1 urine homovanillic acid and vanillylmandelic acid testing.
- Clarification and updates in the statistical analysis section (e.g. safety analysis).
- An administrative change to include the use of Integrated Response Technology (IRT) for patient enrollment
- Addition of company standard language for End of Trial, overdose, Adverse Events, Serious Adverse Events, pregnancy language, site responsibilities and monitoring, and administrative procedures.
- Administrative changes to correct minor errors and inconsistencies within the document and/or Case Report Forms.