# VII SIMPÓSIO INTERNACIONAL DE Melanoma

HOTEL PULLMAN VILA OLÍMPIA

29 E 30 DE NOVEMBRO 2019

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# O que fazer após a falha de anti-PD-1?

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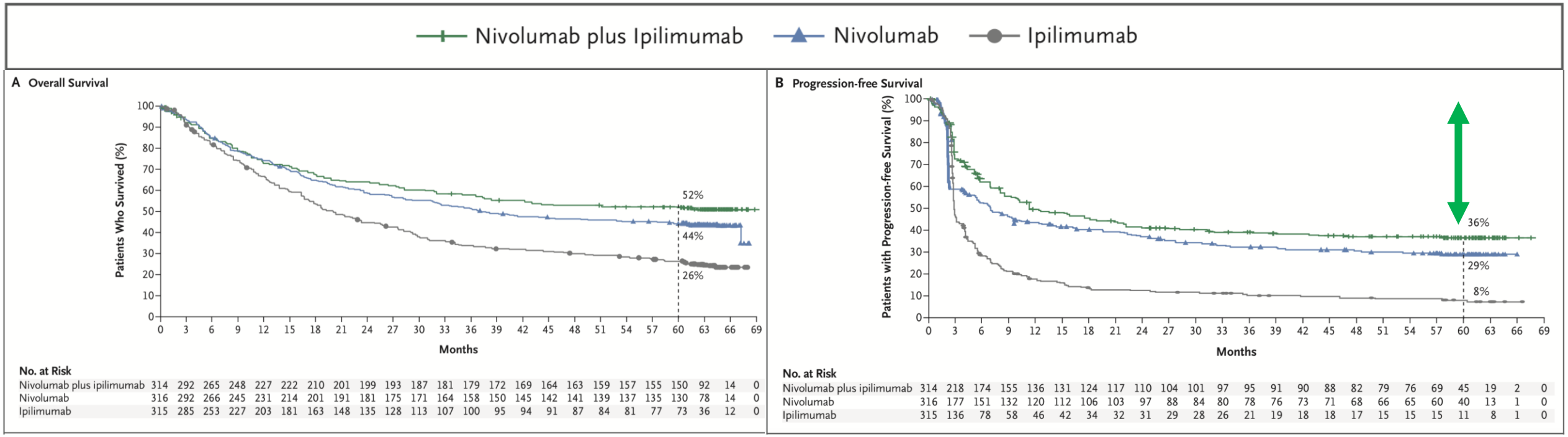
*Hospital Israelita Albert Einstein*

# Outline

- Introdução
- Opções de tratamento: contexto brasileiro
- Opções de tratamento: contexto americano
- Opções de tratamento: experimentais
- Conclusões

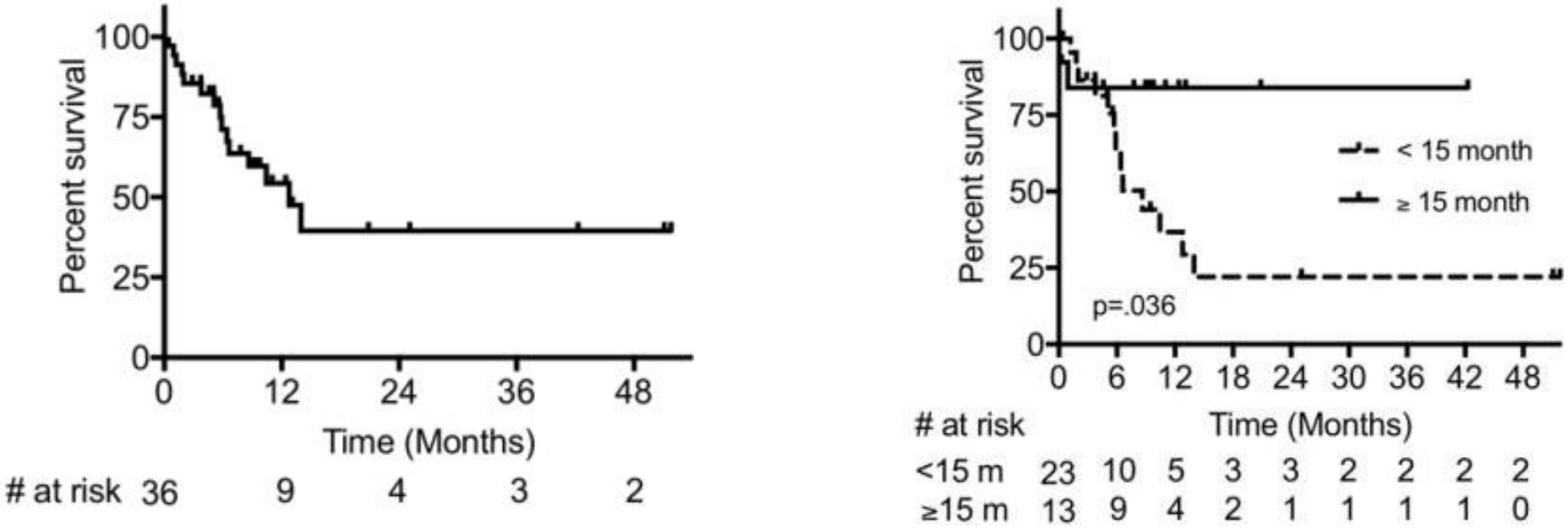
# Introdução



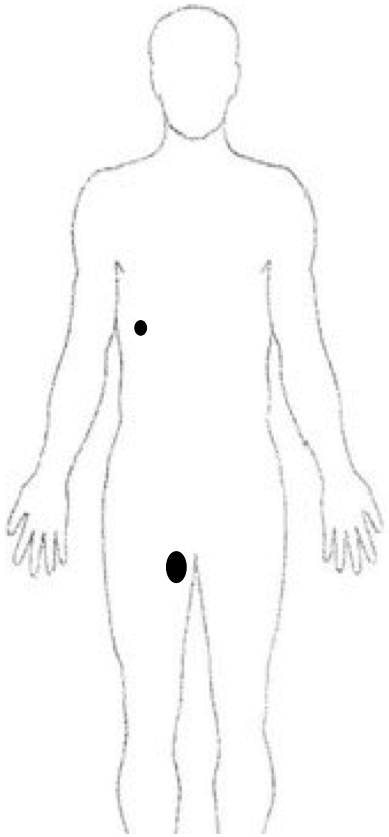

Larkin et al. NEJM, 2019

# Introdução

Post-progression survival




Wang et al. Cancer Immunol Res, 2017



AntiPD1 → se PD → BRAF Status

BRAF Status → MUTADO → iBRAF + iMEK

BRAF Status → SELVAGEM → ?

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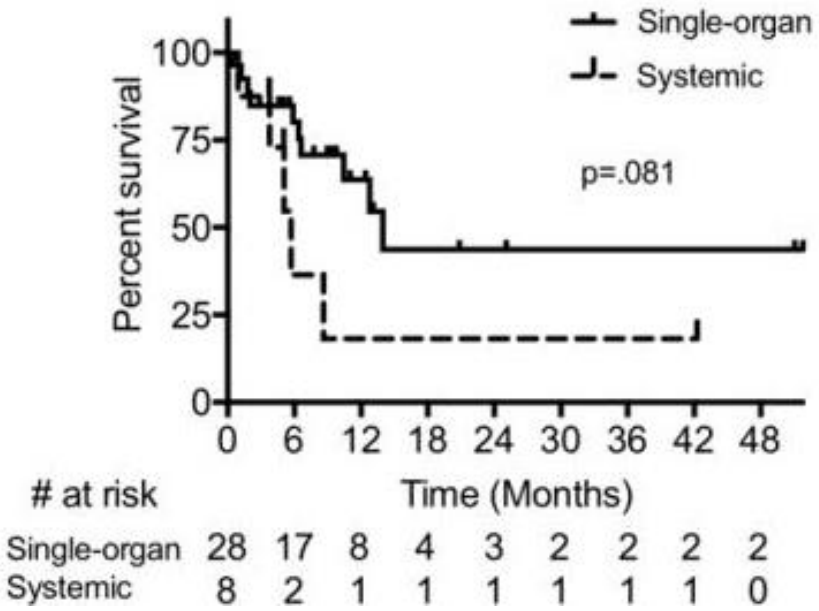
# Oligoprogressão




