

BRISTOL-MYERS SQUIBB COMPANY
BRIEFING DOCUMENT FOR
THE PEDIATRIC SUBCOMMITTEE OF
THE ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING
05-NOV-2013

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1 EXECUTIVE SUMMARY

Bristol-Myers Squibb (BMS) has initiated early development planning to evaluate nivolumab (also referred to as BMS-936558 or MDX-1106) in pediatric subjects with solid tumors. BMS was invited to participate in the 05-Nov-2013 meeting of the Pediatric Subcommittee of the Oncologic Drug Advisory Committee (PODAC). Participation in this meeting will give BMS an opportunity to seek agreement and alignment on a simplified, global pediatric development program. This meeting will allow BMS the opportunity to continue the conversation regarding the evaluation and accelerated development of immuno-oncology (IO) agents in patients with pediatric malignancies, especially in regards to prioritization of target indications and recommendations for monitoring from pediatric experts.

Pediatric cancer is not a single disease entity, but rather a spectrum of different malignancies with a high degree of variation in terms of histological types, site of origin, sex, race and age as well as unmet medical need. Pediatric malignancies are rare and account for <1% of cancers in the US annually. This leads to a unique situation among sponsors who may have interest to pursue a pediatric development in oncology, but are constrained by the limited availability of pediatric patients. BMS sees opportunities in pediatric development through global collaboration with key centers in the United States (US) and European Union (EU), among others.

Nivolumab is a fully human monoclonal immunoglobulin G4 (IgG4-S228P) antibody (HuMAb) that targets the programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. Binding of PD-1 to its ligands, programmed death-ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self antigens.

The PK, clinical activity, and safety of nivolumab has been assessed in completed Phase 1 and ongoing Phase 2 and 3 studies sponsored by BMS in adult subjects with non-small cell lung cancer (NSCLC), melanoma, and renal (clear) cell carcinoma (RCC) in addition to other tumor types. The current Phase 3 clinical program focuses on squamous and non-squamous NSCLC, malignant melanoma, and RCC. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies. Clinical activity and safety information presented in this briefing document focuses primarily on that obtained from a Phase 1 multiple ascending dose study, MDX1106-03 (also known as CA209003), with several expansion cohorts in multiple indications including NSCLC, melanoma, RCC, colorectal cancer (CRC), metastatic castrate-resistant prostate cancer (mCRPC) and a Phase 1 combination study with ipilimumab, MDX1106-04 (also known as CA209004).

The pharmacokinetics (PK) of nivolumab was linear in the range of 0.1 to 10 mg/kg and both elimination and distribution of nivolumab in the dose range studied appear to be independent of dose in the dose range studies while end of infusion and minimum serum concentration (C_{min}) after the first dose were approximately dose proportional. No differences in PK were observed across tumor types in CA209003. Population PK (PPK) analysis indicated that body weight normalized dosing is appropriate for nivolumab therapy.

Objective responses have been observed in subjects with NSCLC, melanoma, and RCC. Time to response ranged from 7 to 48 weeks and responses were durable.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 1500 subjects treated to date. For monotherapy, the safety profile is generally similar across tumor types. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. No maximum tolerated dose (MTD) was reached at any dose of nivolumab monotherapy tested up to 10 mg/kg. The most advanced combination under development is nivolumab + ipilimumab in adult subjects with melanoma. Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases with a greater frequency.

2 MECHANISM OF ACTION OF NIVOLUMAB

In vitro, nivolumab binds to PD-1 on activated human T cells with high affinity (half maximal effective concentration [EC50]: 0.64 nM by FACS analysis and 2.6 nM by Scatchard), and inhibits the binding of PD-1 to its ligands, programmed death-ligand-1 (PD-L1) and programmed death-ligand-2 (PD-L2) (half maximal inhibitory concentration [IC50] of ~1 nM).¹ Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, inducible co-stimulator (ICOS), cytotoxic T lymphocyte associated antigen-4 (CTLA-4) and B and T lymphocyte attenuator (BTLA). Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN- γ release in the mixed lymphocyte reaction (MLR). Using a cytomegalovirus (CMV)-re-stimulation assay with human peripheral blood mononuclear cell (PBMC), the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN- γ secretion from CMV specific memory T-cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and results in tumor rejections and tumor growth delays in MC38 and SA1/N immunocompetent mouse tumor models.²

3 REGULATORY HISTORY

Adult clinical development was initiated by Medarex in 2006, with the initial Investigational New Drug (IND) 100052 submitted on 27-Jun-2006. In 2011 and 2012, BMS initiated discussions with FDA and European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) to pursue Phase 2/3 pivotal clinical development of nivolumab in melanoma, NSCLC, and RCC.

A Pediatric Investigational Plans (PIP) and a Pediatric Study Plan (PSP) were submitted in Mar-2013 to EMA and FDA. BMS is working with EMA's Pediatric Committee of the European Medicines Agency (PDCO) to reach agreement on a proposed pediatric plan and is working with FDA to ensure the pediatric development of nivolumab is initiated under the new FDASIA regulations. The goal is to have a global plan to ensure efficiency in the development of nivolumab in pediatric subjects with the unmet medical need.

In Sept-2013, BMS held a Day 60 clarification teleconference with the EMA PIP reviewers and there was general agreement with the proposed development program which BMS intends to pursue in pediatrics.

4 CHALLENGES IN PEDIATRIC DEVELOPMENT

4.1 Epidemiology in Pediatrics

Pediatric cancer is not a single disease entity, but rather a spectrum of different malignancies with a high degree of variation in terms of histological types, site of origin, sex, race and age. In general, cancer is uncommon below the age of 20, accounting for <1% in the US annually, and its relative importance as a cause of mortality significantly varies from 0 to 19 years old. This leads to competition for clinical trial subjects which may be avoided through global collaboration of key centers in the US and EU.

