IFCT-1602 CHIVA2

Immunotherapy by Nivolumab after prior Chemotherapy for HIV+ patients with Advanced non-small cell lung cancer (NSCLC): IFCT-CHIVA2 phase IIa trial

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PROTOCOL IFCT-1602 CHIVA2 APPROVAL AND SIGNATORIES

Immunotherapy by Nivolumab after prior Chemotherapy for HIV+ patients with advanced non-small cell lung cancer (NSCLC): IFCT-CHIVA2 phase IIa trial

SPONSOR **IFCT**	**Name**	**Date** **(dd-mm-yy)**	**Signature**
President	**Pierre-Jean Souquet**		
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Statistician	**Alexandra Langlais**		

Responsibilities delegated by the sponsor	**Name**	**Date** **(dd-mm-yy)**	**Signature**
Study chair	**Armelle Lavole**		
Study co-chair	**Jacques Cadranel**		

Je reconnais avoir pris connaissance de l'ensemble du protocole et accepte de conduire cet essai en accord avec les Bonnes Pratiques Cliniques, la Loi de Recherche Biomédicale (4 aout 2004) et tel qu'il est décrit dans ce document.

INVESTIGATEUR COORDINATEUR:

Nom : Armelle LAVOLE Date :

Signature :

TABLE OF CONTENTS

1 BACKGROUND INFORMATION

1.1 Anti-PD1 Antibody

The anti-PD1 antibody nivolumab (OPDIVO, BMS®) has become the new standard of care after first-line platinum doublet chemotherapy in metastatic lung squamous cell carcinomas. The Phase III CheckMate 017 showed overall survival improvement with Nivolumab when compared to docetaxel in second line treatment (9.2 months vs. 6 months, p = 0.00025, HR 0.59) and with a better safety. A planned subgroup exploratory analysis showed no difference in efficacy of nivolumab when compared to chemotherapy depending on PDL-1 tumor expression (Brahmer, july 9 NEJM 2015). The CheckMate 057 phase III study showed similar overall survival improvement in non-squamous NSCLC treated by nivolumab compared to docetaxel in 2nd line treatment (12.2 months vs. 9.4 months, p = 0.0015, OR: 0.73). However, in this study in a preplanned subgroup analysis, efficacy was similar between the two treatments when the threshold of PDL-1 expression was <1% (Borghaei NEJM 2015 373:1627). The prognostic and predictive role in the expression of PDL1 will have to be clarified by further studies (Barbee Annals of pharmacotherapy, august 17, 2015).

1.2 Immunotherapy in patient living with HIV/AIDS

Immune Checkpoints inhibitors administration is an efficient and innovative treatment in the general population with lung cancer. However, other populations, such as PLWHIV (People Living With HIV), may well benefit from anti-PD1 therapy, but no specific studies have been realized. It is indeed essential to conduct studies dedicated to PLWHIV with non small cell lung cancer (NSCLC) as:

- NSCLC is the most common of non-AIDS-related malignancy (Lanoy E Int j Cancer 2011);and represents the leading cause of cancer-related death among PLWHIV (Morlat AIDS 2014)

- Some studies have shown that NSCLC prognosis is worse among PLWHIV (Sigel BJC 2013, Suneja AIDS 2013; Coghill JCO 2015); thus any therapeutic innovation in the general population must be applied quickly to PLWHIV population taking into account its specificities;

- IFCT-1001 CHIVA phase II trial study of carboplatin plus pemetrexed followed by pemetrexed as first-line therapy for HIV infected patients with advanced non-squamous NSCLC was effective and reasonably well-tolerated, but the poor median overall survival

(7.6 months) suggested urgent unmet needs for investigations of others therapies than chemotherapy (Lavole Abst9076 ASCO 2016)

- Toxicity profile is better with nivolumab than docetaxel with 7-10% vs 54-71% grade 3-4 events (Borghaei NEJM 2015; Brahmer NEJM 2015)

- Oncological cytotoxic treatments and antiretrovirals (ARV) can cause interactions because of common CYP450 metabolism, or additive adverse events, thus increasing incidence of haematological, hepatic and renal toxicities, (Makinson, JTO 2010 and 2011). By contrast, nivolumab is a monoclonal antibody and does not have hepatic metabolism and therefore probably won't show interactions with antiretrovirals;

- Oncogene addiction is rare in PLWHIV with NSCLC (Crequit Lung cancer 2015) due to the almost constant smoking status of the study population. Therefore, the use of specific inhibitors is exceptionally an option; by contrast nivolumab has showed an efficacy in smoking populations (Borghaei NEJM 2015; Brahmer NEJM 2015).

- Standard chemotherapy reduces the number of CD4 altering the immunity of HIV patients.

- Strong evidence suggests that blocking the PD-1/PD-L1 axis with monoclonal antibodies could be of highest interest during HIV-associated NSCLC in order to 1°/ restore the HIV-specific T cell responses for potential effect on the HIV reservoir and HIV replication, together with antiretroviral therapies. (Trautmann Nat Med 2006 Nature Day 2006, Velu Nature 2009, Palmer J Immunol 2013) alongside ARVs and 2°/ thus contribute to the control of inflammation induced by HIV. Also, the high PD-1 expression levels on circulating CD8 during HIV infection (Day Nature 2006) suggests that blocking the PD-1/PD-L1 axis could restore tumor-specific cytotoxic T lymphocytes (CTL) functions – as much as in patients seronegative for HIV.

- A phase I-II study of escalating doses of nivolumab in 47 patients with hepatocellular carcinoma, carriers of hepatitis B or C, showed a good toxicity profile and a sustainable response, which suggests the safety of this molecule in a given virological context (El Khoueiry ASCO 2015, abst LBA101).

- To our knowledge, an ongoing phase I study is evaluating the association of nivolumab and ipilimumab in solid tumors including PLWHIV with lung cancer (NCT02408861), and another phase I study is evaluating pembrolizumab in PLWHIV with relapsed, refractory, or disseminated malignant neoplasms including lung cancer (NCT02595866).

- Therapeutic strategy is challenging in patients with advanced NSCLC and a poor performance status (PS≥2). In general PS is rather a prognostic factor than a predictive factor. Moreover, cytotoxic chemotherapy (particularly later lines of therapy) is associated with substantial toxicities, impaired quality of life, and a short lifespan in patients with a PS≥2. By contrast, immune checkpoint inhibitors (ICIs), particularly anti-PD1/PD-L1 monotherapy, often have favorable toxicity profiles, even in patients with a poor PS (Johnson DB et al. Cancer June 1, 2017). There is very little published experience to guide oncologists in terms of whether to use ICIs in patients with a poor PS. One phase II study with atezolizumab in cisplatin-ineligible patients with urothelial carcinoma reported a response rate of 25% for patients with a PS=2 (vs 23% for all patients) (Balar AV et al, Lancet. 2017;389:67-76). In the French cohort IFCT CLINIVO (Girard N et al ESMO 2017) for treatment of advanced non-small cell lung cancer (NSCLC) by nivolumab reporting the efficacy/toxicity of more than 900 patients included in the ATU of Nivolumab in France, more than 70% of patients were treated in third line setting or more and 20% had a PS≥2. In this large cohort of fragilized patients, overall survival and progression free survival were similar to that reported in phase III trial including only highly selected patients. Moreover, phase II trial has been projected by the IFCT to evaluate ICIs in PS≥2 patients, however HIV patients will be excluded, as usual. On the other hand, docetaxel - the standard of care previously proposed before the era of ICIs, is associated in HIV patients with substantial toxicities additive to that of anti-retrovirals and with an increased risk of pharmacological interactions. Moreover, results of the phase II CHIVA1 trial (Lavolé A et al ASCO 2016) has shown that chemotherapy by carboplatin plus pemetrexed provides a poorer results than in the general population. Altogether, these findings suggest that HIV patients with advanced NSCLC should not be excluded for CHIVA2 phase II trial in case of PS2, although statistical analysis will be analyzed by subgroups. Finally, it is important that HIV patients can benefit from therapeutic innovations in the field of NSCLC. HIV-NSCLC population is inherently of poor prognosis and patients excluded from therapeutic trials. Moreover, it is aslo important that this access is secured by the administration of ICIs in the context of a therapeutic trial, such as CHIVA 2.