- Progressão isolada

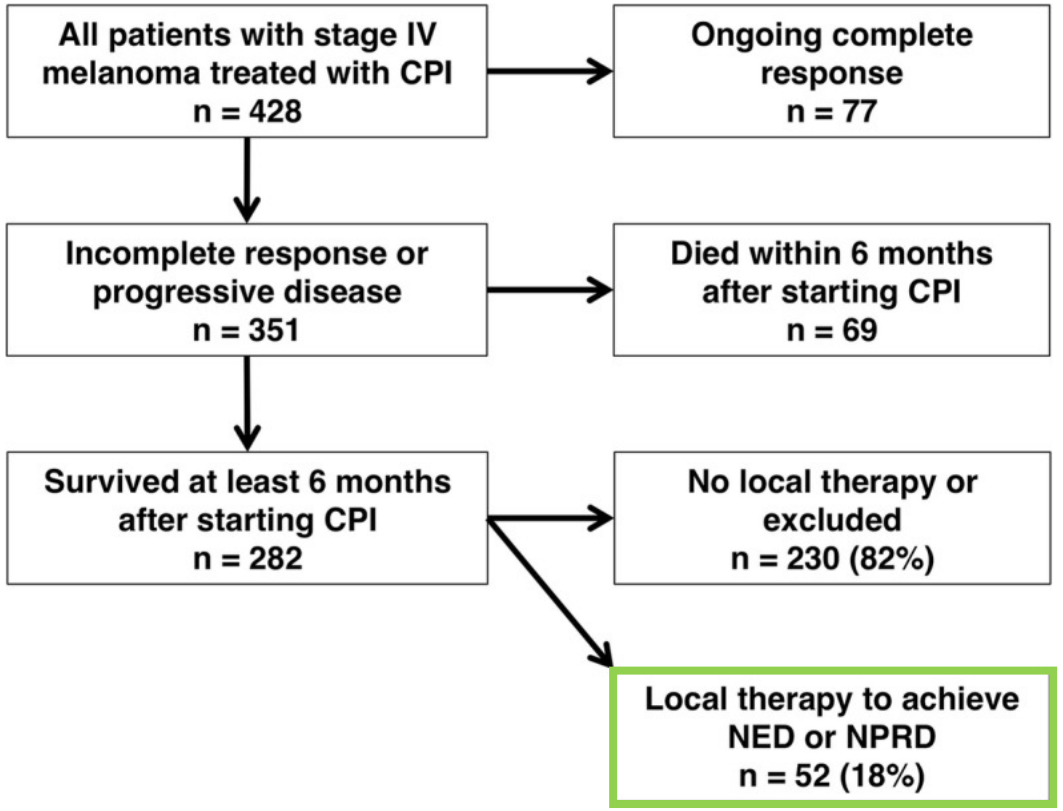
PPS: 14m

- Progressão sistêmica

PPS: 5,7m

Wang et al. Cancer Immunol Res, 2017

# Oligoprogressão




- Lesões pré-existentes tratadas:

3y-PFS 70%

5y-DSS: 93%

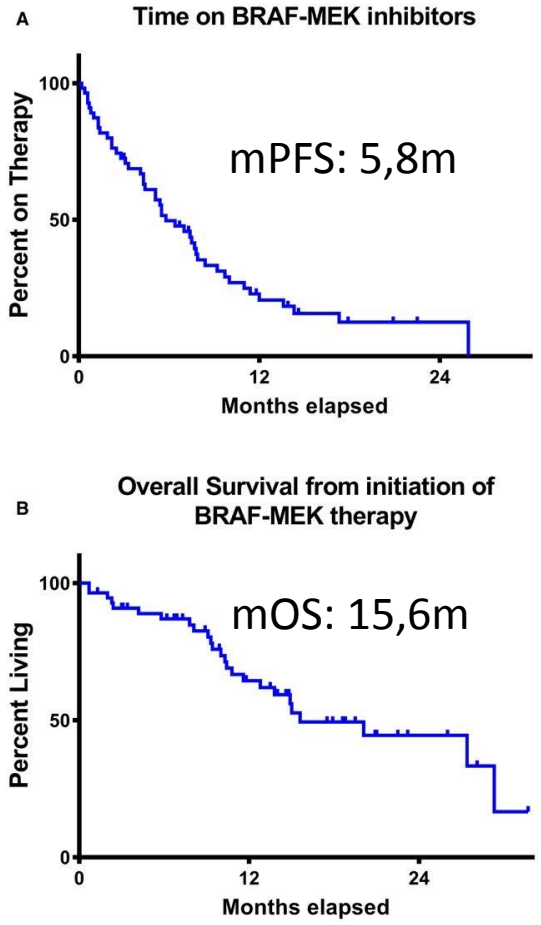
- Lesões novas tratadas:

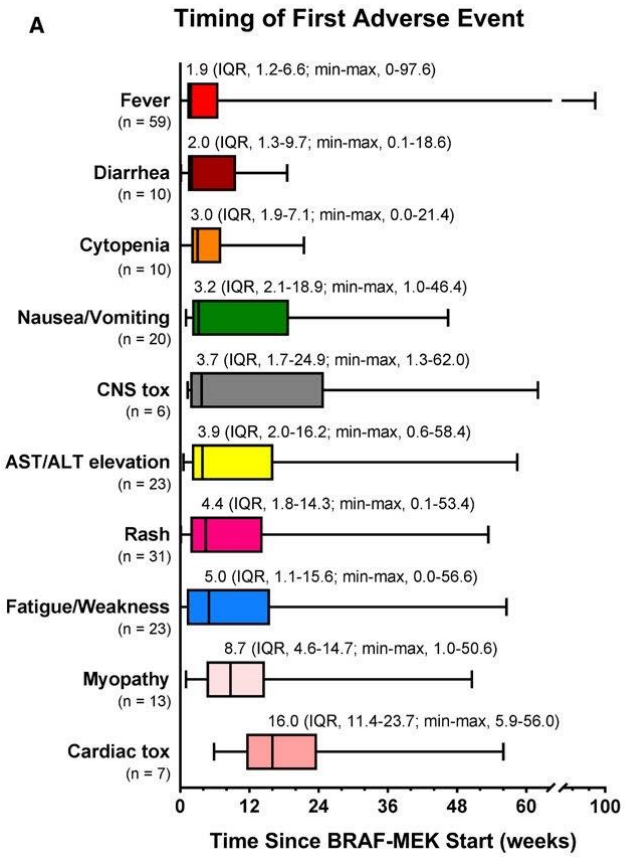
3y-PFS 6%

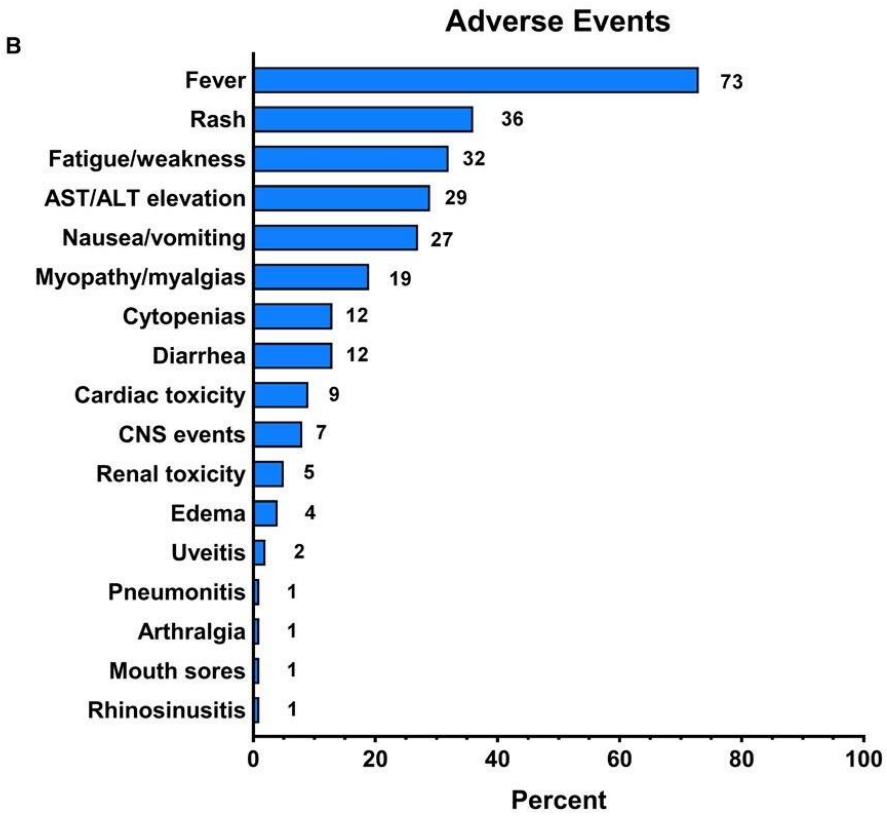
5y-DSS 31%

Klemen et al. J Immunother Cancer, 2019

# Progressão sistêmica: BRAF/MEK

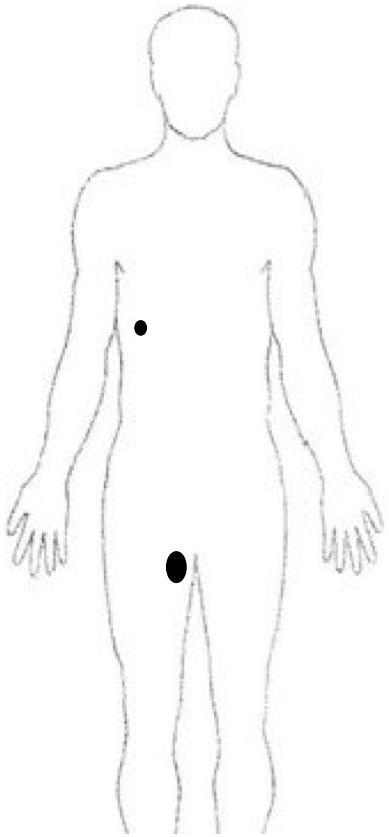



Saab et al. Cancer, 2018

# Progressão sistêmica: Ipilimumab



AntiPD1

PD-1 + Ipi

→ se PD → +

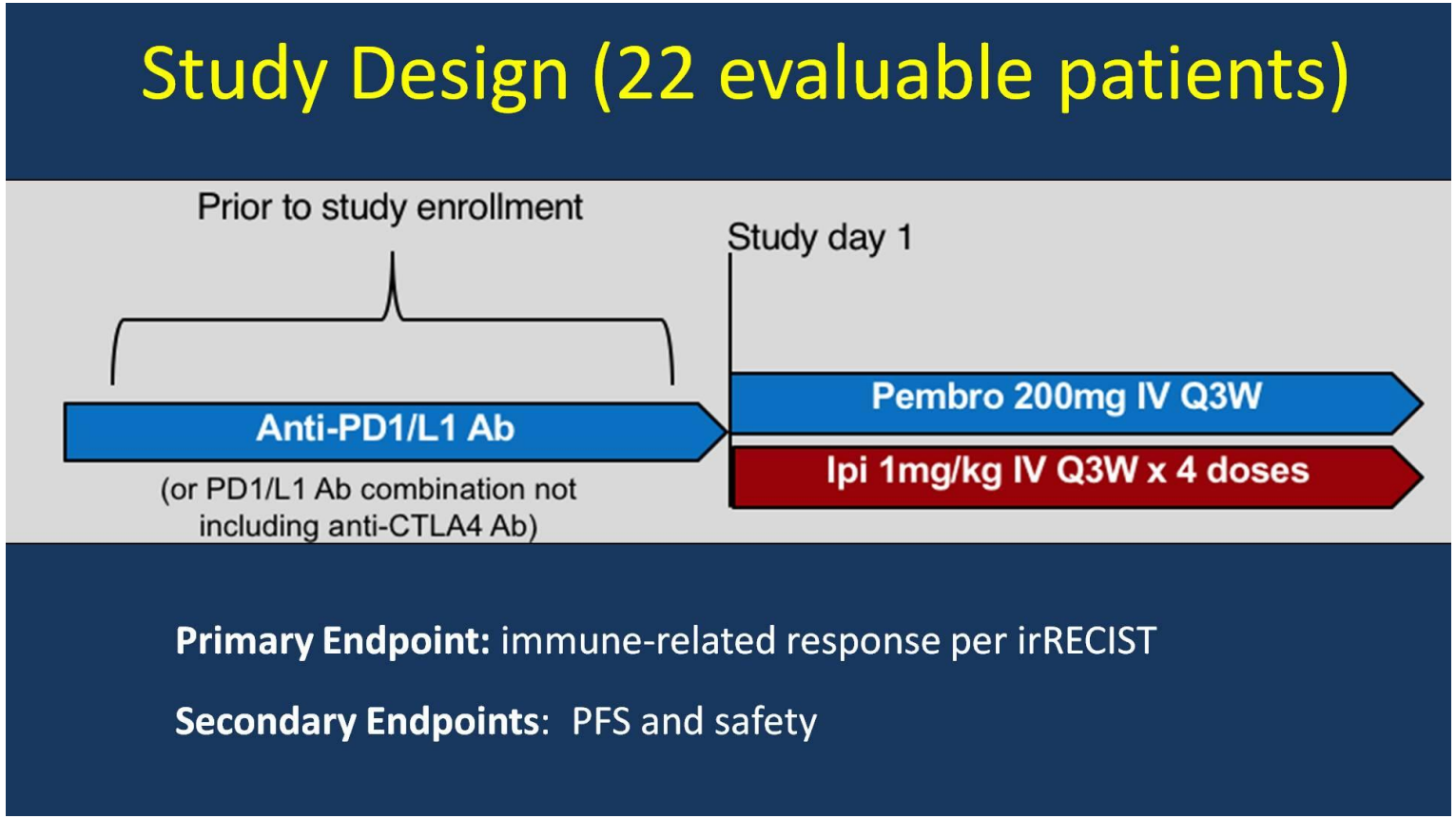
ORR: 21%

Zimmer et al. Eur J Cancer, 2017

ORR: 10-15%

Zimmer et al. Eur J Cancer, 2017
Long et al. SMR 2016
Bowyer et al. Br J Cancer, 2016

# Progressão sistêmica: Ipilimumab



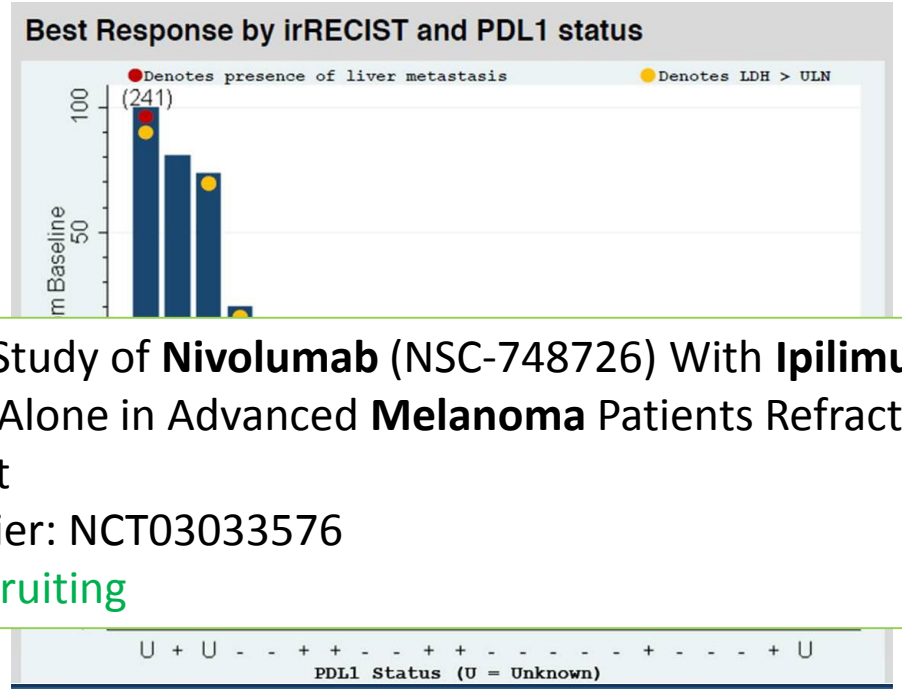

Olson et al. ASCO Annual Meeting, 2018

# Progressão sistêmica - Ipilimumab

- Taxa de resposta:

45% (10/22)

- CR: 13,6%



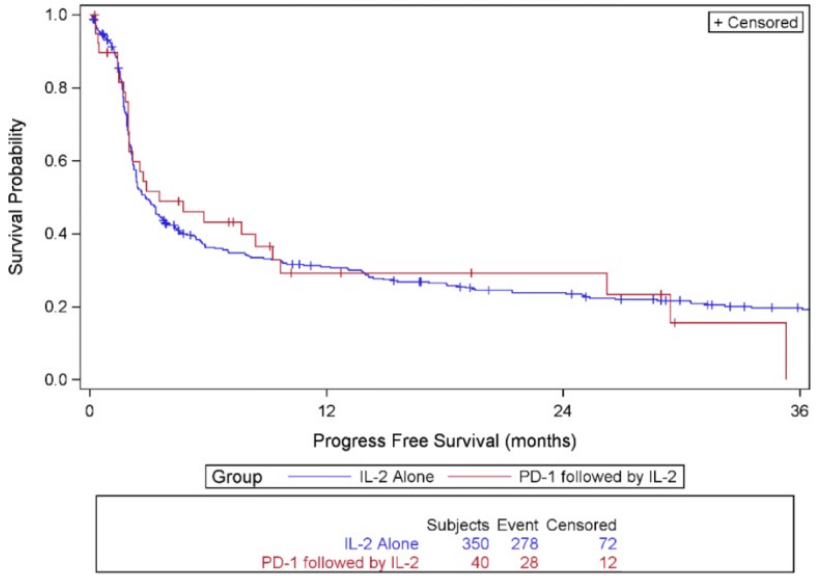

| Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| 10 (32.3%) | 10 (32.3%) | 6 (19.4%) | 5 (16.1%) | 0 (0%) |