In 1995, the Surveillance, Epidemiology and End Results (SEER) data reported a 0.2% rate of cancer mortality in infants, making it a minor cause of death in this age subset.³ However, malignancies are a major cause of mortality in children between 1 and 14 years old. Accidents and congenital anomalies are responsible for more deaths in the age group 1-4 years, whereas only accidents were a more frequent cause of death in the age group 5 to 14 years.⁴ Death rates for most childhood cancers have dramatically declined in the last 30 years, while the incidence of some types of childhood cancers has increased in the same time period. Similar trends in the incidence and mortality of childhood cancers have been observed in the US and in most European countries.^{3,5,6} Recent data from population-based analysis of cancer incidence and survival among children and adolescents in Europe over the period 1978-1997,⁷ showed a total age-standardized incidence of 139 per million children for Europe overall, varying from 116 per million to 173 per million in individual countries. When expressed as a percentage of all malignancies arising in the European population, the frequency of cancer in patients younger than 20 years is low, accounting for 1% of all cases. In the same period survival significantly improved, from 54% to 75% over the period 1978-1982 and 1993-97, respectively.⁷

Despite the dramatic improvement in survival observed in the last 3-4 decades as a result of the multidisciplinary approach applied overall to pediatric solid malignancies, the outcome of patients with recurrent tumors or metastatic sarcomas remains poor. Most of the drugs and biologics used routinely in primary treatment regimens for pediatric cancers were approved before 1990, about half of them before the mid-1980s,⁸ and, therefore, new therapies are needed.

4.2 Requirements for Pediatric Development

Bristol-Myers Squibb is committed to studying nivolumab in pediatrics. The adolescent and young adult (AYA) population also deserves further attention given that no significant improvement has been seen in the treatment of AYA patients with cancer diagnosed between 15 and 39 years and often treated by pediatric oncologists.⁹

EMA requirements for the future melanoma marketing application specify that the sponsor must meet certain obligations by having an approved PIP in place as part of the compliance check for receipt of the application. Currently, under EMA pediatric requirements, lung cancer and renal cancer are class-waiver eligible, but not melanoma. Nivolumab's melanoma indication has been granted orphan drug designation for Stages IIB to IV by FDA. RCC and lung cancer are also

waiver-eligible in the US because the cancers occur predominately in adults and do not exist in children.

BMS is working to meet the necessary regulations to fulfill European obligations for accepting a marketing application that meets validation requirements, while trying to maintain a viable pathway through the proposal for Pediatric Study Request (PSP) mechanism for a Written Request to evaluate other cancers in children with a high unmet medical need. BMS's primary goal is to evaluate nivolumab in pediatric patients with tumor types that have high unmet medical need and that are relevant in this population.

5 OPPORTUNITY TO ADDRESS UNMET MEDICAL NEED IN PEDIATRICS

The greatest area of unmet medical need for pediatric tumors mainly comprises solid tumors, specifically disease that was metastatic at presentation or recurred. Because of the yet unsatisfactory survival rates of pediatric patients with metastatic or recurrent solid tumors, there is a need for new therapeutic approaches. Biologic therapies aimed at enhancing the patient's immune response against the tumor represent an area worth exploring to improve the outcome of children with refractory solid malignancies.

Immuno-oncology agents are designed to harness the natural capabilities of the patient's immune system to fight cancer by targeting the very same pathways tumor cells use to evade recognition and destruction. Bristol-Myers Squibb is committed to the research and development of these IO agents in adult and pediatric malignancies through the development of a robust pipeline of investigational compounds that are designed to directly modulate the immune system through different target pathways.

As such, the potential significant therapeutic benefit with nivolumab is expected to fulfill the following therapeutic needs:

- Nivolumab presents a unique opportunity to further evaluate IO agents which reset the balance between the immune system and cancer.
- Nivolumab's novel mechanism of action of immune check-point blockade provides opportunities for tumor responses and/or long-term control of tumor growth, across multiple tumor types, which have not been achievable with cytotoxic/cytostatic drugs or molecularly targeted agents.
- Benefit from existing treatments including chemotherapeutic and molecularly targeted agents may be limited by development of resistance rendering tumors non-responsive. As demonstrated by its activity in heavily pre-treated lung cancer patients, nivolumab may have activity in the setting of patients who are refractory to other available treatments. Nivolumab may offer a new treatment alternative with an improved benefit-risk balance for patients at risk for development of resistance or who have exhausted other treatment options.

5.1 BMS Immuno-oncology Pipeline

BMS is uniquely poised to evaluate IO agents in adult and pediatric malignancies through nivolumab as well as the rest of the BMS IO pipeline. Bristol-Myers Squibb is committed to continuing to research this new approach to cancer treatment through the development of a robust pipeline of investigational compounds that are designed to directly modulate the immune system. As part of BMS's commitment to the development of IO agents in pediatrics, the potential for benefit from immune checkpoint modulation is already being explored with ipilimumab. Information from the evaluation of clinical efficacy and safety with ipilimumab is relevant to the development of nivolumab monotherapy as well as nivolumab combination therapy with ipilimumab or with other BMS IO agents such as urelumab, lirilumab, and denenicokin in pediatric patients.

BMS is also conducting research on the potential of combining IO agents that target different pathways in the treatment of cancer. Therefore, current information on ipilimumab alone and in combination are included in this document.

5.1.1 *Ipilimumab in Pediatrics*

Early safety data from a clinical study with the cytotoxic T lymphocyte associated antigen-4 (CTLA-4) antibody, ipilimumab, in pediatric cancer patients demonstrated a safety profile that is comparable between adult and pediatric patients.²⁰

Yervoy® (ipilimumab) has been approved for use in over 40 countries including the US (Mar-2011), the EU (Jul-2011), Australia (Jul-2011), Norway, Iceland, Switzerland, Liechtenstein, Canada, Argentina, Australia, New Zealand, Brazil, Chile, Colombia, Mexico, and Israel. Ipilimumab (3 mg/kg monotherapy) is approved in the US and several other countries as a first-line and second-line therapy for advanced melanoma regardless of prior therapy, including previously untreated, chemotherapy naive, or treated patients.

No children have been treated with ipilimumab in combination with other cancer agents, including other immune-based therapies. Clinical data on ipilimumab administered as monotherapy to pediatric patients are available from the ongoing Study National Cancer Institute (NCI) 7458. In this Phase 1 dose escalation study, the safety, tolerability, PK, and immunogenicity of ipilimumab administered to subjects from 2 to 21 years of age with recurrent or progressive solid tumours is being investigated. Ipilimumab is administered at 1, 3, 5, and 10 mg/kg intravenous (IV) in a standard 3 + 3 design with 4 doses of induction therapy q3 weeks followed by maintenance q3 months until disease progression or unacceptable toxicity.²⁰ Tumor assessments are performed after 6 weeks, 12 weeks, and then every 3 months. Study NCI 7458 has enrolled 26 subjects to date with 24 evaluable participants.

