# FBF356 - Ensaios Clínicos
# Bloco 3

## Doenças Oncológicas II - Tumores Linfáticos

Dupla 6 - Estudos Fase 2

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# Ensaios Clínicos Fase 2

Objetivos:

-Avaliar a eficácia terapêutica  do produto de pesquisa;

-Determinação da dose e regime terapêutico;

-Perfil de segurança a curto prazo.

Condução:

-25 ~ 100 voluntários;

-Portadores da patologia ou condição em estudo;

-Duração de semanas a meses;

# “Study of Nivolumab in Patients With Classical Hodgkin’s Lymphoma - CheckMate-205”

- Estudo de Fase 2 de Nivolumab como monoterapia indicado para pacientes com Linfoma de Hodgkin clássico após transplante autólogo de células-tronco e falha terapêutica no tratamento com brentuximab vedotina.
  - Endpoint primário: taxa de resposta geral determinada pelo Comitê Independente de Análises Radiológicas (CIAR).
  - Endpoint secundários e outros: duração da resposta, segurança, avaliação do *loci* PD-L1 / PD-L2 e expressão proteica PD-L1/ PD-L2.

- Patrocinador: Bristol-Myers Squibb


**14.6 Classical Hodgkin Lymphoma**

Two studies evaluated the efficacy of OPDIVO as a single agent in adult patients with cHL after failure of autologous HSCT.

CHECKMATE-205 (NCT02181738) was a single-arm, open-label, multicenter, multicohort study in cHL. CHECKMATE-039 (NCT01592370) was an open-label, multicenter, dose escalation study that included cHL. Both studies included patients regardless of their tumor PD-L1 status and excluded patients with ECOG performance status of 2 or greater, autoimmune disease, symptomatic interstitial lung disease, hepatic transaminases more than 3 times ULN, creatinine clearance less than 40 mL/min, prior allogeneic HSCT, or chest irradiation within 24 weeks. In addition, both studies required an adjusted diffusion capacity of the lungs for carbon monoxide (DLCO) of over 60% in patients with prior pulmonary toxicity.

# Linfoma Clássico de Hodgkin (cHL)

Descrição:

-Neoplasia que envolve linfócitos B anormais, chamados de células de Reed-Sternberg;

-Promove inchaço nos linfonodos, dor, febre, fadiga e outros sintomas relacionados;

Alvo terapêutico do Nivolumab:

-Receptores PD-L1 e PD-L2, associados a resposta imune mediada por linfócitos T;

-Superexpressão dos receptore PD-L protege as células contra resposta imune;

-Nivolumab atua bloqueando tais receptores.

# Desenho do estudo

- Estudo Multicêntrico envolvendo 34 centros de pesquisa distribuídos entre Europa, Canadá e EUA;
- 80 voluntários;
- Não-comparativo;
- Braço-único.

**Critérios de Inclusão**

-Portadores do cHL que apresentaram recaída após quimioterapia padrão, seguida pelo transplante de células tronco e terapia com brentuximab vedotin

-Idade igual ou superior a 18 anos

**Critérios de Exclusão**

-Doenças auto-imunes;

-Diabetes Mellitus I, Vitiligo e/ou Psoríase;

-Radioterapia recente (até 3 semanas antes);

-Tratamento com outros anticorpos recente (até 4 semanas antes);

# Endpoints

**Primário**
**Taxa de Resposta Geral**

- % de pacientes que apresentaram melhor resposta geral de remissão total ou parcial do tumor;
- avaliação do CIAR embasada nos critérios determinados pelo International Working Group, 2007

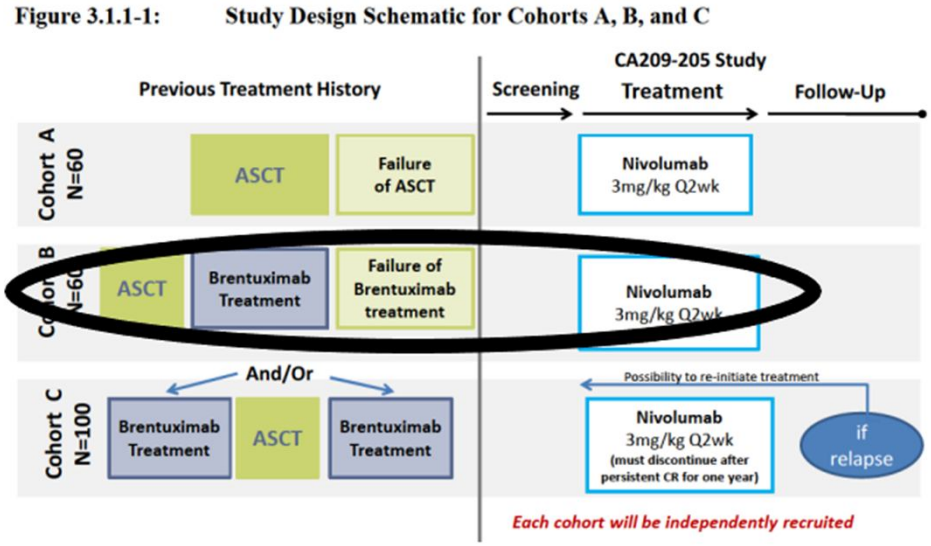
- Resposta tumoral foi avaliada a partir de:
  - Exames de imagem nas semanas 9, 17, 25, 37, 49, 65, 81, 97, 123 e 146;
  - Para pacientes com acometimento da medula óssea também se analisou resultados de biópsia