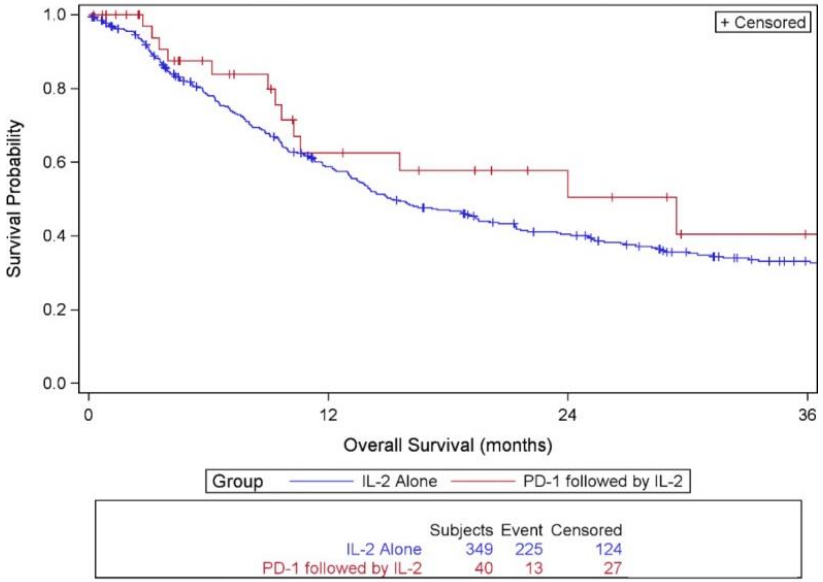
A **Phase** II Randomized Study of **Nivolumab** (NSC-748726) With **Ipilimumab** (NSC-732442) or **Ipilimumab** Alone in Advanced **Melanoma** Patients Refractory to an Anti-PD1 or Anti-PD-L1 Agent
ClinicalTrials.gov Identifier: NCT03033576
Recruitment Status: Recruiting

Olson et al. ASCO Annual Meeting, 2018

# Progressão sistêmica: IL-2 em altas doses

- 40 pacientes tratados após anti-PD(L)1
- Taxa de resposta: 22,5% (4 CRs/5 PRs)
- Toxicidade semelhante ao perfil da droga




Buchbinder et al. J Immunother Cancer, 2019

# Progressão sistêmica: IL-2 intralesional

**Table 1** Patients' characteristics

| P | A | S | Cancer stage (AJCC 2017)/TNM | ECOG | Best response to | | | | AEs | IL-2 therapy |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | PD-1i mono-therapy | PD-1i + IL-2 | | | | |
| | | | | | | Cutaneous | | Visceral | | |
| | | | | | | Injected | Non-injected | | | |
| 1 | 69 | F | IV/T3a N1c M1c (0) | 0 | PD | CR | CR | NA[a] | Chills, aching limbs | Terminated[c] |
| 2 | 70 | M | IV/T4a N3c M1c (1) | 0 | PD | CR | CR | CR | None | Terminated[c] |
| 3 | 75 | M | IIID/T3b N3c M0 (0) | 1 | PD | PR | PD | NA[b] | Chills, eczema | Terminated[d] |
| 4 | 60 | F | IV/T3b N1c M1a (0) | 0 | SD | CR | CR | CR | PNP, neutropenia, muscle cramps | Terminated[c] |
| 5 | 65 | M | IV/T4b N3b M1c (0) | 0 | PD | CR | CR | PD | None | Terminated[c] |
| 6 | 52 | F | IV/T4b N2c M1c (1) | 1 | PD | PR | PR | PR | Nausea, erysipelas | Ongoing[e] |
| 7 | 61 | M | IIIB/T2a N1c M0 (0) | 0 | PD | PR | PR | NA[b] | Fever, asthma | Ongoing[e] |
| 8 | 66 | M | IV/T3b N3c M1c (0) | 0 | PD | PR | PD | PD | Fever, chills, vomiting | Terminated[d] |
| 9 | 85 | F | IV/T4b N1c M1c (0) | 0 | PD | CR | CR | PR | Fever | Terminated[c] |

*P* patient number, *A* age, *S* sex, *LDH* lactate dehydrogenase, (*0*) normal (LDH), (*1*) elevated (LDH), *AJCC 2017* American Joint Committee on Cancer, Melanoma of the Skin Staging, 8th edition, *ECOG* Eastern Cooperative Oncology Group Performance Status, *CR* complete response, *PR* partial response, *PD* progressive disease, *SD* stable disease, *NA* not applicable, *AEs* adverse events, *PNP* peripheral neuropathy, *IL-2* interleukin-2, *PD-1i* PD-1 inhibitor

[a]Status post single successfully irradiated bone metastasis

[b]No distant metastases present

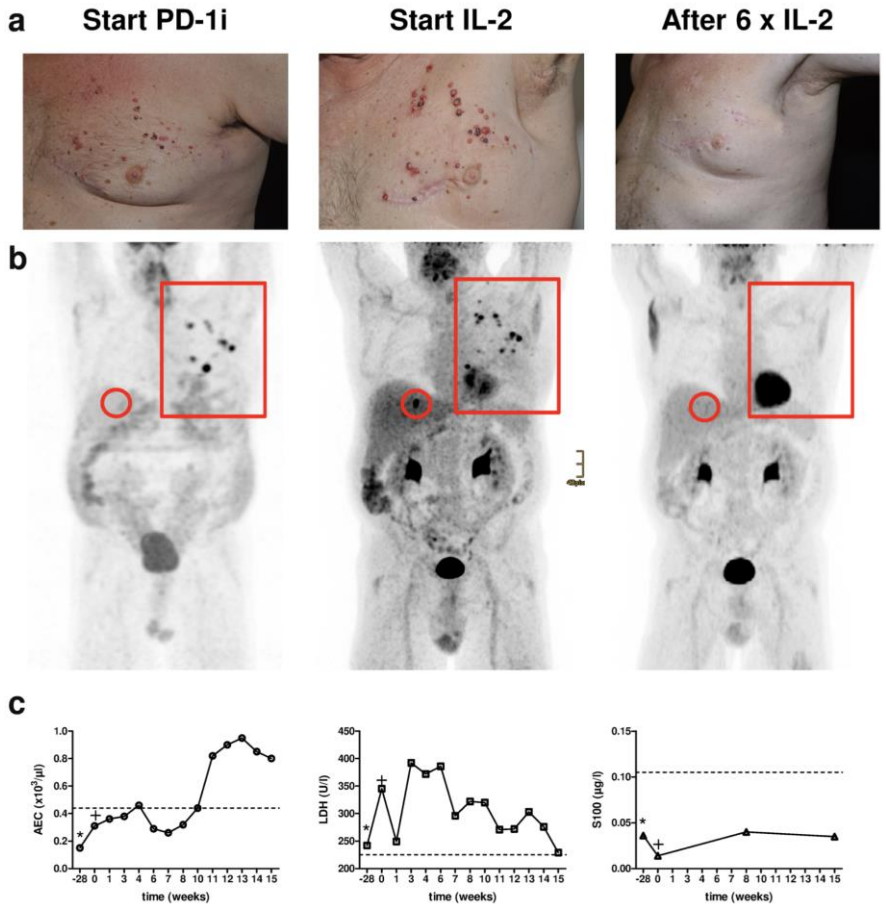
[c]Terminated due to CR of cutaneous metastases

[d]Terminated due to PD of cutaneous and/or visceral metastases

[e]Status as of April 2019

Rafei-Shamsabadi et al. Cancer Immunol Immunother, 2019

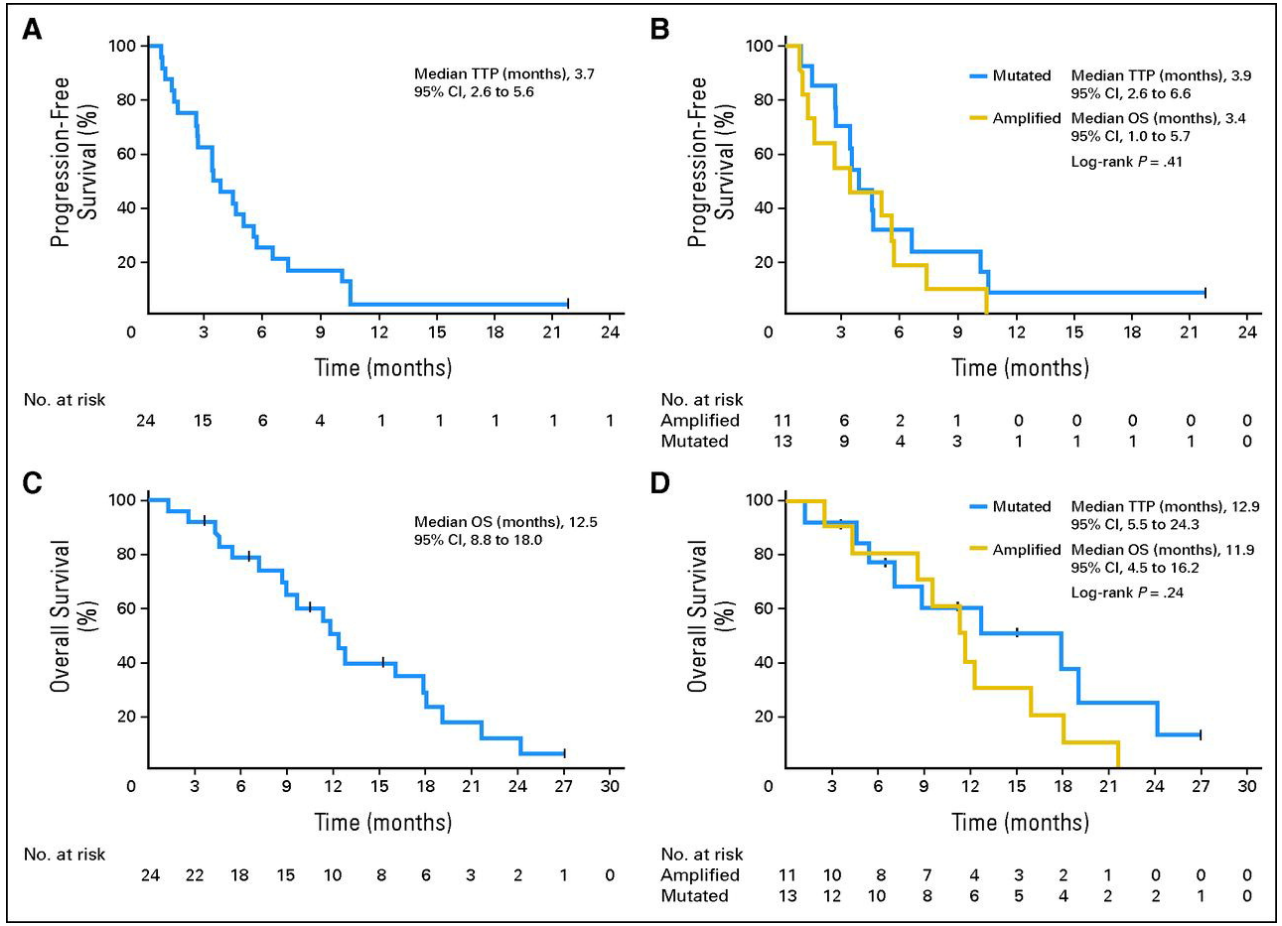
# Progressão sistêmica: IL-2 intralesional