5.1.2 *Clinical Safety of Ipilimumab in Pediatrics*

None of the subjects \geq 12 years of age enrolled at dose levels of 1 and 3 mg/kg experienced dose limiting toxicities (DLT). Of the 7 subjects (ages 13 to 20 years) who received 5 mg/kg, one developed a DLT of Grade 4 pancreatitis. Of the 7 subjects (12 to 21 years of age) who received

10 mg/kg and were evaluable for safety, one experienced a DLT of pleural effusions at Week 2 following a single dose of ipilimumab.

Since the opening of the < 12 years of age cohort during the 5 mg/kg expansion phase, one melanoma subject has been enrolled. This subject developed Grade 3 angioedema after only 4 mL of infusion of the first dose of ipilimumab. The enrollment for subjects < 12 years of age at 5 mg/kg is ongoing. Two subjects, both <12 years of age, were enrolled at 1 and 3 mg/kg and had no DLTs.

Three subjects (ages 7, 10, and 11 years) received ipilimumab at 10 mg/kg. One subject tolerated 10 mg/kg without any significant toxicities. Two subjects experienced a DLT: One subject with neuroblastoma developed Grade 3 colitis and Grade 3 emesis and a second subject with spindle cell sarcoma developed Grade 3 transaminitis. Because 2 out of the 3 subjects, who were < 12 years of age, developed DLTs after treatment with 10 mg/kg ipilimumab, 5 mg/kg is being explored as the MTD for this age group.

5.1.3 Clinical Activity of Ipilimumab in Pediatrics

Based on preliminary data from NCI Study 7458, none of the subjects reached an objective response (partial response [PR] or complete response [CR]) per Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Seven subjects had stable disease as best overall response. Of the 7 subjects with stable disease (SD) reported for best overall response, one subject with melanoma had a long duration of SD, received 14 ipilimumab administrations, and stayed on treatment for over 1 year.²⁰ The remaining 17 subjects had progressive disease as best response.

5.1.4 Pharmacokinetics

Preliminary analysis was conducted to compare ipilimumab PK in pediatric and adult using pediatric PK data that were available as of Jul-2013. Preliminary results suggest that ipilimumab pediatric PK appears to be linear and similar to adult PK.

6 SUMMARY OF NONCLINICAL DATA

Like ipilimumab, nivolumab is an immune checkpoint modulator. In addition to the characterization of nivolumab's mechanism of action described in [Section 2](#), fluorescent-activated cell sorter (FACS) analysis confirmed that nivolumab binds to transfected Chinese hamster ovary (CHO) and activated human T-cells expressing cell surface PD-1 and to cynomolgous monkey PD-1, but not to rat or rabbit PD-1 molecules.² Nivolumab has also been shown to bind to PD-1 on virus-specific CD8+ T-cells from chronically infected hepatitis C virus (HCV) patients.¹⁰

Nivolumab was well tolerated in intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys at doses up to 50 mg/kg, administered up to twice weekly (Q2W). However, a combination study with ipilimumab, indicated that the combination of these two immunostimulatory agents has the potential for enhanced toxicity. Dose-dependent gastrointestinal toxicity was evident in cynomolgus monkeys treated weekly for 4 weeks with a

combination of nivolumab + ipilimumab at combinations of 10 and 3 mg/kg and 50 and 10 mg/kg, respectively.²

7 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

Clinical experience with nivolumab has been limited to adult populations, and no experience exists in pediatric populations. The PK, clinical activity, and safety of nivolumab has been assessed in completed Phase 1 and ongoing Phase 2 or 3 studies sponsored by BMS in subjects with NSCLC, melanoma, and RCC in addition to other tumor types.

Nivolumab monotherapy has demonstrated anti-tumor activity with a CR or PR in subjects with NSCLC, melanoma, RCC, (as determined by modified RECIST v1.0. The majority of responses were durable and exceeded 6 months (Section 7.2.1).

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 1500 adult subjects treated to date. In general, for monotherapy, the safety profile is similar across tumor types. For monotherapy, no MTD has been reached at any dose tested up to 10 mg/kg (Section 7.3.1). There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Based on this safety, efficacy, and PD/PL analysis from MDX1106-03, the recommended Phase 2/3 dose for nivolumab monotherapy trials in NSCLC, melanoma, and RCC is 3 mg/kg every 2 weeks. The most advanced combination under development is nivolumab + ipilimumab in subjects with melanoma which is being evaluated in MDX1106-04 (also referred to as CA209004). Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases with a greater frequency (Section 7.3.2).

7.1 Pharmacokinetics

The PK of nivolumab is linear and dose proportional in the range of 0.1 to 10 mg/kg with every 2 week administration. The mean terminal elimination half-life of nivolumab determined from a single dose in MDX-1106-01 study is 17 to 25 days

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 adult subjects. Clearance (CL) of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights, and, therefore, confirms the appropriateness of this body weight adjustment of nivolumab dose.

7.2 Clinical Activity

7.2.1 Nivolumab Monotherapy - MDX1106-03 (CA209003)

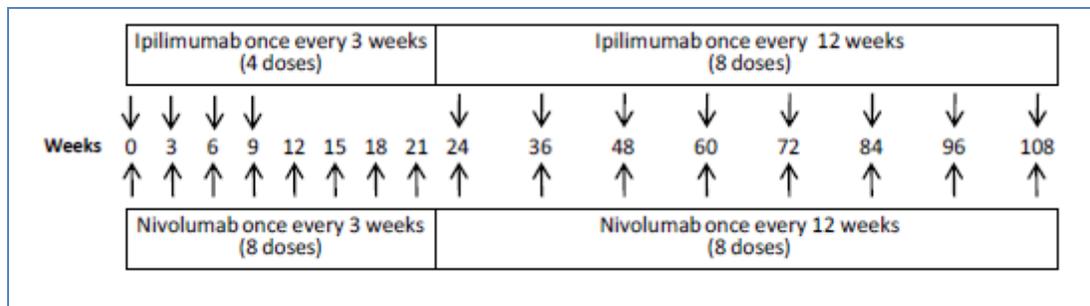
MDX1106-03 (also referred to as CA209003) is a Phase 1 open-label, multicenter, multidose, dose-escalation study of nivolumab in subjects with selected advanced or recurrent malignancies. The primary objective of the study was to assess the safety and tolerability of multiple doses of nivolumab in subjects with selected advanced or recurrent malignancies, including mCRPC, RCC, CRC, malignant melanoma, and NSCLC.

Among the 236 response-evaluable adult subjects, objective responses (as determined by RECIST v1.0) were observed in those with NSCLC (22 of 129 subjects, 17%), melanoma (33 of 107 subjects, 31%), or RCC (10 of 34 subjects, 29%) at doses ranging from 0.1 to 10 mg/kg nivolumab.¹¹ Responses were durable and persisted off drug; 42 of 65 responses lasted > 1 year in subjects with 1 year or more of follow-up and 35 of the 65 (54%) of subjects had responses that were ongoing at the time of data analysis.