**Secundários e Exploratórios**

- Duração da resposta;
- Taxa parcial e completa de remissão;
- Duração parcial e completa de remissão;
- Avaliação do PI para duração da resposta geral;
- Qualidade de vida;
- Análise PD-L1/PD-L2

- Exames de imagem;
- Investigação de células células de Reed-Sternberg.
  - Exames imunohistoquímicos
- Aplicação de questionários para análise de QoL.
  - EQ-5D;
  - EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30);

# Procedimentos




- Intervenção investigada: benefício clínico com Nivolumab 3 mg/kg a cada 2 semanas.
  - 1 ciclo de tto = período de 14 dias;
  - Redução de dose não permitida;
- Exames laboratoriais.
  - Hemograma completo;
  - Eletrólitos;
  - Função hepática;
  - Função renal;
  - TSH.
- Exames de imagem.
  - Tomografia computadorizada;
  - Ressonância magnética.

# Resultados

**Table 2**

Objective response rate as assessed by the IRRC and investigators

| Response | IRRC (n=80) | Investigator (n=80) |
|---|---|---|
| Objective response rate * | 53 (66·3%), 54·8–76·4 | 58 (72·5%), 61·4–81·9 |
| Best overall response † | | |
| Complete remission | 7 (8·8%) | 22 (27·5%) |
| Partial remission | 46 (57·5%) | 36 (45·0%) |
| Stable disease | 18 (22·5%) | 18 (22·5%) |
| Progressive disease | 6 (7·5%) | 3 (3·8%) |
| Unable to determine | 3 (3·8%)‡ | 1 (13%)§ |

Data are n (%) or 95% CI. IRRC=Independent Radiologic Review Committee.

*Objective response rate was defined as the percentage of treated patients with a best overall response of complete remission or partial remission according to the revised International Working Group criteria for Malignant Lymphoma (2007 criteria[18]).

†Best overall response was defined as the best response designation recorded between the date of the first dose and the date of initial objectively documented progression per the 2007 International Working Group criteria or the date of subsequent therapy, whichever occurred first.

‡n=2, no post-baseline tumour assessment available before or on the day of subsequent therapy (if any); n=1, all post-baseline tumour assessments before or on the day of subsequent therapy (if any) are unknown.

§No radiographic assessment was performed after the first dose of nivolumab.

## ENDPOINT PRIMÁRIO

Taxa de resposta geral = 66.3% (53/80)

## ENDPOINTS SECUNDÁRIOS E EXPLORATÓRIOS

Duração média da resposta = 7.8 meses;
Taxa de resposta geral (PI) = 72.5%;
Qualidade de Vida aumentou;
EQ-5Q: aumento da média em 18 pontos comparando baseline e semana 33 (62 vs. 80)
EORTC QLQ-C30: melhora nos scores sintomas, funcional e saúde global comparado a baseline.