1.3 Evaluation of risk-benefit ratio

Two Phase III trials showed superiority in terms of efficacy and tolerance of nivolumab in second-line treatment compared to docetaxel in metastatic NSCLC in the general population, so it is important to evaluate this treatment in PLWHIV in maximum security conditions, taking into account their specificities and complex underlying immunological status. As NSCLC in PLWHIV is a rare tumour, a phase 2 trial, using DCR data, would be

able to recruit a sufficient number of patients, in a reasonable period of time, to provide a proof of concept of the safety and efficacy of nivolumab in this population. Therefore, we think that an open-label, one arm phase 2 trial, with a rapid accrual, would be currently a crucial approach and a window of opportunity to explore whether nivolumab could find its place in PLWHIV with NSCLC. Such a trial is typically a trial for an academic sponsor, experienced in PLWHIV with NSCLC, which previously showed its ability to recruit patients with such a rare disease as the IFCT did with the IFCT1001-CHIVA trial, testing carboplatin plus pemetrexed followed by pemetrexed.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary objective/endpoints

- Efficacy of the anti-PD1 antibody (nivolumab) as measured by DCR.

2.2 Secondary objectives/endpoints

- tolerance: Adverse Events (AEs) grade (NCI-CTC 4.0),
- impact on HIV control and immunological (CD4, CD8, HIV viral load each evaluation), other associated chronic infection susceptible of reactivation (HHV8, CMV, EBV, tuberculosis) and potential occurrence of autoimmunity (organ specific i.e. thyroiditis, adrenalitis and hypophysitis, or non organ specific)
- duration of response
- Reponses rate according to tissue PD-L1 expression
- progression-free survival
- Overall survival
- Quality of life (LCSS)

2.3 Exploratory objectives / endpoints

- Monitor HIV, CMV, EBV, HBV, HCV, HHV-8-specific T cell responses in PBMC under anti PD-1 therapy: quantification, polyfunctionality, expression of immune check points
- Monitor the HIV reservoirs (HIV-DNA) and the residual HIV replication by ultrasensitive viral load, as well as EBV, CMV, HBV, HCV, HHV-8 viral load
- Monitor T cell activation/ exhaustion/differentiation and immune check point expression by flow cytometry and ultrasensitive cytokine/chemokine plasma measurements. Explore the tumor somatic mutanome by RNA sequencing on paraffin initial biopsy or fresh new biopsy by studying normal tissue in parallel

before treatment in order to characterize neoepitopes; if normal tissue not available, explore somatic tumoral mutations by comparing whole tumor exome sequencing with whole PBMC exome sequencing; further characterization of neo-epitope specific T cells in PBMC : polyfunctionality, expression of immune check points.

- Description of gene mutation that appear to be crucial for the response to immunotherapy or for adverse effects of immunotherapy, in particular MHC genes
- Immune monitoring of adverse effects: T cell phenotyping, cytokine/chemokine measurements, antibody dosage, auto-antibody dosage.
- Describe the tumoral microenvironment of NSCLC before nivolumab exposure (CD4, CD8, CD3 infiltrate, PD-1, PD-L1 expression).

This will be done on a special 68 mL blood sample that will be done on C1, C2, C3, C9, C15, C27, C51, end of treatment and in case of immune related adverse event. This will also be done on initial FFPE biopsies that will be repatriated from the different centers.

3 REGIMEN

Thirty eligible patients, previously treated by at least one line of platinum-based chemotherapy, will be included.

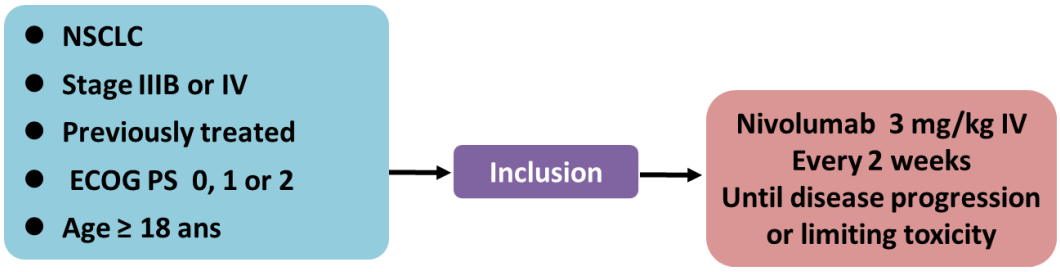
TREATMENT:

Nivolumab is administered intravenously (IV), over 30 minutes at 3 mg/kg every 2 weeks, until disease progression, death, limiting toxicity or patient refusal.

Premedication is not required.

Patients with tumoral progression will stop the treatment but will have a follow-up for the secondary endpoints of OS, and the toxicities assessment till a last study visit 4 weeks (± 1 week) after the last injection of the drug.

Twenty centers will be opened.



Schedule of the study design.

4 ELIGIBITY

4.1 Inclusion Criteria

1. Age ≥ 18 years old
2. HIV1 or HIV2, regardless of CD4 cell count
3. HIV Viral load <200 copies/mL
4. Proven histologically and/or cytologically, stage IIIB-IV or metastatic relapse post-surgery non-small cell lung cancer (NSCLC)
5. Disease recurrence or progression during/after at least one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease
6. Measurable disease by Computed tomography (CT)/Magnetic resonance imaging (MRI) per RECIST 1.1 criteria
7. Performance status (PS) 0, 1 or 2
8. Written informed consent
9. Patients must have adequate organ function: creatinine clearance > 40 mL/min (Cockroft, MDRD or CKD-Epi formula or 24h Urine Calculate creatinine clearance from a 24h urine collection), neutrophiles count > 1500/mm3; platelets > 100 000/mm3 ; hemoglobine > 9 g/dL; hepatic enzymes < 3N with total bilirubin ≤ 1.5 × ULN (upper limit of normal) except subjects with documented Gilbert's syndrome (≤ 5 × ULN) or liver metastasis, who must have a baseline total bilirubin ≤ 3.0 mg/dL
10. Patients must receive appropriate care and treatment for HIV infection including ART when clinically indicated and subjects should be under the care of a physician experienced in HIV management. In case of recent introduction of cART and CD4 levels <50 cells/ml, inclusion will be possible provided subjects had at least 4 weeks of

treatment prior to inclusion, to avoid clinical type IRIS (immune inflammatory syndrome reconstitution). All antiretroviral treatments are allowed.

11. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception for 28 days prior to the first dose of investigational product, and must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of contraception after this point should be discussed with the referent physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. They must also refrain from egg cell donation for 6 months after the final dose of investigational product. Men receiving nivolumab and who are sexually active with women of childbearing potential will be instructed to adhere to contraception (appendix I) for a period of 31 weeks after the last dose of nivolumab.

12. Persons deprived of liberty could be eligible because the expected benefice (improvement of disease control rate) justifies the foreseeable risk (adverse reaction of nivolumab).

4.2 Exclusion Criteria:

1. Concurrent malignancies requiring active intervention

2. Active Infection

3. Patient with known EGFR activating tumor mutation or known ALK or ROS1 gene rearrangement not treated with the appropriate targeted therapy.

4. History of immunological events related to HIV: lymphoid interstitial pneumonitis (LIP), non-infectious uveitis, encephalitis and other manifestations of CD8 lymphocyte infiltration syndrome, HIV-associated nephropathy (HIVAN).

5. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

6. Active or history of inflammatory bowel disease (eg, diverticulitis, colitis, Crohn's, coeliac disease or other serious gastrointestinal chronic conditions associated with diarrhea). Note that diverticulosis is permitted.

7. Symptomatic cerebral metastasis unless treated by brain radiotherapy which will be completed for at least 15 days before the beginning of the treatment; subjects with carcinomatous meningitis.

8. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

9. The last dose of prior chemotherapy or radiation therapy (with the exception of palliative radiotherapy) was received less than 3 weeks prior to inclusion;

10. History of primary immunodeficiency, history of organ transplant that requires therapeutic immunosuppression and the use of immunosuppressive agents within 28 days of inclusion or a prior history of severe (grade 3 or 4) immune mediated toxicity from other immune therapy.

11. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of inclusion. Intranasal/inhaled or topical steroids, and adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

12. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.

13. Legally protected adults.

5 Concomitant treatment

5.1 Authorized concomitant treatment

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, corticosteroids (with minimal systemic absorption). Adrenal replacement steroids dosed < 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids >= for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions is permitted.

Concomitant palliative and supportive care for disease related symptoms is allowed if initiated prior to first dose of study therapy. Prior palliative radiotherapy must have been completed at least 2 weeks prior to inclusion.

5.2 Prohibited concomitant treatment

The following medications are prohibited during the study (unless required to treat a drug related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (>3 weeks of prednisone 10 mg per day or equivalent dose if administration of antiher corticosteroid)
- Any concurrent anti-neoplasic therapy (ie chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of lung cancer)

6 Criteria for early termination, withdrawal from the trial or study termination

6.1 Withdrawal from the trial

Reasons for withdrawal from the trial are:

- Patient withdraws consent

- Death

Patients have the right to withdraw their consent and request to leave the study at any time for any reason (which they are not obligated to explain). This should not affect their right to future care.

6.2 Early treatment termination

The investigator may terminate a patient's participation early in the event of:

- Tumour progression during treatment

- Toxicity requiring termination of study treatments

- Intercurrent illness

- Protocol violation

- Non-compliance (nivolumab)

- Administrative reasons

- Pregnancy

7 PRE-TREATMENT EVALUATION:

Investigations		Timing
History and Physical Exam including:	• history including (occupational), smoking history • physical examination including height, weight, pulse, blood pressure • performance status (PS)	Within 14 days of inclusion
Haematology	• CBC including haemoglobin, differential, platelet count	Within 14 days of inclusion
Biochemistry	• AST (SGOT) and ALT (SGPT) • alkaline phosphatase • bilirubin • albumin • serum creatinine • lipase • fasting glucose • K, Cl, Na, Mg, Ca, P • LDH • CRP • TSH (T3, T4 if TSH abnormal) • INR/APTT	Within 14 days of inclusion
Immunovirology	• Serology EBV, HCV/HBV, CMV, Toxoplasmosis – TPHA-VDRL, HHV-8 • Quantiferon	Before inclusion
	• CD4/CD8 cell counts • HIV viral load (VL) • HCV/HBV VL, HHV-8 VL in the case of co-infection • EBV VL, CMV VL	Within 28 days of inclusion ; those VL will be monitored further in case of positivity
Radiology[1]	• baseline CT brain, chest and abdomen (with iodine injection) *(Wang 2004)* • baseline PET-CT : highly recommended (but optional) (*Ceresoli 2006b, von Schulthess 2006, Francis 2007)*	Within 28 days of inclusion
	• other baseline imaging (e.g. bone scan,…)	Required, within 28 days of inclusion, only if suspicious signs/symptoms are present
Correlatives	• tumour tissue for assessment of PD-L1 status	From initial diagnosis block

	• whole blood, serum, plasma for correlatives	Prior to cycle 1, day 1 dosing
Other Investigations	• ECG	Within 14 days of inclusion
	• pregnancy test if applicable	Within 24hrs of first drug administration
Adverse Event	Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	Within 14 days of inclusion
Quality of Life	LCSS questionnaire	Within 14 days of inclusion

8 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

8.1 Evaluation during Protocol Treatment

Investigations		Timing
History and Physical Exam including:	• physical examination including, pulse, blood pressure, weight • performance status	Prior to each infusion until off protocol therapy
Hematology	• CBC including hemoglobin, differential, platelet count	Prior to each infusion until off protocol therapy
Biochemistry	• AST (SGOT) and ALT (SGPT) • alkaline phosphatase, gamma GT • Bilirubin, LDH • albumin • creatinine, urea • lipase (and amylase if abnormal lipase) • fasting glucose • K, Cl, Na, Ca, Mg2+ • Urinary test	Prior to each infusion until off protocol therapy
	• TSH (T3, T4 if TSH abnormal) • Antinuclear antibody and in case of positivity anti-ENA and anti-DNA; anti-thyroperoxydase, anti-thyroglobulin	Every 6 weeks,until off protocol therapy
Immunolovirology (2)	• Hbs antigen, HCV/HBV VL, HHV-8 VL in the case of co-infection • EBV VL, CMV VL, •	Cycle 2, 3, 9, 15, 27, 51, end of treatment and in case of immune related adverse event. Every 3 cycles for Hbs antigen, HCV/HBV VL

Immunolovirology (1)	• CD4/CD8 cell counts • HIV viral load (VL)	Prior to each infusion until off protocol therapy
Radiology*	• CT-scan of chest and upper abdomen • Other imaging used for baseline tumoral assessment	Every 8 weeks from randomization (CTs schedule must be maintained regardless of treatment delays)
Other Investigations	• ECG	As clinically indicated
	• lung function tests: FEV1, FVC, TLCO and blood gas at room atmosphere	Only if pulmonary symptoms or suspicion of pneumonitis
	• pregnancy test if applicable	Every 3 cycles ± 1 weeks
Correlatives	• whole blood, serum, plasma	Cycle 2, 3, 9, 15, 27, 51, end of treatment and in case of immune related adverse event.
Adverse Events	patients must be evaluated at each visit for adverse events according to CTCAE v4	
Quality of Life	• LCSS questionnaire	Cycle 2, 3, 5, 7, 9
* Radiology assessments must be kept to schedule irrespective of any delays in a treatment cycle. If the schedule cannot be kept all attempts must be made to undertake the required imaging as soon as possible. Thereafter, patients must be put back on original imaging schedule.		