7.2.2 Nivolumab + Ipilimumab Concurrent or Sequential Therapy - MDX1106-04 (CA209004)

Using modified World Health Organization (mWHO) criteria, 82 subjects with unresectable Stage III or Stage IV malignant melanoma treated with nivolumab concurrently or in sequence with ipilimumab were response evaluable. A total of 53 subjects received concurrent therapy with nivolumab + ipilimumab (Figure 7.2.2-1) and 33 subjects received sequential treatment. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥24 weeks) was observed in 65% of subjects. The objective response rate (ORR, mWHO criteria), regardless of dose, was 40% and 20% in subjects in the concurrent-regimen group and in the sequential regimen group, respectively.¹²

Figure 7.2.2-1: Concurrent Treatment Scheme - MDX1106-04



In the concurrent regimen groups, subjects were treated with up to 8 IV infusions of nivolumab on Days 1, 22, 43, 64, 85, 106, 127, and 148 and up to 4 IV infusions of ipilimumab on Days 1, 22, 43, and 64 during an induction period followed by a maintenance period consisting of up to 8 IV infusions of nivolumab + ipilimumab every 12 weeks. Within a cohort, nivolumab + ipilimumab doses were kept constant. The dose-limiting-toxicity evaluation period was through Week 9. Tumor assessments were at weeks 12, 18, 24, 30, and 36 and then every 12 weeks thereafter (Figure 7.2.2-1). With 1 mg/kg nivolumab + 3 mg/kg ipilimumab, 53% of subjects had confirmed objective responses (3 CRs and 6 PRs). All 9 of these had ≥80% tumor reduction, 7 at 12 weeks and 2 at their first assessment, which was after week 12.¹²

In the sequential regimen groups, subjects who were treated with ≥ 3 doses of ipilimumab monotherapy, prior to enrollment in MDX1106-04, began nivolumab monotherapy within 4-12 weeks after receiving the last dose of ipilimumab. With sequenced nivolumab after prior

ipilimumab, 20% of subjects had confirmed objective responses. Of these, 13% of subjects had $\geq 80\%$ tumor reduction at their first scheduled 8-week tumor assessment (rapid and deep responses).¹²

Based on these data, the doses which will be used in future combination studies will be 1 mg/kg nivolumab + 3 mg/kg ipilimumab.

7.3 Clinical Safety

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low-grade (Grade 1 to Grade 2) with relatively few related high-grade (Grade 3 to Grade 4) AEs.

Most nivolumab-related events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies).

7.3.1 Nivolumab Monotherapy in Subjects with Combined Advanced Malignancies - MDX1106-03 (CA209003)

Overall, the safety profile of nivolumab monotherapy observed in MDX1106-03 was manageable and generally consistent with that observed in other completed and ongoing clinical trials. No MTD was reached at any dose tested up to 10 mg/kg. The spectrum, frequency, and severity of treatment-related safety events were similar across tumor types and dose levels with no clear relationship to treatment duration.¹³

The majority of reported AEs were low-grade and considered related to nivolumab treatment.¹³ Grade 3 or 4 drug-related AEs occurred in 14% of the 296 patients who received treatment through 24-Feb-2012. The most frequently reported treatment AEs included fatigue, rash, diarrhea, and pruritus. The most frequently reported treatment-related high grade AE was fatigue. Most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies).

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of preferred terms (PTs) have been used to describe similar kinds of organ-related AEs with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, select AEs include a category for infusion reactions. Each category is composed of a discrete set of preferred terms, including those of greatest clinical relevance. These select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs. Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms (which are updated regularly) have been developed for suspected

pulmonary toxicity, diarrhea or suspected colitis, hepatotoxicity, endocrinopathy and nephrotoxicity. In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Subjects should have a thorough diagnostic work-up to evaluate potential drug and non-drug related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve, corticosteroids can be tapered (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and utilizes the same safety management algorithms.

The majority of reported select AEs were low-grade. Treatment-related select AEs were reported in 41% of subjects. The most frequently reported treatment-related select AEs included rash, diarrhea, and pruritus. Most high grade events resolved after dose delay, drug discontinuation, and/or treatment with corticosteroids.

Drug-related pneumonitis occurred in 9 of the 296 subjects (3%). Grade 3 or 4 pneumonitis developed in 3 subjects (1%). No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received was noted. Early-grade pneumonitis in 6 subjects was reversible with treatment discontinuation, glucocorticoid administration, or both. There were three drug-related deaths due to pneumonitis (two in subjects with NSCLC and one in a subject with CRC).

Of the select AEs observed in adults, the effects on the endocrine system could be of particular relevance for pediatric patients because of potential impacts on growth and development. In addition, immune-mediated inflammation resulting from nivolumab-related immune activation may present differently in pediatric patients based on developing immune systems and may have different effects in growing organ systems compared to effects in adults.

7.3.2 Nivolumab + Ipilimumab Combination Therapy in Subjects with Melanoma- MDX1106-04 (CA209004)

Overall, the safety profile of nivolumab in combination with ipilimumab observed in MDX1106-04 was manageable. The frequency and severity of treatment-related safety events reported in subjects treated with nivolumab + ipilimumab concurrently were greater than that reported in subjects treated with sequential nivolumab monotherapy. In the sequential portion of the study, the 1 mg/kg and 3 mg/kg cohorts were enrolled sequentially. Subjects were required to have prior ipilimumab and their last treatment must have occurred within 4-12 weeks. Based on ipilimumab PK, pharmacodynamically active ipilimumab was present at the outset of treatment in all subjects so the monotherapy safety profile in the sequential cohorts was expected to differ from the monotherapy safety profile reported in MDX1106-03.

As of the clinical cut-off date, all deaths reported in MDX1106-04 were attributed to disease progression and unrelated to study therapy.

The most frequently reported treatment-related AEs in all subjects treated in MDX1106-04, regardless of causality or severity, included fatigue, rash, and pruritus. The related AEs described

in Table 7.3.2-1 were observed during the DLT observation period and met the protocol criteria for DLTs. Cohort 3 exceeded the protocol-defined MTD and Cohort 2 and 2a were identified as the MTDs.