Rafei-Shamsabadi et al. Cancer Immunol Immunother, 2019

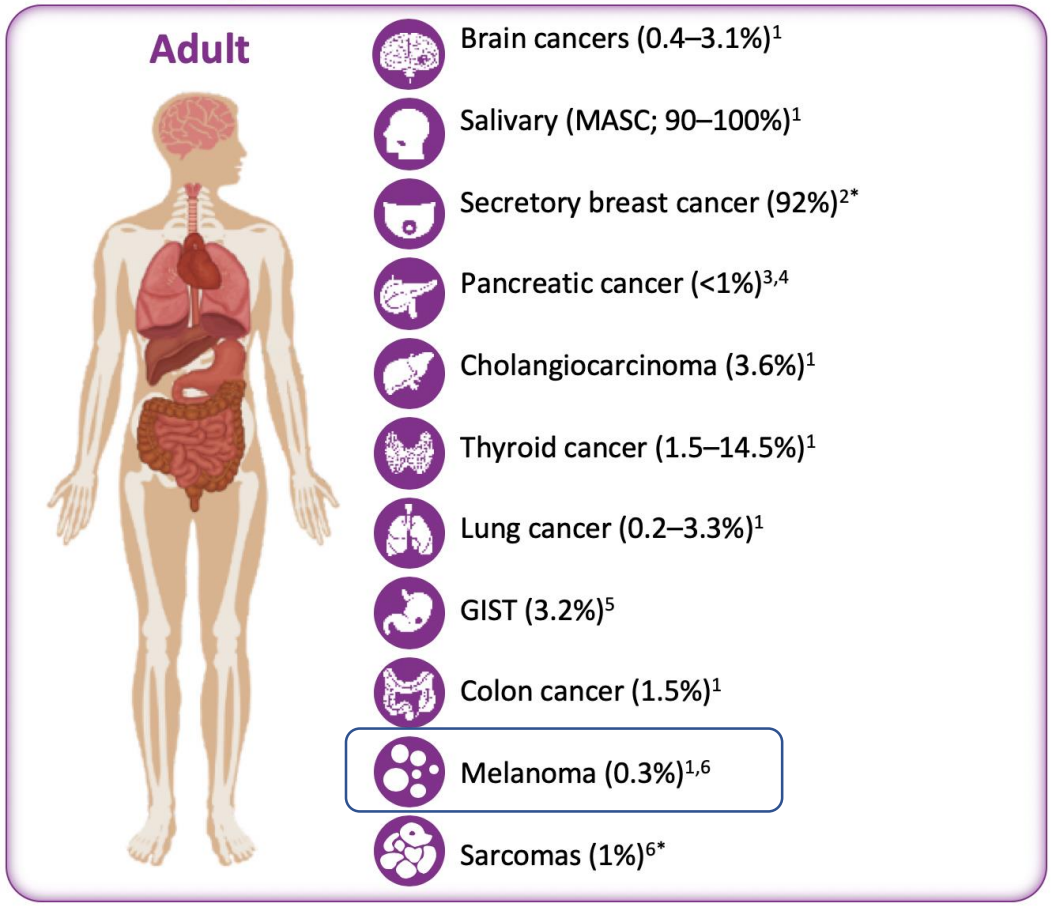
# Progressão sistêmica: KIT e imatinibe

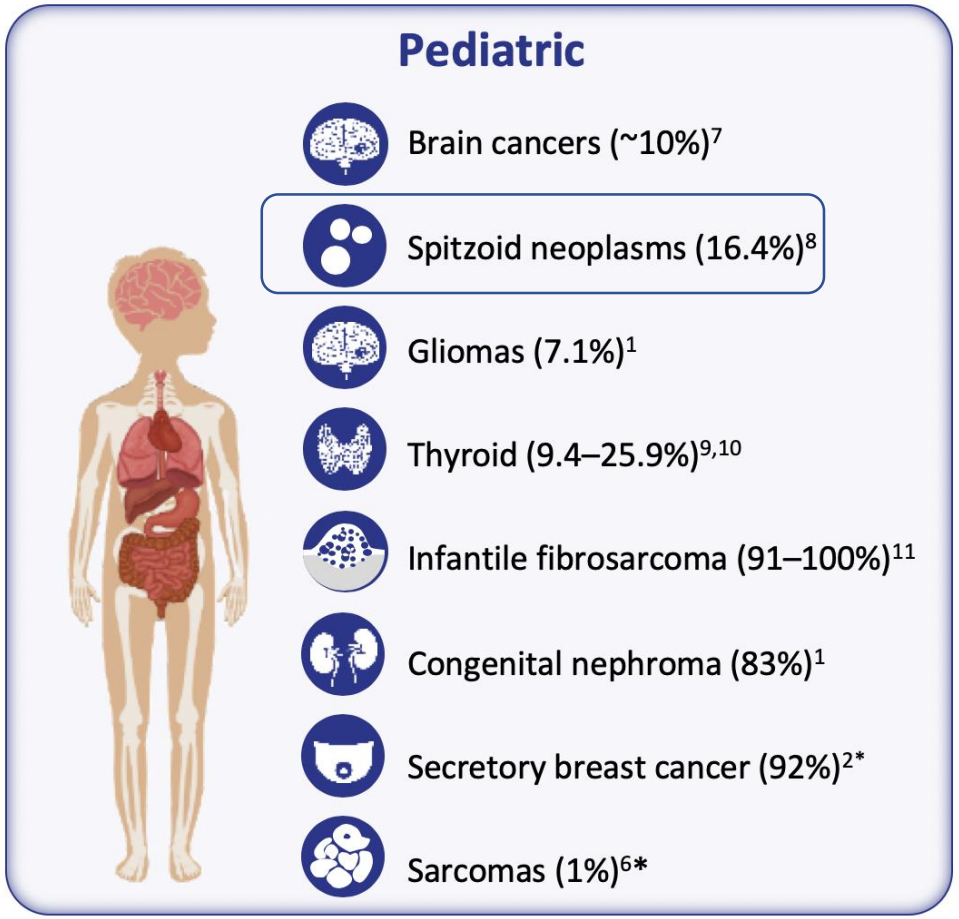
- Prevalência: cerca de 10% de melanomas acrais/mucosa
- 25-50% de taxa de resposta em KIT mutado
- 0% de resposta em KIT amplificado apenas