8.2 Evaluation after protocol treatment

Investigations		Timing
History and Physical Exam including:	• physical examination including, pulse, blood pressure, weight • performance status	Within 30 days following last treatment day
Hematology	• CBC including haemoglobin, differential, platelet count	Within 30 days following last treatment day
Biochemistry	• AST (SGOT) and ALT (SGPT) • alkaline phosphatase • bilirubin • albumin • creatinine • lipase (and amylase if abnormal lipase) • fasting glucose • K, Cl, Na, Ca	Within 30 days following last treatment day
	• TSH (T3, T4 if TSH abnormal)	As clinically indicated
Radiology*	• CT-scan of chest and upper abdomen	Every 8 weeks
Other	• ECG	As clinically indicated

Investigations	• lung function tests: FEV1, FVC, TLCO and blood gas at room atmosphere	As clinically indicated
Adverse Events	Patients must be evaluated for treatment related adverse events until resolution	

* Only for patients who have not yet discontinued the study treatment

9 STUDY TREATMENT

The study treatments are explained in table 1.

Table 1.

Active substance	**Nivolumab**
Commercial Name	Opdivo©
Pharmaceutical form	Concentrate for solution for infusion
Dosage	10 mg/mL
Posology	3mg/kg
Storage	Store in refrigerator (2°C - 8°C) in its original package in order to protect from light
Laboratory	BMS

The treatment has to begin within 15 days following inclusion.

These treatments will be labeled according to the regulation. These treatments will be administered until progression or limiting toxicities.

Nivolumab has a concentration of 10mg/mL and is provided in a 10mL vial.

Storage Conditions & Handling:

- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.
- If any temperature excursions are encountered during storage, please report these to IFCT for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.

- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

Use Time/Stability: Please refer to the appropriate section of the current Investigator Brochure or Addendum. Due to parameters surrounding the use time of nivolumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP]

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-°-8°C (, 36°-46°F) and used within 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of nivolumab injection in the IV bag includes the product administration period.

Preparation and Administration:

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles. *Note: Mix by gently inverting several times. Do not shake.*
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection
3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*
4. ***Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL [IBV15 Addendum Section 3.2.2]***
5. *Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.*
6. Attach the IV bag containing the nivolumab solution to the infusion set and filter.

7. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

10 TREATMENT BEYOND DISEASE PROGRESSION

Accumulating evidence indicates a minority of subjects treated with immunotherapy may have clinical benefits despite initial evidence of PD.

Subjects treated with Investigational Treatment will be permitted to continue treatment beyond initial RECIST 1.1 defined PD – at 8 weeks CT scan assessment – if they meet all of the following criteria:

1. Investigator-assessed clinical benefit, and subjects do not have rapid disease progression

2. Continue to meet all other study protocol eligibility criteria

3. Good tolerance of study drug

4. Stable performance status

After the 8 weeks CT-scan, a new CT-scan assessment should be performed within 4 weeks ± 1 week from original PD scan to determine whether there has been a decrease in the tumour size or disease stabilization, or alternatively continued PD, which would terminate the trial treatment.

For the subjects who continue IP beyond progression, further progression is defined as an additional 10% increase in tumour volume from time of initial PD. This possibility has been introduced to take into account the pseudo-tumoral progressions sometimes observed under immune check-point inhibitors treatment. In case of the second evaluation would confirm disease progression and the clinical benefit no longer confirmed, the date of progression will be set at the date of the first CT-scan showing mRECIST criteria of progression *(Wolchok 2009)*.

In case of disease control, the experimental treatment will be given until disease progression (tumor assessment every 8 weeks ± 1 week).

11 SAFETY

11.1 Definition of Adverse Events

The term adverse event covers any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study, reported for 100 days (3 months) post last treatment.

Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g., requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) are considered to be adverse events.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfills the definition of "serious adverse event", it must be recorded as such.

The adverse event may be:

• A new illness

• Worsening of a concomitant illness

• An effect of the study medication, including comparator

• A combination of two or more of these factors

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "adverse event".

Adverse events fall into the categories "non serious" and "serious".

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

The following laboratory abnormalities should be documented and reported appropriately:

• Any laboratory test result that is clinically significant or meets the definition of an SAE

• Any laboratory abnormality that required the participant to have study drug discontinued or interrupted

• any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

11.2 Serious Adverse Events

• Death.

• Life-threatening.[1]

• Unplanned hospitalization or prolongation of existing hospitalization (for > 24 hours). [2]

• Persistent or significant disability or incapacity.[3]

• Pregnancy

• Congenital anomaly or birth defect.

• Is an important medical event.[4]

• Drug-induced liver injury (DILI). [5]

[1] "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2] The following hospitalizations are not considered SAEs:

- Hospitalization < 24h

- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
    - The patient has not experienced an adverse event.

- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

[3] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[4] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred.

Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, or suspected transmission of an infectious agent (eg pathogenic or nonpathogenic) via the study drug, or overdose of treatment, or lab test abnormalities clinically significant.

A diagnosis of cancer during the course of a treatment should be considered as medically important. The List of Critical Terms (1998 adaptation of World Health Organization Adverse Reaction Terminology Critical Terms List, provided in the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form") should be used as guidance for adverse events that may be considered serious because they are medically important.

[5] Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs. Potential DILI is defined as:

1) ALT or AST elevation >3 times upper limit of normal (ULN)

AND

2) Total bilirubin >2 times ULN, without initial findings of cholestasis (elevated se-rum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AST/ALT elevation and hyper-bilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

A hepatic AE management algorithm has been established according to nivolumab IB for appropriate management of DILI cases (cf; appendix II).

The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

Clarification of the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) 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 is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAEs/AEs will be reported up to 100 days (3 months) for both study drugs, and SAEs notification will be made within 24 hours.

11.3 Period of Observation

For the purposes of this study, the period of observation for collection of adverse events extends from the date of signature of the informed consent until 100 days after the last day of study treatment except for adverse events related to study drug, which must be reported during follow-up period until resolution or initiation of further anti-tumor therapy.

If an Investigator detects a serious adverse event in a study subject after the end of the period of observation, and considers the event possibly related to prior study treatment,

he or she should contact the Sponsor to determine how the adverse event should be documented and reported.

At each visit/assessment AEs will be assessed from information collected from the source documents and information transcribed into the CRF.

11.4 Documentation and Reporting of Adverse Events by Investigator

All adverse events that occur during the observation period set in this protocol must be documented on the pages provided in the case report form in accordance with the instructions for the completion of adverse event reports in clinical studies. These instructions are provided in the case report form itself.

The following approach will be taken for documentation:

• All adverse events (whether serious or non-serious, or considered as an alert term) must be documented on the "Adverse Event" page of the case report form.

• If the adverse event is serious, the investigator must complete, in addition to the

"Adverse Event" page in the case report form, a "Serious Adverse Event/Expedited

Report from a Clinical Trial" form at the time the serious adverse event is detected.

This form will be filled in the eCRF. In case of unavailability of the eCRF, a paper form will be sent by email to sae@ifct.fr.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All patients who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. All questions on the completion and supply of adverse event report forms and any further forms issued to the investigator at a later date to clarify unresolved issues should be addressed to the IFCT.

11.5 Immediate Reporting by Investigators to IFCT

Serious adverse events and adverse events that fulfill a reason for expedited reporting to Pharmacovigilance must be documented on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form in accordance with the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form". This form must be completed and supplied to the Sponsor within 24 hours or at the latest on the following working day. The "Serious Adverse Event/Expedited Report from a Clinical Trial" form and the instructions are provided in the investigator's study file.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s).