Table 7.3.2-1: Dose-limiting Toxicities Observed in MDX1106-04 After Concurrent Treatment with Nivolumab and Ipilimumab

Cohort No.	Nivolumab Dose (mg/kg)	Ipilimumab Dose (mg/kg)	DLT Observed
1	0.3	3	Grade 3 elevated AST/ALT (1 subject)
2	1	3	Grade 3 uveitis (1 subject) Grade 3 elevated AST/ALT (1 subject)
2a	3	1	None
3	3	3	Grade 4 elevated lipase (2 subjects) Grade 3 elevated lipase (1 subject)

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, DLT: dose-limiting toxicity, No.: number

Source: Preliminary data, MDX1106-04. Clinical cut-off date 15-Feb-2013.

A greater number of treatment-related select AEs including pulmonary AEs, GI AEs, hepatic AEs, endocrinopathy, skin AEs, renal AEs, and others were reported in subjects treated with nivolumab + ipilimumab concurrently than in sequential nivolumab monotherapy. The most frequently reported treatment-related Select AEs in both treatment groups included rash, pruritus, diarrhea and were generally Grade 1-2.

8 PEDIATRIC DEVELOPMENT PLAN

8.1 Opportunities to Accelerate the Nivolumab Pediatric Development Program

BMS has been in active discussions with health authorities to discuss the acceleration of a pediatric development plan for nivolumab by having a simplified global development program in adolescents and children that is not focused on the same types of tumors BMS is studying for licensure in the adult population. The proposed development plan rather aims at confirmation of safety and demonstration of anti-tumor activity in several tumor types most relevant to the pediatric population and mechanism of action for both monotherapy as well as the combination with ipilimumab.

BMS has engaged various pediatric oncology experts from organizations such as the Innovative Therapies for Children with Cancer (ITCC) Consortium, the New Approaches to Neuroblastoma Therapy Consortium (NANT), the Children’s Oncology Group (COG), and the NCI and has received supporting feedback on the proposed pediatric development plan. The discussions with the experts covered pediatric tumor types to include in the clinical studies, Phase 1/2 study designs, age ranges, extrapolation approach to support the adolescent melanoma condition,

biomarker studies and their impact on study design, and feasibility to conduct the Phase 1/2 study at centers in the EU and the US.

8.2 Proposed Pediatric Development Program

In a joint meeting with NCI Cancer Therapy Evaluation Program (CTEP) Pediatric group, FDA and BMS in Jul-2013, a Phase 1/2 study approach was proposed by NCI and endorsed by the FDA participants as a means to focus the development of nivolumab in a more efficient way in pediatrics. In particular, the approach included going directly to the 3 mg/kg dose in pediatric patients as the selected adult dose with an option to deescalate, if needed.

Based on this approach, BMS proposes to conduct the clinical, non-clinical and pharmacometric studies summarized in Figure 8.2-1 with details provided in Table 8.2-1. A summary of the proposed Phase 1/2 study, CA209070 is provided in Figure 8.2-2. In addition to the proposed pediatric clinical studies, appropriate mechanisms to enable enrolment of adolescent melanoma patients in ongoing and planned clinical trials conducted in the adult population are being considered.

