MEL-DRAGONFLY

Étude de phase 1/2, réalisée pour la première fois chez l'homme, en ouvert et en plusieurs parties, à doses multiples croissantes, visant à évaluer la sécurité d'emploi, la tolérance, la pharmacocinétique et l'activité biologique et clinique du DF6002 chez des patients présentant des tumeurs solides localement avancées ou métastatiques, avec extension pour des indications sélectionnées en tant que traitement en monothérapie et en association avec le nivolumab

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https://clinicaltrials.gov/ct2/show/NCT04423029

Population cible : Mélanome métastatique ou localement avancé en Xième ligne ayant progressé après un traitement anti-PD-1 ou anti-PD-L1

Traitement à l'étude : cytokine IL12 (Le DF6002) +/- antiPD1 (Nivolumab)

Schéma de traitement :
Phase 1 et 1b (escalade de dose) actuellement applicable en France
-DF6002 administré sous forme d'injection SC 1x/4 sem. (c.-à-d. le Jour 1 de chaque cycle) dans les cohortes de monothérapie et d'association
-Nivolumab administré à une dose de 480 mg, 1x/4 sem. par perfusion IV

Rythme des visites : 1 cycle=28 jours
- Quatre premiers cycles: J1,J2,J3,J5 J8,J15
- Puis chaque J1 des cycles suivants

Critères d'inclusion	O	N
Dose Escalation: Phase 1 (DF6002 Monotherapy) and Phase 1b (Combination with Nivolumab)		
1. Signed written informed consent.		
2. Male or female patients aged ≥ 18 years.		
3. Histologically or cytologically proven locally advanced or metastatic solid tumors, for which no standard therapy exists, or standard therapy has failed among the following tumor types: melanoma, NSCLC, small cell lung, head and neck squamous cell, urothelial, gastric, esophageal, cervical, hepatocellular, Merkel cell, cutaneous squamous cell carcinoma, renal cell, endometrial, TNBC, ovarian, and prostate		
4. ECOG performance status of 0 or 1 at study entry and an estimated life expectancy of at least 3 months.		
5. Clinical or radiological evidence of disease.		
6. Adequate hematological function defined by white blood cell (WBC) count ≥2×109/L with absolute neutrophil count (ANC) ≥1.5×109/L, lymphocyte count ≥0.5×109/L, platelet count ≥75×109/L, and hemoglobin ≥9 g/dL (may have been transfused).		
7. Adequate hepatic function defined by a total bilirubin level within normal range, an AST level ≤2.5×ULN, and an ALT level ≤2.5×ULN or, for patients with documented metastatic disease to the liver, AST, and ALT levels ≤5×ULN.		
8. Adequate renal function defined by an estimated creatinine clearance >50 mL/min according to the Cockcroft-Gault formula.		

9. Experienced resolution of toxic effect(s) of the most recent prior anti-cancer therapy to ≤Grade 1 (except alopecia) per NCI CTCAE v5.0 or patient's prior baseline. If a patient underwent major surgery or radiation therapy of >30 Gray, the patient must have recovered from the toxicity and/or complications from the intervention (patients with ≤Grade 2 neuropathy, ≤ Grade 2 endocrinopathy and ≤Grade 2 alopecia are an exception).		
10. Effective contraception for women of child bearing potential (WOCBP) patients as defined by World Health Organization (WHO) guidelines for 1 "highly effective" method or 2 "effective" methods.		
Additional Inclusion Criteria, Phase 1/1b Safety PK/PD Expansion Cohorts:	NA ☐	
1. Signed written informed consent.		
2. A Male or female patients aged ≥ 18 years.		
3. ECOG performance status of 0 or 1 at study entry and an estimated life expectancy of at least 3 months.		
4. Measurable disease, as determined by the Investigator using RECIST, version 1.1.		
5. Agrees to undergo a pre-treatment biopsy and another biopsy while on treatment (Table 1).		
6. Has a clinical/radiological presentation of their disease consistent with the execution of a pre-treatment biopsy and another biopsy while on treatment.		
7. Adequate hematological function defined by white blood cell (WBC) count ≥2×109/L with absolute neutrophil count (ANC) ≥1.5×109/L, lymphocyte count ≥0.5×109/L, platelet count ≥75×109/L, and hemoglobin ≥9 g/dL (may have been transfused).		
8. Adequate hepatic function defined by a total bilirubin level within normal range, an AST level ≤2.5×ULN, and an ALT level ≤2.5×ULN or, for patients with documented metastatic disease to the liver, AST and ALT levels ≤5×ULN.		
9. Adequate renal function defined by an estimated creatinine clearance >50 mL/min according to the Cockcroft-Gault formula.		
10. Experienced resolution of toxic effect(s) of the most recent prior anti-cancer therapy to ≤Grade 1 (except alopecia) per NCI CTCAE v5.0 or patient's prior baseline. If a patient underwent major surgery or radiation therapy of >30 Gray, the patient must have recovered from the toxicity and/or complications from the intervention (Patients with ≤Grade 2 neuropathy, ≤Grade 2 endocrinopathy and ≤Grade 2 alopecia are an exception).		