Hodi et al. J Clin Oncol, 2013; Carvajal et al. JAMA, 2011

# Progressão sistêmica: latrotrectinibe



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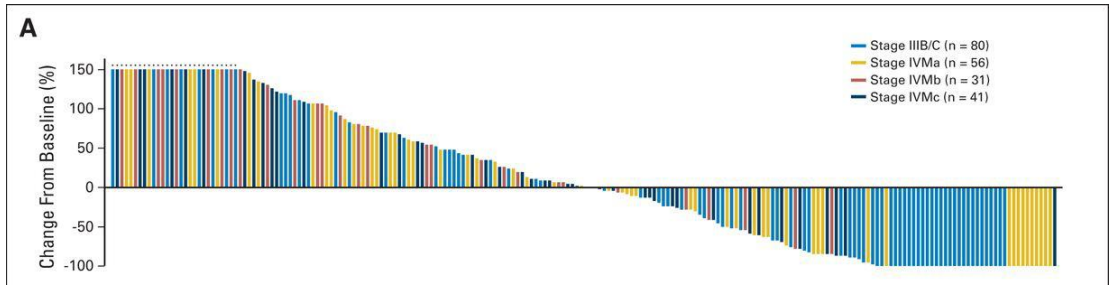
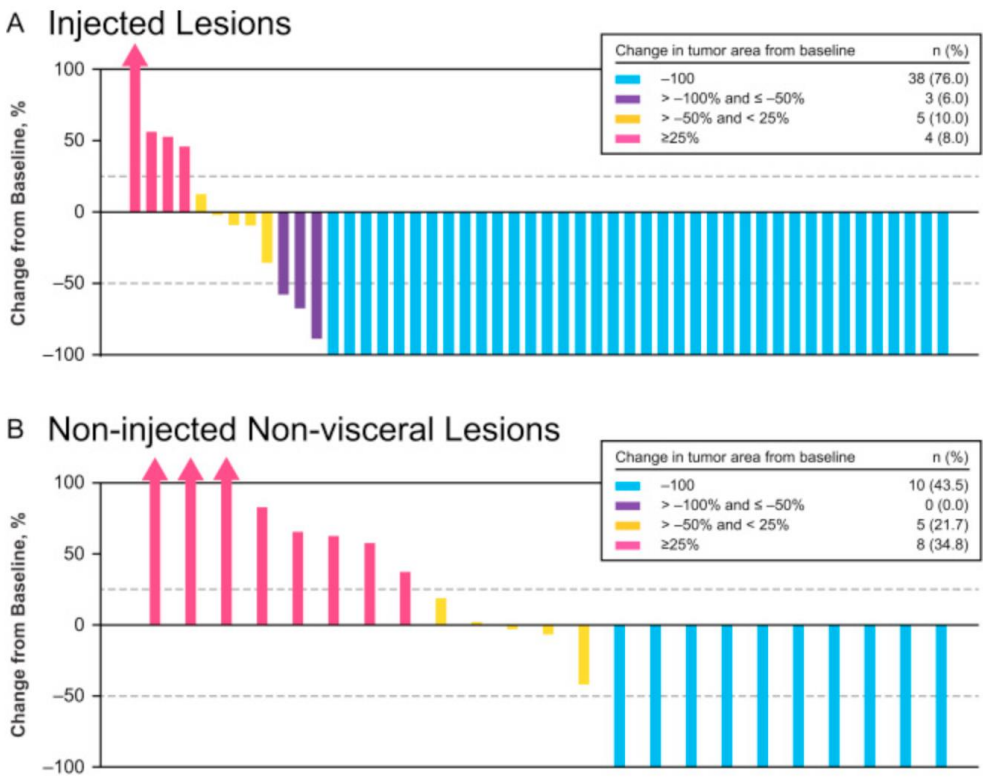
# T-VEC

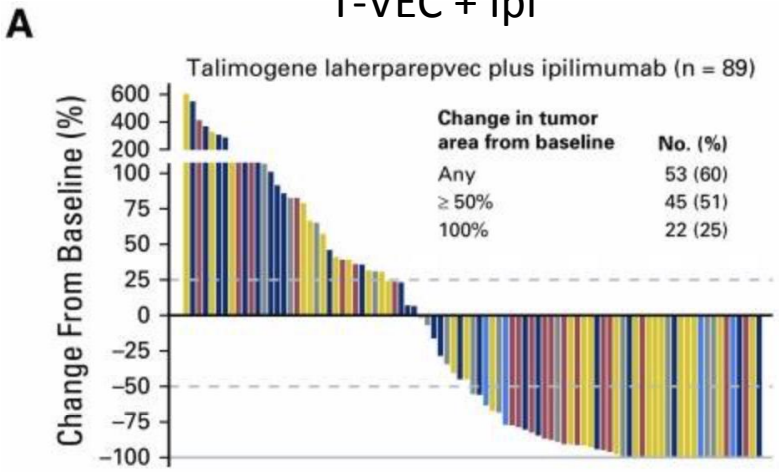
T-VEC isolado




T-VEC + Pembro




T-VEC + Ipi




Andtbacka et al. J Clin Oncol, 2015; Ribas et al. Cell, 2017; Chesney et al. J Clin Oncol, 2018

# T-VEC

**Table 3.** Talimogene Laherparepvec Treatment Details

| TVEC therapy | n | % |
|---|---|---|
| Reason for stopping talimogene laherparepvec | | |
| No evidence of disease/complete remission | 29 | 37 |
| Partial response | 6 | 8 |
| Stable disease | 15 | 19 |
| Systemic progression | 24 | 30 |
| Other | 5 | 6 |
| Local response | | |
| Complete response | 31 | 39 |
| Partial response | 14 | 18 |
| Stable disease | 20 | 25 |
| Local progression | 14 | 18 |

Louie et al. J Am Coll Surg, 2018

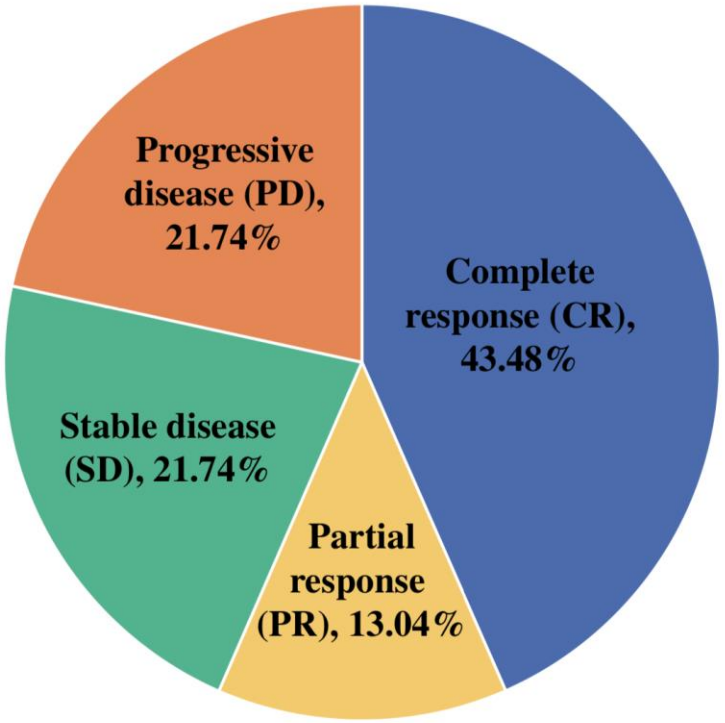
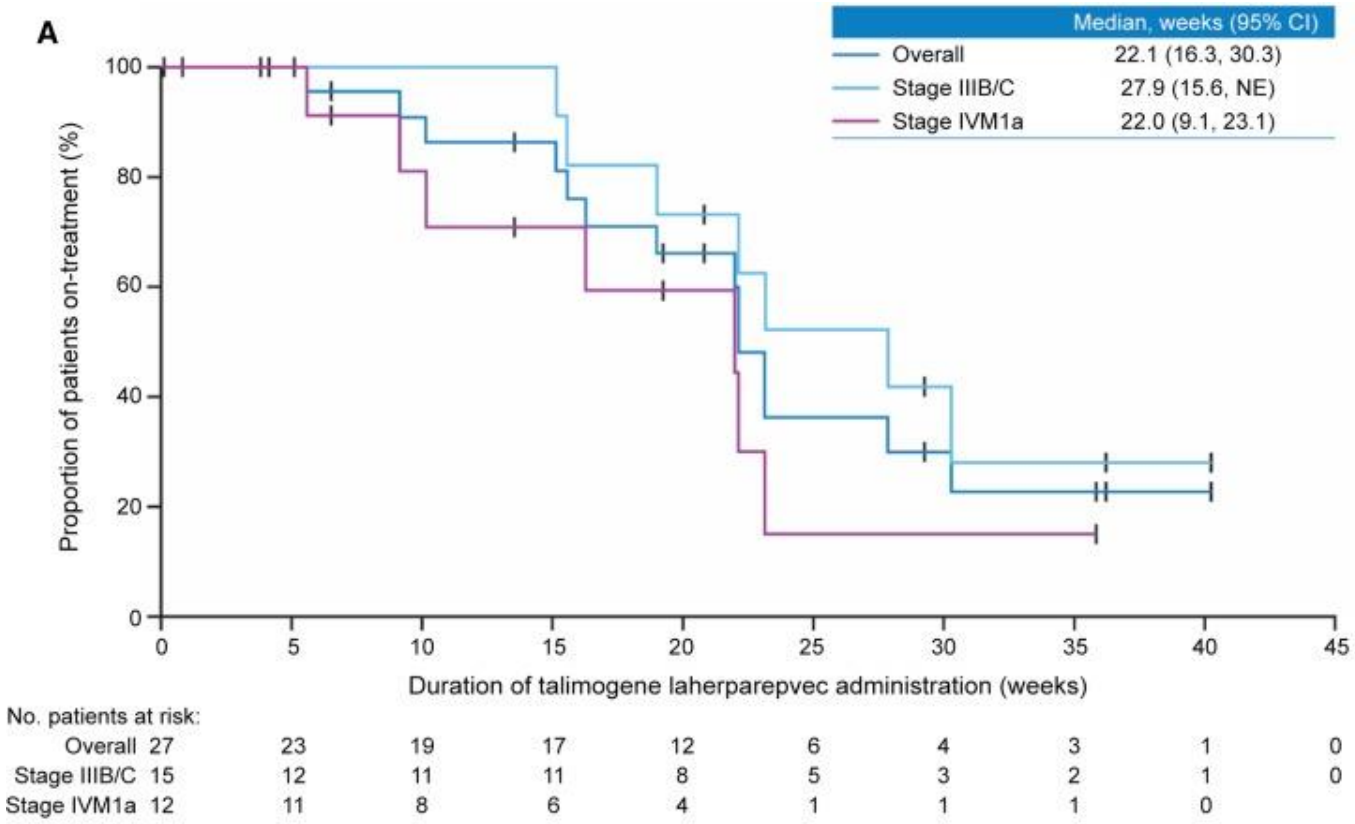