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

The "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form" give more detailed guidance on the reporting of serious adverse events, adverse events that comply with alert terms, and adverse events initially reported as non-serious that become serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately to the Sponsor on a "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

11.6 Pregnancy/Exposure Reporting

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure This means pregnancies occurring in female participants, female partners of male participants, or females exposed through direct contact with the agent during their pregnancy (for example, environmental exposure involving direct contact with the agent). Pregnancies occurring up to 6 months after the completion of nivolumab must also be reported. The investigational product will be permanently discontinued.

The investigator is required to inform IFCT within 24 hours of learning of the pregnancy using the pregnancy reporting form. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy reporting Form.

12 DOSE TOXICITIES AND ADJUSTEMENT

12.1 Dose reductions

There is no dose reduction for nivolumab.

12.2 Dose Delay

Nivolumab administration should be delayed for the following:

- Grade 2 pneumonitis
- Grade 2 or 3 diarrhea or colitis
- Grade 2 elevation in AST, ALT or total bilirubin
- Grade 2 or 3 creatinine elevation
- Symptomatic endocrinopathies (including hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency and diabetes)
- Grade 3 rash
- Any AE, laboratory abnormality or intercurrent illness which in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

12.3 Criteria to resume dosing

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by IFCT.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with IFCT.

- Subjects who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. IFCT should be consulted prior to resuming nivolumab in such subjects.
- Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation.

12.4 Discontinuation of treatment

Treatment with nivolumab should be permanently discontinued for any of the following:

- Any Grade ≥ 3 drug-related pneumonitis or interstitial lung disease
- Grade 4 colitis or diarrhea
- Grade ≥ 3 elevation in AST, ALT or total bilirubin
- Grade 4 creatinine elevation
- Grade 4 rash, grade 4 pruritus
- Grade 2 or 3 immune-related adverse reactions that persist despite treatment modifications or for inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.
- Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by IFCT. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, IFCT must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue or more frequently if clinically indicated during such dosing delays.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

12.5 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered immuno-oncology agents in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

  - Gastrointestinal

- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in Appendix II.

12.6 Treatment of infusion reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction was to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to IFCT and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment (antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicateds for ≤ 24 hours).

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart

the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: Life threatening; pressor or ventilatory support indicated)

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

13 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1 Study design considerations

The maximum sample size (N) is calculated based on α, ß, and the expected effect size, using a test for single binomial proportion for a two-stage design with O'Brien-Fleming (OF)

stopping rules, allowing for early stopping for futility after Stage I. The software East 6.0 was used

13.2 Sample size assumption

It is a phase II non randomized, multicenter, open study, assessing nivolumab efficacy.

Tested hypothesis

The hypothesis underscoring our study is that the disease is controlled (stable disease or response) in at least 57% of patients at first evaluation (8 weeks) of nivolumab therapy.

H0: control rate ≤ 30% (unacceptable control rate)

H1: control rate ≥ 57% (acceptable control rate)

α=5% (one-sided), ß=90%

Step 1 (n=14 patients): ≤ 4 patients with a disease controlled → futility (H0 accepted)

Final decision (n=28 patients): ≥ 13 patients with a disease controlled → rejected H0 (positive trial)

30 patients included, taking into account possible non eligible patients (5%)

13.3 Analyzed Populations

Subjects will be included according to the Intent-to-Treat (ITT) analysis.

The safety population will comprise all patients included who receive at least one dose of treatment.

The population of patients eligible will consist of patients ITT having no major deviation judged on the criteria of inclusion and non-inclusion.

The protocol deviations will be reviewed by the principal investigators and classified minor or major deviations, and listed.

13.4 Efficacy Analyses

13.4.1 Primary endpoint analysis

Analysis of the primary efficacy endpoint will be conducted on all eligible patients, based on the disease control rate after 8 weeks of treatment. Analysis of the primary efficacy endpoint will be also conducted on all patients (ITT analysis) as sensitivity analysis.

It will be presented associated with its 95% confidence interval. Patients for whom the answer cannot be evaluated will be considered as treatment failures.

13.4.2 Secondary endpoints

- Progression-free Survival (PFS) and Overall Survival (OS)

PFS is defined as the time between the date of inclusion and the first date of documented progression or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment.

The duration of overall survival is defined as the time elapsed between the date of inclusion and death. Subjects who did not die will be censored on the last date a subject was known to be alive.

The median survival, 95% confidence intervals and an estimation of progression-free survival (PFS) and overall survival according to the Kaplan-Meier Method will be calculated using standard methods

This analysis will be performed on all eligible patients.

PFS and OS will be also conducted on all patients (ITT analysis) as a sensitivity analysis.

- Tolerance

The toxicity analysis will be performed on the safety population.

13.5 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study. The DMC will provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab. The DMC will act in an advisory capacity to IFCT and will monitor subject safety data for the study.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data.

The Intergroup will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required.

A safety run will be done after the first 5 patients then every 10 patients (8 weeks follow up) and will be reviewed by the DMC in attempt to detect unexpected immunovirologic side effects, ie increase in HIV viral load, decrease of CD4 cell count or unexpected high frequency of IRIS.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

The DMC recommendations will be sent to ANSM for information.

14 CORRELATIVE BIOLOGICAL STUDIES ("BIO-CHIVA2")

As for other trials previously conducted by the IFCT, several biological specimens will be centrally collected for correlative biological studies (BIO-CHIVA2). Two cores from archived or fresh paraffin embedded tissue specimens will be collected to perform IHC of PDL1 expression on tumoral and immune cells and other phenotyping biomarkers associated with immune check point inhibitors efficacy (CD8, HLADR, interferon gamma and foxp3).
Plasma will be also collected before treatment to evaluate the presence of circulating tumor DNA using a lung panel NGS approach. Presence, number of detected alterations and quantification of molecular alterations were correlated to the efficacy of nivolumab treatment.
These analyses will be performed by the GRC-04 Theranoscan laboratory of P&M Curie Paris 6 university (Pr Jacques Cadranel, Pr Marie Wislez, Dr Martine Antoine, Ms Nathalie Mathiot).

Otherwise, the HLA class I restriction of CD8 T cell plays an important role in the antiviral response in term of both repertoire and avidity of the cellular response (Lissina AIDS. 2014 Feb 20;28(4):477-86, Appay, Curr Opin HIV AIDS. 2011;6:157). But the efficacy of immune checkpoint inhibitors is based on the activation of the response of cytotoxic T cell. This response could be modulated by the HLA class I restriction. The modulation by immune checkpoint inhibitors of CD4+ T cells antitumor function, restricted to HLA class II, has also been described (Pardoll Nature Reviews Cancer 2012 ; 12, 252 ; Kwek, Cancer Immunol Res. 2015;3:1008). A HLA class I and II typing by standard technique (PCR-SSO) with a 2-digit resolution will be done in the biological study BIO-CHIVA-2 for all the patient and,

even more so, for patients experiencing immune related adverse events. This technique could be complemented by a technique with 4-digit alleles resolution.
Furthermore, all genes which have a major interest in the response to immune check point inhibitor or in the occurrence of an event will be sequenced after the registration of a significant number of patients. For that purpose, a dried cell pellet of 5 to 10 millions of PMBC will be stored for the genetic study of relationships between cancer and HIV infection.