11. Highly effective contraception methods, as defined by the Clinical Trials Facilitation Group (CTFG).		
12. Has one of the following tumor types: melanoma, non-small cell lung cancer (NSCLC), or triple negative breast cancer (TNBC [enrolling in the US only]) and has progressed on their last line of therapy.		
13. Criteria specific to patients with melanoma: • Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer staging system. • Participants with ocular or uveal melanoma are ineligible. • PD-L1 status must be documented if available. • BRAF (V600) mutation status must be known. Both BRAF-mutated and wild-type participants are permitted in this cohort. • BRAF-mutated participants must have been treated with approved targeted therapies. • Must have documented progressive or recurrent disease on or after discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria: • Participants who received anti-PD-(L)1 in the adjuvant setting must have documented progressive or recurrent disease on or within 6 months of discontinuation of anti-PD- (L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria		
14. Criteria specific for patients with NSCLC • Histologically confirmed NSCLC meeting stage criteria for stage IIIB, stage IV, or recurrent disease. • Participants must have recurrent or progressive disease during or after platinum doublet-based chemotherapy or at least two prior lines of systemic therapy for advanced or metastatic disease OR Must have recurrent or progressive disease within 6 months after completing platinum-based chemotherapy for local disease. After receiving platinum doublet-based chemotherapy or at least two prior lines of systemic chemotherapy, participants must have been evaluated for additional lines of cytotoxic chemotherapy (e.g., docetaxel or pemetrexed) and considered ineligible for or refused such therapy. The reason for ineligibility or refusal must be clearly documented in the medical record. • Participants must have received and progressed on or after anti-PD-(L)1 therapy, if available. • Status for actionable mutations (e.g., EGFR, ALK, ROS1, RET, etc.) must be known (when testing is available as per country/region standard of care practices); participants with actionable mutations must have received and progressed on, have been intolerant to, or not be a candidate for, standard tyrosine kinase inhibitors (as available per country/region standard of care practices).		
Phase 2, Advanced Melanoma (Cohort 2A and 2C)		

1. Signed written informed consent.		
2. Male or female patients aged ≥18 years.		
3. Histologically confirmed, unresectable Stage III or Stage IV melanoma, as specified in the American Joint Committee on Cancer staging system. a. Participants with ocular or uveal melanoma are ineligible.		
4. PD-L1 status must be documented if available.		
5. BRAF (V600) mutation status must be known. Both BRAF-mutated and wildtype participants are permitted in this cohort. a. BRAF-mutated participants must have been treated with approved targeted therapies.		
6. Must have documented progressive or recurrent disease on or after discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria:		
7. Prior anti-PD-(L)1-based therapy must be the most recent treatment.		
8. Participants who received anti-PD-(L)1 in the advanced/metastatic setting, must have documented progressive or recurrent disease on or within 3 months of discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria.		
9. Participants who received anti-PD-(L)1 in the adjuvant setting must have documented progressive or recurrent disease on or within 6 months of discontinuation of anti-PD-(L)1 therapy (administered as monotherapy or as part of a combination) as per RECIST 1.1 criteria.		
10. Confirmation of radiographic progression on prior anti-PD-(L)1 therapy is required with a scan confirming progression at least 4 weeks after the initial progression. Screening scans can be used as the confirmation of progression.		
11. Prior treatment with ipilimumab is acceptable.		
12. ECOG performance status of 0 or 1 at study entry and an estimated life expectancy of at least 3 months.		
13. Measurable disease, as determined by the Investigator using RECIST, version 1.1.		
14. Adequate hematological function defined by WBC count ≥2×109/L with ANC ≥1.5×109/L, lymphocyte count ≥ 0.5×109/L, platelet count ≥75×109/L, and hemoglobin ≥9 g/dL (may have been transfused).		

15. Adequate hepatic function defined by a total bilirubin level within normal range, an AST level ≤2.5×ULN, and an ALT level ≤2.5×ULN or, for patients with documented metastatic disease to the liver, AST, and ALT levels ≤5×ULN.		
16. Adequate renal function defined by an estimated creatinine clearance >50 mL/min according to the Cockcroft-Gault formula.		
17. Experienced resolution of toxic effect(s) of the most recent prior anti-cancer therapy to Grade ≤1 (except alopecia) per NCI CTCAE v5.0 If a patient underwent major surgery or radiation therapy of >30 Gray, the patient must have recovered from the toxicity and/or complications from the intervention (Patients with ≤Grade 2 neuropathy, ≤Grade 2 endocrinopathy, and ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study).		
18. Highly effective contraception methods, as defined by the Clinical Trials Facilitation Group (CTFG).		