Figure 8.2-1: Proposed Pediatric Development Program

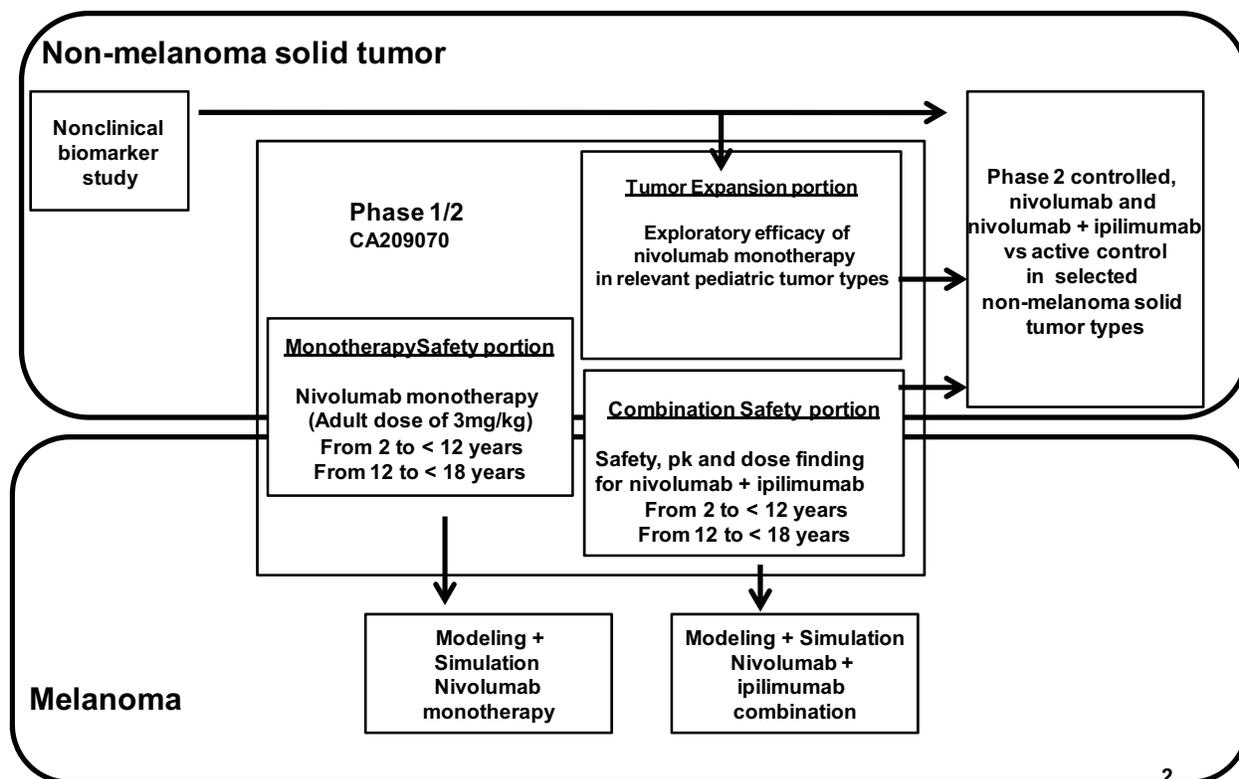


Table 8.2-1: Summary of Planned and Ongoing Studies in Pediatric Subjects

Study Number	Primary Objective	Study Design	Randomization Dosage, Route, and Duration of Treatment	No. of Subjects Planned (Treated)	Type of Subject	Expected Start Date
Study 1	PD-L1 expression on tumor cells and tumor infiltrating lymphocyte assessed by IHC	Biomarker study	NA	Na	NA	Ongoing
Study 2	To determine the safety profile of nivolumab and the nivolumab /ipilimumab combination in patients from 2 to <18 years of age. To describe preliminary evidence of anti-tumor activity in specific pediatric tumor types in patients older than 2 years	Multicenter, open-label Phase 1/2 study of nivolumab monotherapy and combination therapy with ipilimumab	Nivolumab monotherapy administered IV over 60 minutes at 3 mg/kg Q2W until progression or nivolumab administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 or 3 mg/kg Q3W for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.	70	Subjects from 2 to <18 years of age with refractory or relapsed solid malignant tumors	Oct-2014
Study 3	To characterize nivolumab PK in pediatric subjects, who are receiving nivolumab monotherapy using a PPK model To recommend a nivolumab monotherapy dosing regimen in adolescent (12 to <18 years of age) advanced melanoma subjects	Application of the PPK model to determine a nivolumab monotherapy dosing regimen for advanced melanoma adolescent patients, that will achieve exposures similar to that produced in adults by the recommended nivolumab monotherapy dosing regimen for adult melanoma	No subjects will be actively treated as a part of this study.	Intensive and sparse PK data from pediatric and adult subjects	Adult patients (>18 yrs) with advanced (unresectable or metastatic) melanoma subjects from MDX1106-01, MDX1106-03, CA209037, CA209066 Pediatric patients with refractory or relapsed solid malignant	Feb-2016

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Table 8.2-1: Summary of Planned and Ongoing Studies in Pediatric Subjects

Study Number	Primary Objective	Study Design	Randomization Dosage, Route, and Duration of Treatment	No. of Subjects Planned (Treated)	Type of Subject	Expected Start Date
					tumors in monotherapy safety portion of CA209070	
Study 4	<p>To characterize nivolumab PK in pediatric subjects who are also receiving ipilimumab</p> <p>To characterize ipilimumab PK in pediatric subjects who are also receiving nivolumab</p> <p>To recommend a combination dosing regimen in adolescent (12 to <18 years of age) advanced melanoma subjects</p>	<p>Application of the PPK model to determine a nivolumab and ipilimumab combination therapy dosing regimen for advanced melanoma adolescent patients, that will achieve exposures similar to that produced in adults by the recommended combined dosing regimen for adult melanoma</p>	<p>No subjects will be actively treated as a part of this study.</p>	<p>Intensive and sparse PK data from ~ 396, ~ 205, and ~541 subjects treated with nivolumab monotherapy, combination therapy, and ipilimumab monotherapy, respectively</p>	<p>Adult subjects (>18 yrs) with advanced (unresectable or metastatic) melanoma from nivolumab studies (MDX1106-01, MDX1106-03, MDX1106-04, CA209069) and ipilimumab studies (CA184004, CA184007, CA184008, CA184022)</p> <p>Pediatric subjects with refractory or relapsed solid malignant tumors from</p>	<p>Feb-2018</p>

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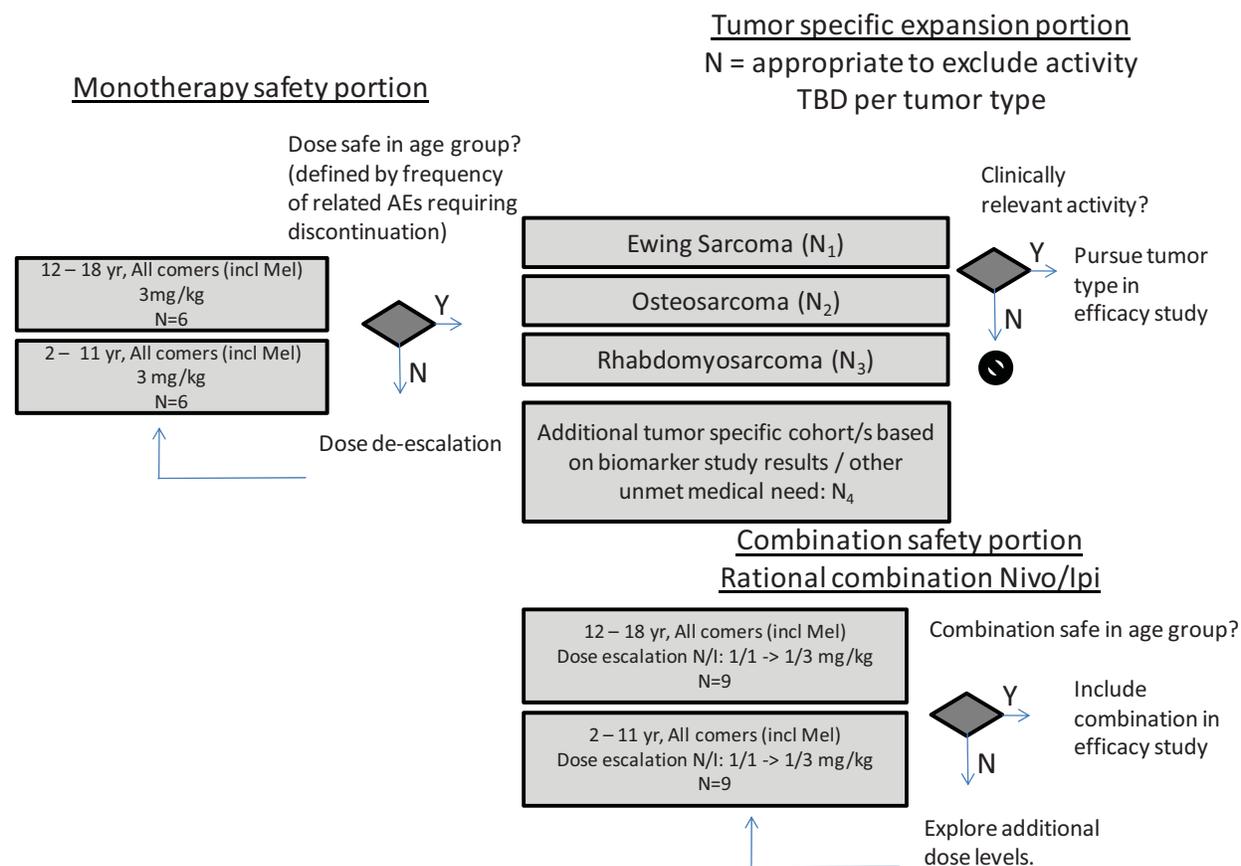
Table 8.2-1: Summary of Planned and Ongoing Studies in Pediatric Subjects