14.1 Protocol for Immunology and Virology (Pitié Salpêtrière);

Samples for cell bank, plasma and serum analysis will be made by a 68 mL blood sample before first nivolumab infusion, at cycle 2, 3, 9, 15, 27, 51, at the end of treatment , and in the case of immune adverse effect. The following tubes will be collected and sent to the centralized laboratory within 24h:

- 6 acid Citrate Dextrose tubes of 9 mL
- 2 EDTA tubes of 7 mL

The plasma bank will measure the concentration of anti PD1 / PDL-1 and optionally the anti-antibody levels, and the residual HIV replication. The plasma dosage will also measure cytokines / chemokines and other inflammation markers based on scientific knowledge on the subject. The cell bank will: 1°/ assess the size of the HIV reservoir (cell-associated DNA), 2°/ assess the anti-HIV immune response (quantitative and qualitative study of antiviral T cells: count, polyfonctionality, expression of immune checkpoints ...), 3°/ assess the state of differentiation / activation of T cells expressing immune checkpoints, 4°/ evaluate the immune responses against the other virus (EBV, CMV, hepatitis B and C, HHV-8) if co-infected, and 5°/ finally assess the anti-neoepitope CTL directed against tumor neoantigens. Finally, paraffin embedded tumor and peritumoral biopsies will be punched in centers in order to sample tumoral and healthy tissue; those punches will be rerouted to the immunology laboratory (Pitié Salpêtrière) in order to perform RNAseq studies, then identification of tumoral neo-epitopes by sequence alignment, HLA typing, and finally neoepitope prediction. If punch sample is not available, FFPE tumor slides will be rerouted to the Pitie Salpetrière hospital: 20µm thickness or 4x10µm thickness, for tumoral whole exome sequencing and definition of neoepitopes.

15 ADMINISTRATIVE SECTION

15.1 Sponsor obligations

Before the trial

The sponsor will:

- Ensure regulatory requirements are met before the trial is implemented
- Ensure that all administrative procedures are in place for each department in the associated establishments
- Provide centres with the complete protocol and its appendices, the adverse event report form, CPP (Independent ethics committee) permission, statement of insurance and authorization from the French health authority (ANSM).

The sponsor and their representatives will:

- Provide centres with the instructions and documents needed to conduct the trial properly (protocol, data collection form and investigator file)
- Organise an orientation session to train study investigators and coordinators (during this session, all protocol sections will be reviewed and how to fill out case report forms and study procedures will be explained)

During the trial

The sponsor and their representatives will:

- Regularly visit the investigating centres
- Be available at all times for consultation and remain in contact with the personnel of the investigating centre by email, telephone and/or fax
- Examine and evaluate the data in the case report form and look for possible errors in data collection

In cooperation with the principal investigator, the sponsor will provide all of the investigators involved with the study with any new information that may interfere with conducting the trial.

In terms of the trial

It is the sponsor's responsibility to make sure that the procedures are completed at the end of the trial.

15.2 Investigator obligations

The investigator agrees to conduct the study in compliance with the 1974 Declaration of Helsinki, revised in 1975 and 1989, good clinical practice, and French current regulations.

In regards to the French law of 9 August 2004, the investigator from each centre agrees to collect the informed written consent from each patient participating in the trial. One copy of the consent form will be given to the patient and the other will be kept in the patient's clinical file. Patients must be able to give their informed consent freely and not be under guardianship or suffer from any type of mental impairment that may affect their judgement.

The investigator also agrees to fill out the case report form needed for study follow-up.

The investigator also agrees to:

- Inform the sponsor of any serious or unexpected adverse event occurring during the trial within the time periods described in chapter 7.1 using the appropriate form
- Agree to monitoring with access to source documents to validate data from the case report forms and if needed, agree to an internal or external audit by the sponsor or a representative from the regulatory authorities
- Archive trial documents (copies of case report forms, written consent forms) for a period of at least 15 years
- Include at least one patient during the first six months following the trial's implementation
- Make sure that there is no interference with another trial for the same indications
- Respect the confidentiality of the documents provided

15.3 Ethical considerations

Participant information and consent

Before conducting this biomedical research on a person, they must provide their **free, informed** and **express** consent (including consent for genetic studies) after being informed of the purpose of the research, the study procedures and duration, the benefits, and potential risks and constraints of the study, as well as the type of product being researched and the opinion of the CPP (art. L.1122-1).

The patient and investigator or representing physician will personally date and sign the consent form (original copy archived by the investigator, a copy will be given to the patient or their legal representative).

Request for CNIL authorisation for automated data processing

This biomedical research will produce scientific information. This coded, directly or indirectly personal information is part of the legal framework of file use (Law n° 78-17 from 6 January 1978 and law n° 94-548 from 1 July 1994)

The sponsor (IFCT) has authorisation (*n°1227585*) to process personal data for the purpose of Biomedical Research on medication and diseases under the law of 20 December 1988 modified by law n° 2004-806 of 9 August 2004.

To the extent that this biomedical research is conducted within the strict regulatory and legal requirements (the "Huriet-Sérusclat" law of 20 December 1988 modified by law n° 2004-806 of 9 August 2004) and according to standard methods, the CNIL has adopted a standard method (MR001 according to article 54 from the law of 6 January 1978 modified), which now covers all personal data processing conducted as part of biomedical research - including pharmacogenetic trials - as defined in the public health code, and commitment to comply with said method.

15.4 Amendment and additional clauses procedures

The study's principal investigator or sponsor will suggest any substantial change in the protocol, and will then inform the other party. This will be an amendment submitted to the CPP and AFSSAPS. No change can be made without agreement from the committee. The sponsor will inform each investigator and send them the amendment and related statement of intent.

15.5 Quality control and assurance

Regulatory considerations: medical procedures for this trial comply with the most recent recommendations from the Declaration of Helsinki and public health law no. 2004-806 of 9 August 2004 related to the protection and safety of humans.

Confidentiality: the protocol and its appendixes, as well as all of the data, are confidential as noted at the beginning of the protocol.

Data monitoring: The IFCT's Clinical Research Unit will monitor this trial in order to ensure accurate, complete and reliable data collection. It will also provide logistical support to

investigating centres. An inspection by an employee obligated to professional secrecy mandated by Regulatory Authorities may be required to ensure that all of the source documents needed are available and that the clinical trial is being conducted according to Good Clinical Practices and the law from 9 August 2004.

15.6 Study schedule

The protocol should begin in June 2017. The trial recruitment period is expected to be 42 months. The study will be ended one year after the last treatment of the last patient. The trial should be ended by December 2021.

15.7 Early study termination

The sponsor and coordinating investigator will issue any early termination of the study. The sponsor will provide written notification. This letter will be sent to the Agence Nationale de Sécurité du Médicament (French agency for the safety of health products) and to each investigator, as well as the CPP.

15.8 Statement of commitment

New investigators

Investigators can only participate in the trial after submitting a written request to the sponsor. It should include the following items:

- A statement of commitment indicating the expected number of patients that the investigator can include in the protocol per year
- A recent *CV* with French medical board registration number

Site opening

Before inclusions can begin, a site must be officially opened; in other words, the investigator's name, institution, telephone and fax number, and email address must be duly issued to the sponsor, CPP and Ministry (initial and additional authorization statement). The investigator must have all of the documents needed to conduct the trial properly (protocol, investigator brochure, case report form). He must have obtained agreement from the facility's pharmacist to distribute treatments and resolve any problems with the study coordinator. He must have informed the director of his facility by letter of his participation. An agreement must be signed between the director of his facility and the sponsor.