**FIG. 1** Response to therapy

Perez et al. Ann Surg Oncol, 2018

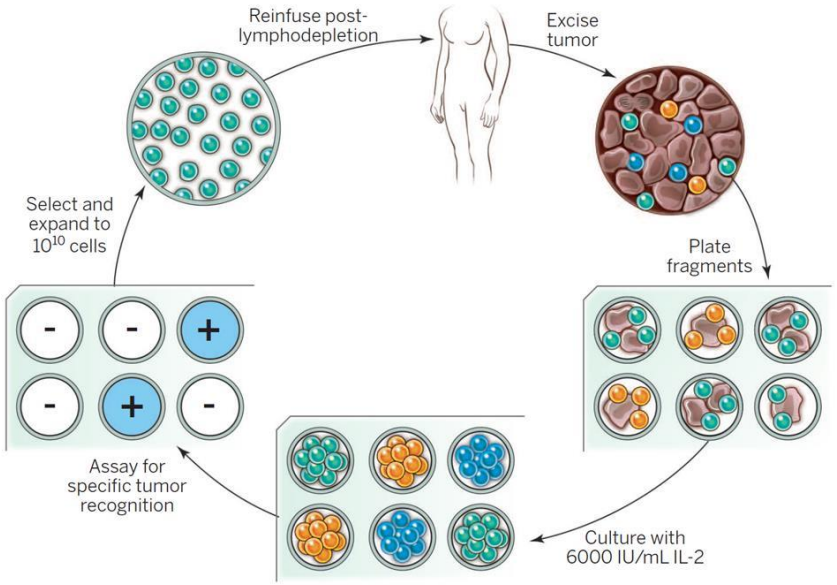
# T-VEC

- Stage III > IV

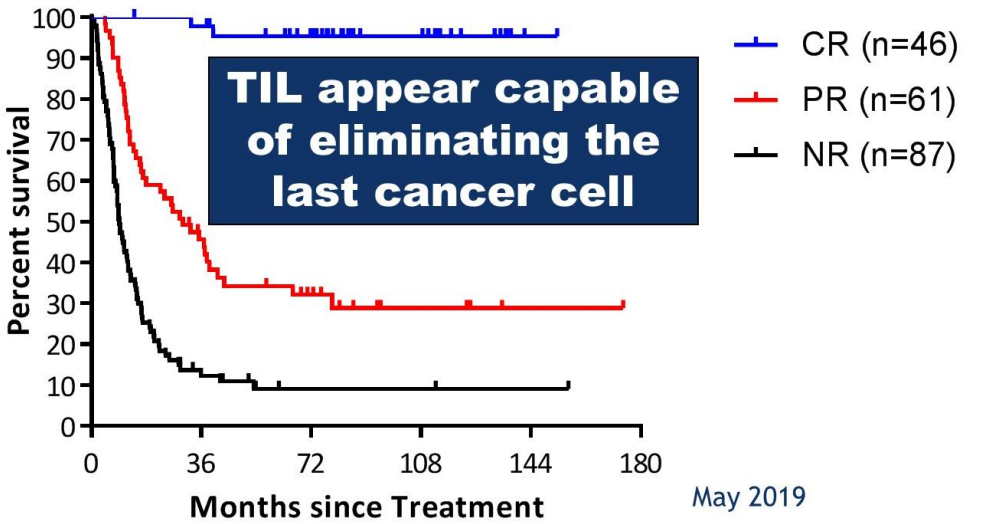



Mohr et al. Adv Ther, 2019

# Tumor-infiltrating lymphocytes




*Rosenberg, S. Science, 2015*



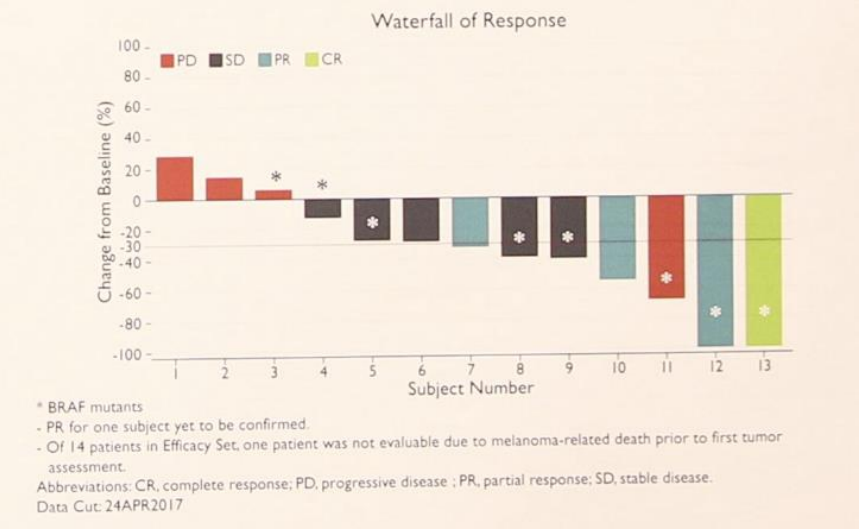

*Stephanie Golff, ASCO 2019*

# Tumor-infiltrating lymphocytes

- Laboratório central para protocolo multicêntrico:
- Moffitt; Yale; James Graham; Earle Chiles
- Pacientes refratários a anti-PD1

**Table 3. Efficacy**

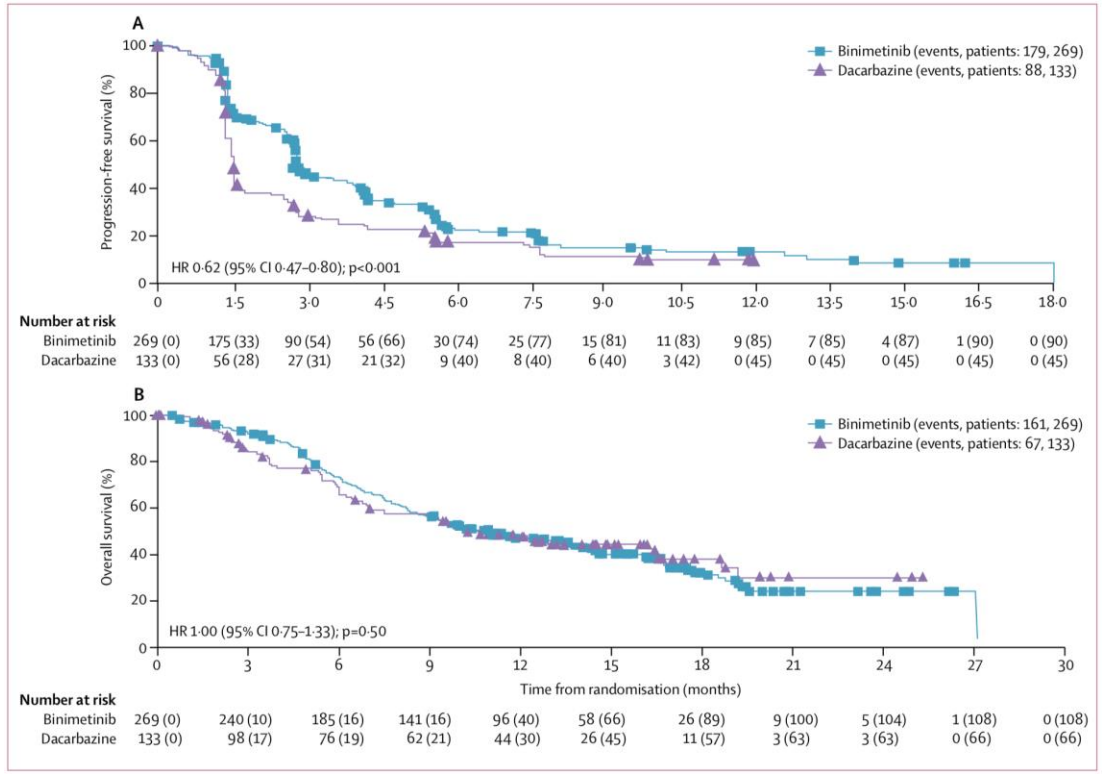
| RESPONSE | PATIENTS, N=14 n (%) |
|---|---|
| Objective Response Rate | 4 (29%) |
| Disease Control Rate | 9 (64%) |
| Complete Response | 1 (7%) |
| Partial Response | 3 (21%) |
| Stable Disease | 5 (36%) |
| Progressive Disease | 4 (29%) |
| Non-Evaluable* | 1 (7%) |