Study Number	Primary Objective	Study Design	Randomization Dosage, Route, and Duration of Treatment	No. of Subjects Planned (Treated)	Type of Subject	Expected Start Date
					nivolumab CA209070 and ipilimumab CA184070	
Study 5	To evaluate the PFS after treatment with nivolumab or the nivolumab/ipilimumab combination relative to standard of care therapy in a selected pediatric tumor type.	Controlled, parallel, open-label study of efficacy and safety	To be further agreed with the PDCO based on data from Study 2	TBD	Pediatric subjects with a selected solid malignant tumor type prioritized by observed antitumor activity of nivolumab monotherapy in Study 2	Planned

Abbreviations: IHC: immunohistochemistry, IV: intravenous, PDCO: Pediatric Committee of the European Medicines Agency, PFS: progression-free survival, PK: pharmacokinetics, PPK: population PK, Q2W: every 2 weeks, Q3W: every 3 weeks

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Figure 8.2-2: Proposed Phase 1/2 Study



Abbreviations: AEs: adverse events, Ipi: ipilimumab, Mel: melanoma, Nivo: nivolumab, TBD: to be determined

8.2.1 Study Design of Proposed Studies

8.2.1.1 Dosing Regimen for Proposed Phase 1/2 Study, CA209070

The proposed Phase 1 study (CA209070) will consist of 3 parts.

- A monotherapy safety portion in order to characterize safety and appropriate dose of nivolumab. The planned dose to be used in this portion is the clinical dose used in adults (3 mg/kg).
- A tumor specific expansion portion in which subjects enrolled to tumor specific cohorts will be treated with nivolumab in order to characterize anti-tumor activity.
- A combination safety portion in order to characterize safety and appropriate doses of the nivolumab + ipilimumab combination. This portion will include a dose-escalating safety evaluation of nivolumab+ ipilimumab at dose levels of 1 + 1mg/kg and 1 + 3mg/kg.

Based on advice from expert discussions, tumor types explored in the expansion cohorts will include Ewing Sarcoma, osteosarcoma, rhabdomyosarcoma, and neuroblastoma as target tumor types with high unmet medical needs for the expansion cohorts in the Phase 1/2 study. The inclusion of the sarcoma tumor types also was a specific request from experts at the PDCO/EMA during review of a draft pediatric investigational plan submitted to EU health authorities.

Prioritization of one of these tumor types or potentially other tumor types included in the Phase 1/2 study will be driven by results of non-clinical and clinical results from the proposed studies.

Nivolumab monotherapy will be administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression. Nivolumab combination therapy will be administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 1 or 3 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression.

8.2.1.2 Study Population

Subjects, aged from 2 to less than 18 years, with advanced and/or refractory solid malignant tumors will be enrolled. Safety and appropriate dose for nivolumab monotherapy and for the nivolumab/ipilimumab combination will be identified in individual age cohorts of subjects by age subsets from 2 to <12 (children) and from 12 to <18 years (adolescents) of age.

Subjects will be enrolled to the tumor specific cohorts in the tumor specific expansion portion or the combination safety portion once safety and appropriate dose of nivolumab monotherapy have been confirmed for their age subset in the monotherapy safety portion of the trial.

Tumor specific expansion cohorts will enroll subjects older than 2 years in one cohort per tumor type. Young adults > 18 years old can be enrolled in these tumor cohorts since disease recurrences specifically for the sarcoma tumor types may occur beyond the adolescent age range and these subjects are treated at pediatric oncology sites, often as a continuation of their previous care. Inclusion of the young adult population into these cohorts is scientifically appropriate since data from these patients will contribute to the understanding of anti-tumor activity.

8.2.1.3 Dosing Regimen in Adolescents

A modeling and simulation approach will be employed to recommend a dosing regimen for the adolescent melanoma population, based on the guidance for extrapolation of adult efficacy data to the pediatric population.

Upon completion of the monotherapy safety portion of the planned pediatric Phase 1/2 study, a PPK model will be developed to characterize monotherapy nivolumab PK in pediatric patients with data from CA209070 and selected adult studies. Extension of the adult PPK model to predict pediatric exposures has previously been successfully accomplished for several other mAbs.^{14,15,16,17,18,19} PPK model-based simulation will be employed to determine a nivolumab monotherapy dosing regimen that achieves exposures similar to that produced in adults by the recommended monotherapy dosing regimen for adult melanoma.

Upon completion of the combination safety portion of the planned pediatric Phase 1/2 (CA209070) study, the previously developed PPK model will be updated to characterize nivolumab PK in pediatric patients who are also receiving ipilimumab with data from CA209070 (monotherapy safety portion and combination cohort) and selected adult studies. PPK model will also be developed to characterize ipilimumab PK in pediatric patients who are also receiving nivolumab with data from CA209070 and selected ipilimumab adult studies. A PPK model-based simulation will be employed to determine nivolumab and ipilimumab combination therapy

dosing regimens that achieve exposures similar to the corresponding nivolumab and ipilimumab exposures produced in adults by the recommended combined dosing regimens for adult melanoma.

8.2.1.4 Dose Escalation

Based on the evaluation of PK and safety in adults, dose escalation may not be warranted for nivolumab in pediatric patients. Treatment with nivolumab monotherapy was well tolerated in adults subjects with no MTD reached up to 10 mg/kg (CA209003). No meaningful differences in safety profiles are expected at dose levels between 1 and 10 mg/kg. Therefore, the time needed for a conventional dose escalation design may lead to unnecessary delay of explorations of anti-tumor activity in larger tumor-specific expansion cohorts.

Dose de-escalation, guided by observation of DLTs, will be allowed within the protocol to ensure patient safety.

8.2.2 Safety Monitoring and Guidelines

Based on the immune-mediated mechanism of action, it can be anticipated that the nature and frequency of the expected nivolumab-related adverse events (AEs) would be similar in children and adults. However, since there is potential for nivolumab to act differently in patients with maturing immune systems, its activity and safety profiles as well as appropriate doses for use in younger pediatric subjects needs to be identified.

No data are currently available on long-term effects, specific effects on the immune system or specific ages, or development stages during which pediatric cancer patients treated with immune-based therapies may be more susceptible to effects from this treatment. This may be explained by the study designs, low patient numbers and the populations treated in early Phase 1 studies, which are typically patients with multiple prior therapies and limited follow up because of short survival. Future studies with immune-based therapies that provide a survival benefit will provide an opportunity to generate data on long-term effects, including effects on the developing immune system.