15.9 Study organization

The Steering Committee makes all of the decisions concerning the study's implementation, execution, analysis and reporting. It meets three times per year two times, and periodically sends information on the study's progress to investigators.

It is comprised of members of the editorial board, study statisticians and a sponsor representative.

The Coordination Centre will be the Clinical Research Unit (Unité de Recherche Clinique - URC) of the IFCT, located at 10 rue de la Grange-Batelière, 75009 PARIS. Its purpose is to ensure that the trial is being conducted as intended in the protocol: patient inclusion management, data collection, data management, SAE management, organization of investigator and committee meetings. It informs the Steering Committee of any issues concerning the trial's progress.

Moreover, the Steering Committee can organize regular investigator meetings during which the files of included patients will be reviewed. The purpose of this review panel will be to jointly verify compliance and understanding of the eligibility criteria and treatment methods dictated by the protocol. In addition, it will conduct a progress analysis for retrospective validation.

16 FINAL REPORT AND PUBLICATIONS

Once the study is finished, a clinical trial report will be published by the study's principal investigators and statistician. The coordinating investigator will sign the final version of the clinical trial report for this study, and by doing so will indicate his approval of the report's analyses, results and conclusions.

The key participants in a clinical study are the principal investigator, investigators, IFCT-employee team members, and members of the management and scientific boards who all collaborate to various degrees from designing the trial to writing the final report.

1. The coordinator can choose between first and last place. In both cases, he must have participated significantly in designing the trial, inclusions and writing the article.
2. If the investigator chooses the first place, last place goes to the president, one of the secretaries, or one of the other elected members of the Management Board or Scientific Council. The person must be chosen based on their participation in designing the trial, inclusions and writing the article. If there is difficulty in choosing this person, a secret vote by the management board will decide.

3. If the investigator chooses the last place, the next-to-last place goes to the president, one of the secretaries, or another elected member of the Management Board or Scientific Council under the same conditions, unless he/she takes the first position if, in agreement with the principal investigator, he writes the article. If there is difficulty in choosing this person, a secret vote by the management board will decide.
4. Investigators appear by the order in which eligible patients were included. All other investigators must appear in a list in the appendix.
5. Two members of the same team cannot sign the same article unless one of them appears as a principal investigator (coordinator?), Management Board member, or Scientific Council member signing as such in first, second, or next-to-last place.
6. Members of the IFCT employee team play a vital role in clinical studies. For this reason, those who were involved in designing the trial, managing it or writing the article must systematically appear in the acknowledgements or as signatories. The director will provide their names to the principal investigator (coordinator). If they appear as signatories, they cannot be included in the first six or last two positions. There can be no more than two if the number of signatories is more than 10, and only one if the number is equal to or less than 10.
7. If a university statistician has worked on developing or processing trial data, he can sign with the approval of the principal investigator (coordinator) in a place on which they both agree (generally 3rd or 4th place).
8. Under no circumstances can someone sign for having provided a patient with routine care that was unrelated to the research.
9. All investigators (one per IFCT investigating centre) will be listed after each article in a table that may also include pathologists, surgeons and radiation therapists from the centre based on the article, so that this citation appears on Medline.
10. For ancillary studies (biological, radiology, or others), if the article or abstract has a maximum of 10 signatures, the principal investigator (coordinator) of the biological study can choose between first and last position. In both cases, he must have participated widely in the study's design, financing, inclusions and writing the article. The rules above apply to last position if he chooses last position. Next-to-last place can go to the research lab director who contributed most to the study. The last but two places can go to the study's principal investigator (coordinator) if it is not taken by the biological study's principal investigator. The first four places can

be taken by scientists or physicians, with the IFCT or not, who contributed the most to the ancillary study. This may also include the university statistician if suggested by the coordinating investigator and management board office, and validated by the management board. If there are a maximum of 10 signatures, three to four places in the middle will be reserved for the best clinical contributors (in the sense that they contributed the most in terms of pathology specimens). In the case of articles with 20 signatures, two to three places will be reserved for pathologists who contributed the most to the study (either in collecting specimens or reviewing the IFCT's pathology panel). All of the labs that participated in the study shall be represented by one signatory, the remaining signatory places must be attributed to clinicians according to the rules above, including one permanent member of the IFCT team who contributed the most to the study (decision made by the CI + Director + President), as well as the CI for the clinical study.

11. All articles should include the mention "…on behalf of IFCT" at the end of the signatories list, and include the acronym IFCT-XXYY in the title of the clinical trial to which the ancillary study is related.
12. The IFCT can receive assistance with the English formatting of an article, but can never delegate the writing itself to an agency or industry.

These rules were created and validated by the IFCT Management Board in September 2010.

APPENDIX I

Exigences concernant la contraception

Votre médecin investigateur a connaissance des différentes méthodes de contraception acceptables et pourra vous donner les conseils appropriés sur la meilleure méthode contraceptive vous concernant.

Le tableau ci-dessous liste les différentes méthodes de contraception.

	Méthode de contraception
Hautement efficace	Contraceptif hormonal uniquement progestatif associé à l'inhibition de l'ovulation
	Méthodes hormonales de contraception, comprenant les pilules contraceptives orales combinées (estrogène + progestérone), anneau vaginal, produits injectables, les implants et les dispositifs intra-utérins (DIU) (ex: stérilet tel que Mirena®)
	Parfois, les niveaux hormonaux des méthodes de contraception peuvent être affectés par le(s) produit(s) à l'étude. Votre médecin vous précisera quelles formes de contraception hormonales sont autorisées dans le cadre de cette étude
	Dispositif intra-utérin (DIU) non-hormonal (ex : stérilet ParaGard®)
	Ligature bilatérale des trompes
	Partenaire ayant subi une vasectomie
	Système hormonal intra-utérin (SIU)
	Abstinence totale
	Préservatif masculin pour les hommes ayant des partenaires susceptibles d'avoir des enfants
Méthodes non autorisées	Abstinence périodique (méthodes du calendrier, symptothermale, post-ovulation) Retrait (coït interrompu)
	Spermicides seuls Méthode de l'aménorrhée lactationnelle (MAMA)

Vous devez utiliser une méthode de contraception hautement efficace (taux d'échec de moins d'1% par an), et en discuter avec votre médecin investigateur si vous débutez cette méthode pendant l'étude.

Vous devez informer votre médecin investigateur si vous débutez une méthode de contraception non-autorisée pendant l'étude.