Critères d'exclusion	O	N
1. Concurrent treatment with a non-permitted drug (see Section 8.6.2).		
2. Prior treatment with rhIL2 or with any drug containing an IL2 or IL12 moiety.		
3. Concurrent anticancer treatment (e.g. cytoreductive therapy, radiotherapy [with the exception of palliative bone directed radiotherapy], immune therapy, or cytokine therapy except for erythropoietin), major surgery (excluding prior diagnostic biopsy), ?concurrent systemic therapy with steroids or other immunosuppressive agents, or use of any investigational drug within 28 days before the start of study treatment. Short-term administration of systemic steroids (i.e., for allergic reactions or the management of irAEs) or replacement dose steroids for insufficiency of 10 mg per day of prednisone or equivalent is allowed. Continued androgen deprivation therapy for castrate-resistant prostate cancer is permitted. Note: Patients receiving bisphosphonates are eligible provided treatment was initiated at least 14 days before the first dose of DF6002.		
4. Previous malignant disease other than the target malignancy to be investigated in this study within the last 3 years, with the exception of localized or resected basal or squamous cell carcinoma of the skin, localized prostate cancer or cervical carcinoma in situ.		
5. Rapidly progressive disease.		
6. Any Grade 2 and higher neurological or pulmonary toxicity during a treatment with an anti-PD-1 or PD-L1 agent administered as a monotherapy or in combination if there is no doubt about the causality of the PD-1 or PD-L1 agent.		

7. Active or history of central nervous system (CNS) metastases, unless all of the following criteria are met: a. CNS lesions are asymptomatic and previously treated. b. Patient does not require ongoing steroid treatment daily for replacement for adrenal insufficiency (except oral steroids at a dose less than ≤ 10 mg prednisone [or equivalent]) c. Imaging demonstrates stability of disease 28 days from last treatment for CNS metastases.		
8. Receipt of any organ transplantation including autologous or allogeneic stem-cell transplantation.		
9. Active acute or chronic infections treated with antibiotics must be resolved and antibiotic therapy completed at least 7 days prior to start of study drug(s). Historic positive test for human immunodeficiency virus [HIV], or active or latent hepatitis B or active hepatitis C tested during the Screening window are also exclusionary.		
10. Preexisting autoimmune disease (except for patients with vitiligo) needing treatment with systemic immunosuppressive agents for more than 28 days within the last 3 years or clinically relevant immunodeficiencies (eg, dys-gammaglobulinemia or congenital immunodeficiencies), or fever within 7 days of Day 1. Exceptions may be considered by the Sponsor medical monitor for non-severe autoimmune disease that is well controlled without steroids, such as mild asthma or autoimmune endocrinopathies.		
11. Known severe hypersensitivity reactions to active substances and excipients of DF6002 and nivolumab, monoclonal antibodies (mAbs) (≥Grade 3 NCI CTCAE v5.0), any history of anaphylaxis, or uncontrolled asthma (i.e., 3 or more features of partly controlled asthma).		
12. Persisting toxicity related to prior therapy ≥Grade 2 NCI CTCAE v5.0, however alopecia ,sensory neuropathy and endocrinopathy ≤Grade 2 is acceptable.		
13. Pregnancy or lactation in females during the study.		
14. Known alcohol or drug abuse.		
15. Serious cardiac illness or medical conditions including but not limited to: a. History of New York Heart Association class III or IV heart failure or systolic dysfunction (left ventricular ejection fraction [LVEF] <55%). b. High-risk uncontrolled arrhythmias i.e., tachycardia with a heart rate >100/min at rest. c. Significant ventricular arrhythmia (ventricular tachycardia) or higher-grade atrioventricular (AV)-block (second degree AV-block Type 2 [Mobitz 2] or third-degree AV-block). d. Angina pectoris requiring anti-anginal medication. e. Clinically significant valvular heart disease. f. Evidence of transmural infarction on ECG.		

g. Poorly controlled hypertension (defined by: systolic >180 mm Hg or diastolic >100 mmHg). h. Clinically relevant uncontrolled cardiac risk factors, clinically relevant pulmonary disease or any clinically relevant medical condition in the opinion of the Investigator that may limit participation in this study.		
16. All other significant diseases (eg, inflammatory bowel disease), which, in the opinion of the Investigator, might impair the patient's ability to participate.		
17. Any psychiatric condition that would prohibit the understanding or rendering of informed consent.		
18. Legal incapacity or limited legal capacity.		
19. Incapable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.		
20. History of life-threatening toxicity related to prior immune therapy (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) except those that are unlikely to re-occur with standard countermeasures (eg, endocrinopathy). History of severe toxicities related to prior immune therapy must be discussed with and approved by the Sponsor medical monitor.		