Early safety data from a clinical study with the CTLA-4 antibody, ipilimumab, in pediatric cancer patients demonstrated a safety profile that is comparable between adult and pediatric patients.²⁰ The types and frequency of immune related AEs, based on preliminary observation of the ongoing NCI 7458 study, are similar between pediatric patients ≥ 12 years of age and adult patients. The safety experience in pediatric patients < 12 years of age is limited and is under investigation in NCI 7458. Based on preliminary data from 6 patients < 12 years of age, the types of AEs and organs involved appear to be consistent with that of adults. The similarity of the safety profile between pediatric and adult patients suggests that adverse effects of CTLA-4 blockade do not depend on patients' stage of development.

Safety procedures were instituted across the clinical program for nivolumab in adults. These mechanisms include guidance to investigators over potential safety concerns regarding pulmonary toxicities, GI toxicities, hepatotoxicities, endocrinopathies, dermatologic toxicities, and renal toxicities. Similar guidelines are applicable to children, with possible additional

monitoring for potential toxicities specific to the pediatric population, including potential effects on the endocrine system, immune status and growth and development. Appropriate guidance on contraception will be included in all pediatric clinical studies with nivolumab.

8.3 Planned Biomarker Studies

The expression of PD-L1 on tumor cells may predict clinical responses to nivolumab. Published data suggest that patients that harbor PD-L1 negative tumors may be less likely to respond to nivolumab immunotherapy.¹³ BMS views this uncontrolled, retrospectively collected data as insufficient to conclude that PD-L1 is a predictive and/or prognostic biomarker and continues to evaluate the potential of PD-L1 as a predictive biomarker. This hypothesis is being evaluated using a validated PD-L1 immunohistochemistry (IHC) assay and scoring method as part of the ongoing Phase 3 clinical studies in adult patients with solid tumors. In these studies, patients are not selected based on PD-L1 status, but the association between PD-L1 expression and clinical efficacy of nivolumab will be analyzed.

The mechanisms of PD-L1 in control of anti-tumor immunity in pediatric tumors are expected to be similar as seen in adults. However, the frequency of PD-L1 expression on pediatric tumors is poorly understood, therefore, the following nonclinical study to characterize the expression levels of PD-L1 on multiple archived or tissue sample from pediatric tumor types is currently being conducted and will serve to identify which pediatric tumor types may have a higher frequency of PD-L1 expressing tumors. This information may help prioritize tumor types for further clinical evaluation.

Tumor biopsies, to be acquired from multiple centres, will be evaluated for expression of PD-L1 on the surface of tumor cells. A verified IHC assay developed by the Applicant and Dako will be utilized to confirm expression of PD-L1 and this data will be utilized to help inform potential indications to pursue in the pediatric program.

In addition, tumor biopsies will be evaluated by IHC for the phenotype of immune cells to determine if particular indications are distinct in their recruitment of phenotypically distinct immune cells. These observations will provide further information in the guidance of indication selection for use of nivolumab.

Additionally, archived biopsy samples will be assessed for the type and quantity of tumor-infiltrating lymphocytes (TIL), including, but not limited to CD3, CD4, CD8, FoxP3, and CD45RO to further inform on tumor types and method of action (Table 8.3-1). The localization and density of memory T-cells (CD45RO) and cytotoxic T-cells (CD8) within the tumor is strongly associated with prognosis of patients. Therefore, the quantification and characterization of TIL in pediatric tumor indications may elucidate tumor types that may have a higher propensity to engage the immune system and respond to nivolumab immunotherapy.

Table 8.3-1: Pediatric Biomarker Study

Study Identifier	Objectives	Outcome Measure	Test system/species (age)
Study 1: Biomarker Study	Assessment of PD-L1 expression on tumor cells by IHC	BMS-defined criteria for PD-L1 positivity	At least 40 patients/tumor type; 3 slides from tumor types including, but not limited to Sarcomas, Gliomas, Neuroblastoma
	Assessment of tumor infiltrating lymphocyte	% positive for immune cell markers	5-10 slides from tumor types including, but not limited to Sarcomas, Gliomas, Neuroblastoma

Abbreviations: BMS: Bristol-Myers Squibb, IHC: immunohistochemistry, PD-L1: programmed-death ligand 1

9 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC(TAU)	area under the concentration time curve in one dosing interval, in Cycle 1 and Cycle 3
AYA	Adolescent and young adult
BMS	Bristol-Myers Squibb
BTLA	B and T lymphocyte attenuator
CD279	Cluster of differentiation 279
CHMP	Committee for Medicinal Products for Human Use
CL	clearance
C _{max}	maximum serum concentration
C _{min}	minimum serum concentration
CMV	cytomegalovirus
COG	Children's Oncology Group
CR	complete response
CRC	colorectal cancer
CTEP	Cancer Therapy Evaluation Program
CTLA-4	cytotoxic T lymphocyte associated antigen-4
DC	dendritic cells
DLT	Dose-limiting toxicity
EC50	half maximal effective concentration
EMA	European Medicines Agency
ePPND	enhanced peri and postnatal development
EU	European Union
FDA	Food and Drug Administration
GD	Gestational day
GI	gastrointestinal
HuMAb	human monoclonal antibody
IC ₅₀	half maximal inhibitory concentration
ICOS	inducible co-stimulator
IgG4	immunoglobulin G4
IFN	interferon
IHC	immunohistochemistry
IND	Investigational New Drug
IO	Immuno-oncology

Abbreviation	Definition
ITCC	Innovative Therapies for Children With Cancer
IV	intravenous
mAb	monoclonal antibody
mCPRC	metastatic castrate-resistant prostate cancer
MLR	mixed lymphocyte reaction
MTD	maximum tolerated dose
mWHO	Modified World Health Organization
NANT	New Approaches to Neuroblastoma Therapy Consortium
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rates
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PDCO	Pediatric Committee of the European Medicines Agency
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PFS	Progression-free survival
PFSR	Progression-free survival rate
PIP	Pediatric Investigation Plan
PK	pharmacokinetics
PK/PD	pharmacokinetics/pharmacodynamics
PODAC	Pediatric Subcommittee of the Oncologic Drug Advisory Committee
PPK	Population pharmacokinetics
PR	partial response
PSP	Pediatric Study Plan
PT	preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SQ	Squamous
T ₃	triiodothyronine
T ₄	thyroxin

Abbreviation	Definition
TSH	thyroid stimulating hormone
US	United States

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