APPENDIX II

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 <u>Diarrhea:</u>< 4 stools/day over baseline; <u>Colitis:</u> asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately <u>If worsens</u>: • Treat as Grade 2 or 3/4
Grade 2 <u>Diarrhea</u>: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL <u>Colitis:</u> abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	<u>If improves to grade 1</u>: • Resume I-O therapy per protocol <u>If persists > 5-7 days or recur:</u> • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. <u>If worsens or persists > 3-5 days with oral steroids</u>: • Treat as grade 3/4
Grade 3-4 <u>Diarrhea (G3)</u>: ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL <u>Colitis (G3):</u> severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	<u>If improves</u>: • Continue steroids until grade 1, then taper over at least 1 month <u>If persists > 3-5 days, or recurs after improvement:</u> • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN -2.5 x ULN and/or T. bili > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 2.5 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

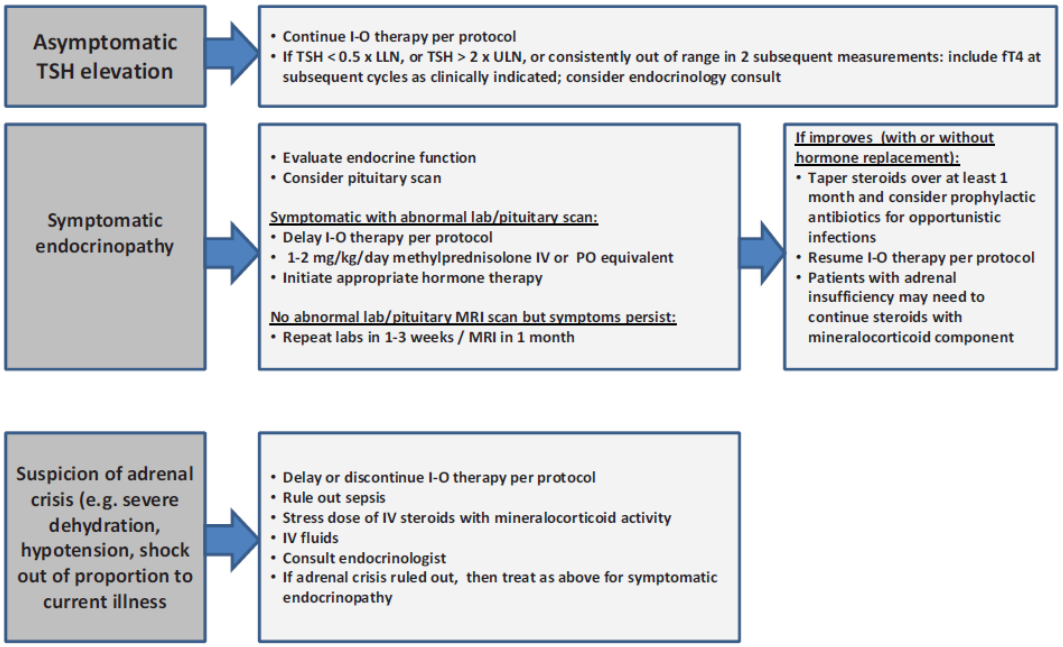
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

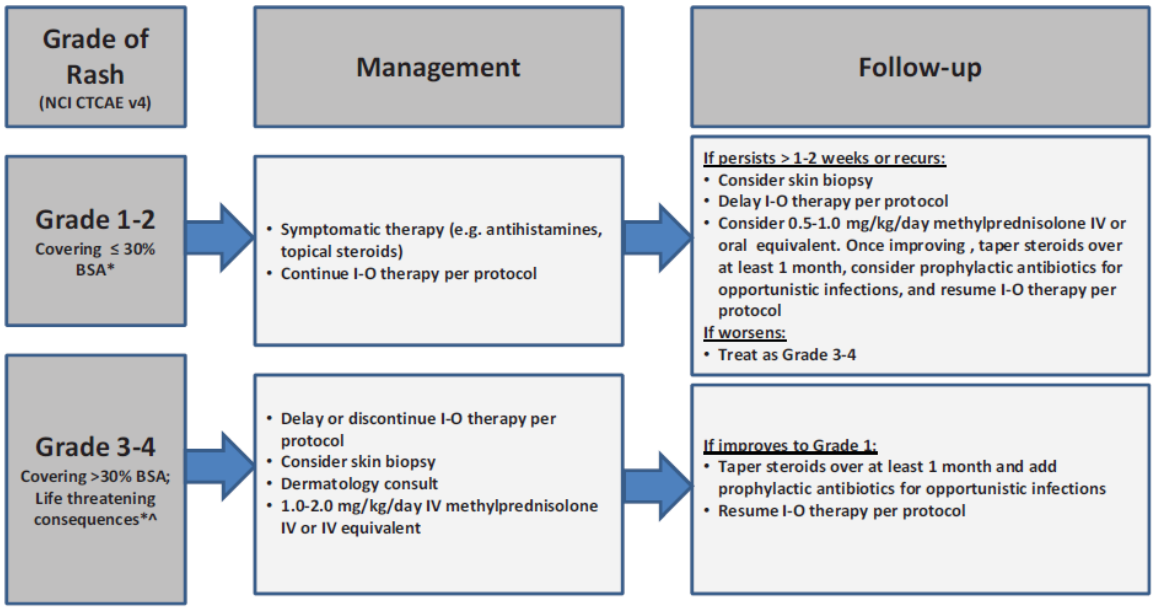
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

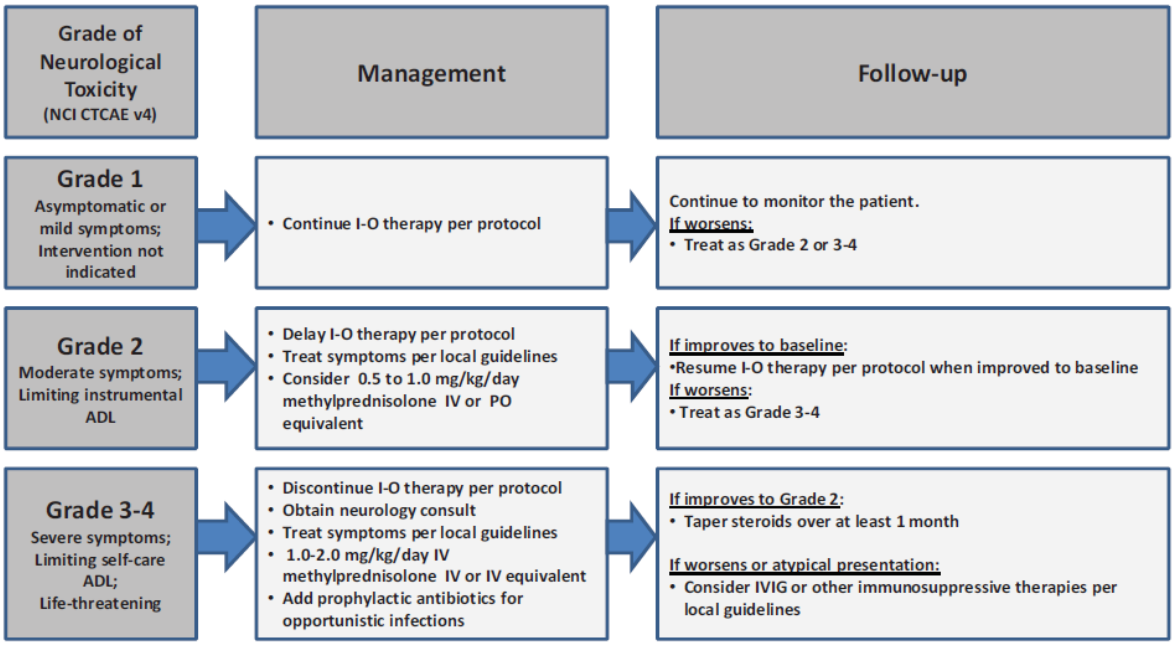
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.