**Table 3**

Adverse events*

| Event | All-cause adverse events (N=80) | | | Drug-related adverse events (N=80) | | |
|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 1–2 | Grade 3 | Grade 4 |
| Total patients with an adverse event | 46 (58%) | 26 (33%) | 6 (8%) | 51 (64%) | 17 (21%) | 3 (4%) |
| Fatigue | 29 (36%) | 0 | 0 | 20 (25%) | 0 | 0 |
| Pyrexia | 24 (30%) | 1 (1%) | 0 | 11 (14%) | 0 | 0 |
| Diarrhoea | 21 (26%) | 0 | 0 | 8 (10%) | 0 | 0 |
| Nausea | 19 (24%) | 0 | 0 | 10 (13%) | 0 | 0 |
| Upper respiratory tract infection | 18 (23%) | 1 (1%) | 0 | 0 | 0 | 0 |
| Pruritus | 18 (23%) | 0 | 0 | 8 (10%) | 0 | 0 |
| Rash | 15 (19%) | 2 (3%) | 0 | 12 (15%) | 1 (1%) | 0 |
| Arthralgia | 17 (21%) | 0 | 0 | 11 (14%) | 0 | 0 |
| Infusion-related reaction | 16 (20%) | 0 | 0 | 16 (20%) | 0 | 0 |
| Nasopharyngitis | 16 (20%) | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 12 (15%) | 1 (1%) | 0 | 6 (8%) | 0 | 0 |
| Constipation | 12 (15%) | 0 | 0 | 5 (6%) | 0 | 0 |
| Dyspnoea | 8 (10%) | 2 (3%) | 0 | 2 (3%) | 1 (1%) | 0 |
| Peripheral neuropathy | 10 (13%) | 0 | 0 | 3 (4%) | 0 | 0 |
| Abdominal pain | 7 (9%) | 2 (3%) | 0 | 4 (5%) | 2 (3%) | 0 |
| Myalgia | 9 (11%) | 0 | 0 | 6 (8%) | 0 | 0 |
| Bronchopneumonia | 9 (11%) | 0 | 0 | 0 | 0 | 0 |
| Back pain | 8 (10%) | 1 (1%) | 0 | 2 (3%) | 0 | 0 |
| Headache | 8 (10%) | 1 (1%) | 0 | 2 (3%) | 0 | 0 |
| Anaemia | 6 (8%) | 2 (3%) | 0 | 2 (3%) | 0 | 0 |
| Hyperglycaemia | 7 (9%) | 1 (1%) | 0 | 4 (5%) | 0 | 0 |
| Increased lipase | 3 (4%) | 3 (4%) | 2 (3%) | 2 (3%) | 2 (3%) | 2 (3%) |
| Neutropenia | 3 (4%) | 4 (5%) | 0 | 3 (4%) | 4 (5%) | 0 |
| Decreased appetite | 6 (8%) | 1 (1%) | 0 | 2 (3%) | 0 | 0 |
| Increased amylase | 3 (4%) | 2 (3%) | 0 | 2 (3%) | 2 (3%) | 0 |
| Increased aspartate aminotransferase | 3 (4%) | 2 (3%) | 0 | 2 (3%) | 2 (3%) | 0 |

# ENDPOINTS SECUNDÁRIOS E EXPLORATÓRIOS

- Eventos adversos mais relatados ( ≥ 15%) foram fadiga, rash e reação relacionada à infusão.
  - Classificação 3 / 4: neutropenia e aumento no nível de lipase (n=4) mais incidentes

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis *[see Warnings and Precautions (5.1)]*
- Immune-Mediated Colitis *[see Warnings and Precautions (5.2)]*
- Immune-Mediated Hepatitis *[see Warnings and Precautions (5.3)]*
- Immune-Mediated Endocrinopathies *[see Warnings and Precautions (5.4)]*
- Immune-Mediated Nephritis and Renal Dysfunction *[see Warnings and Precautions (5.5)]*
- Immune-Mediated Skin Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Immune-Mediated Encephalitis *[see Warnings and Precautions (5.7)]*
- Other Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.8)]*
- Infusion Reactions *[see Warnings and Precautions (5.9)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.10)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to OPDIVO as a single agent in 1994 patients enrolled in the CHECKMATE-037, CHECKMATE-017, CHECKMATE-057, CHECKMATE-066, CHECKMATE-025, CHECKMATE-067, CHECKMATE-205, CHECKMATE-039 trials or a single-arm trial in NSCLC (n=117); OPDIVO 1 mg/kg with ipilimumab 3 mg/kg in patients enrolled in CHECKMATE-067 (n=313) or another randomized study (n=94); and OPDIVO 3 mg/kg administered with ipilimumab 1 mg/kg in 666 patients enrolled in CHECKMATE-214 or CHECKMATE-142.

The data described below reflect exposure to OPDIVO as a single agent in 13 clinical trials (n=3063), OPDIVO with 3 mg/kg ipilimumab in 1 clinical trial (n=313), and OPDIVO with 1 mg/kg ipilimumab in 2 clinical trials (n=666) *[see Clinical Studies (14)]*.

# Discussão

**Limitação:**

-Braço-único.

**Resultados**

-Perfil de Segurança aceitável;

-Condizente com os achados da Fase I;

-⅔ dos pacientes refratários responderam ao Nivolumab;

-Taxa de resposta de 66%.

# Referências bibliográficas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