Sarnaik et al. ASCO Annual Meeting, 2017

# NRAS mutado: binimetinibe

| | Binimetinib (n=269) | Dacarbazine (n=133) |
|---|---|---|
| Best overall response | | |
| Complete response* | 4 (1%) | 0 |
| Partial response | 37 (14%) | 9 (7%) |
| Stable disease | 109 (41%) | 23 (17%) |
| Progressive disease | 72 (27%) | 59 (44%) |
| Non-complete response or non-progressive disease | 7 (3%) | 1 (1%) |
| Unknown† | 40 (15%) | 41 (31%) |
| Overall response‡ | 41 (15%; 11·2–20·1)§ | 9 (7%; 3·1–12·5) |
| Disease control¶ | 157 (58%; 52·2–64·3)** | 33 (25%; 17·7–33·0) |




Dummer et al. Lancet Oncol, 2017

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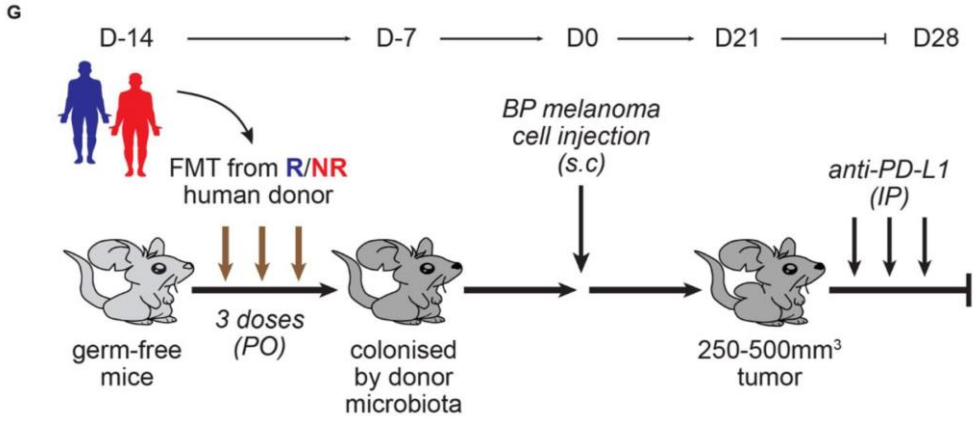
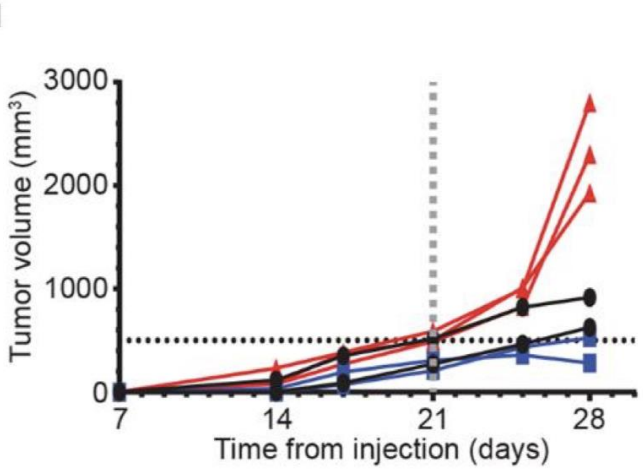
# Tratamentos experimentais: microbioma

Microbioma

- Diversidade de microbioma associada com melhores desfechos
- FMT em modelo animal + anti-PD-L1 bem sucedidos
- Estudo fase 1: 2/3 pacientes com benefício clínico e radiológico

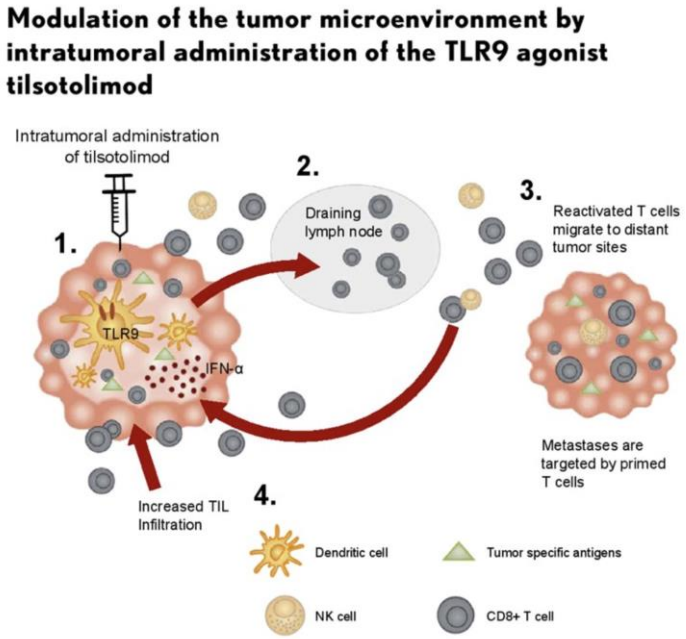


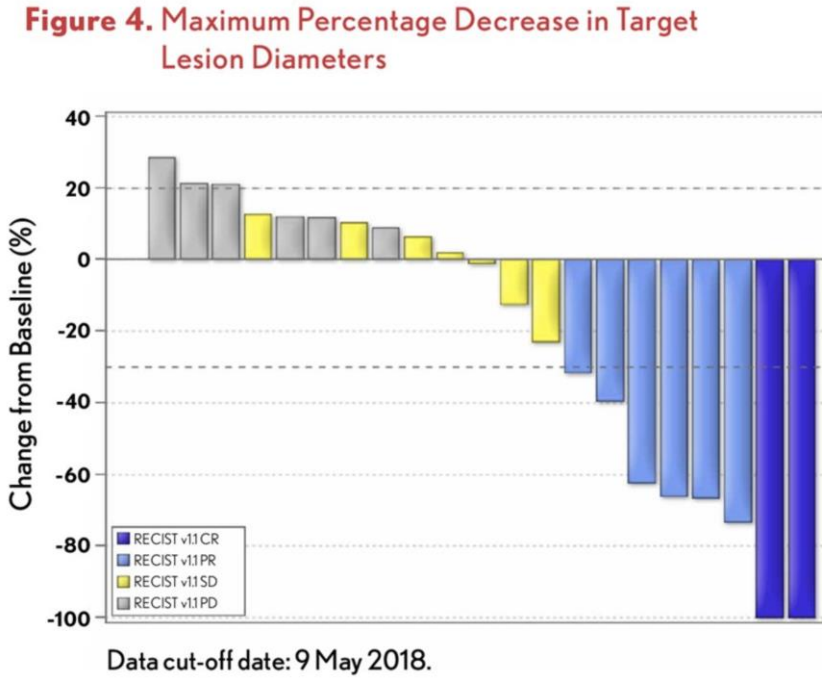




V. Gopalakrishnan, et al. *Science* 02 Nov 2017; Baruch et al. AACR, 2019

# Tratamentos experimentais: TLR9 agonist

- Terapia intra-lesional, estudo fase 1
- 38% ORR em combinação com IPI após falha de anti-PD-1




Diab et al. ASCO 2018

# Tratamentos experimentais: HDACi

- Estudo fase 2, entinostat + pembro

Após falha de anti-PD-1

- 6/34 respostas confirmadas (18%)
- Nenhum paciente havia respondido a anti-PD-1

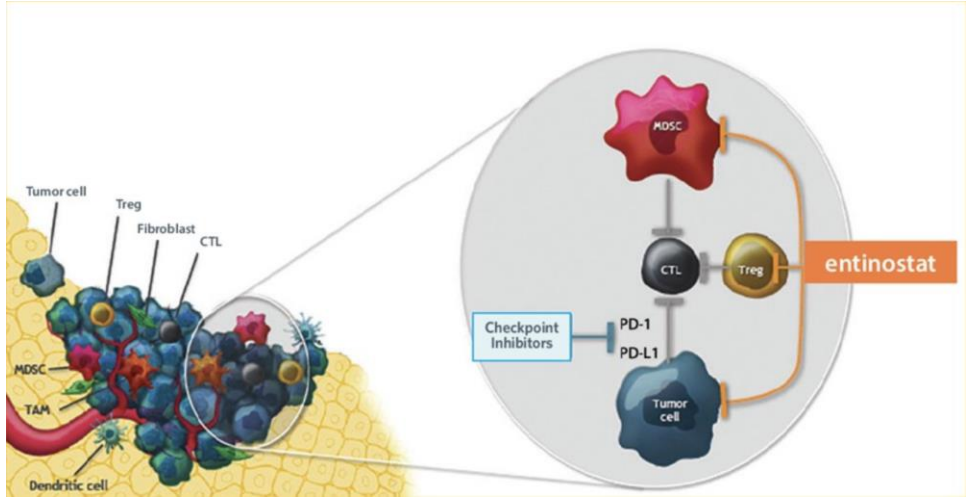



Figure 2. **Percentage Change in Tumor Size from Baseline (Sum of Diameters of Target Lesions).** Nine partial responses have been observed to date.

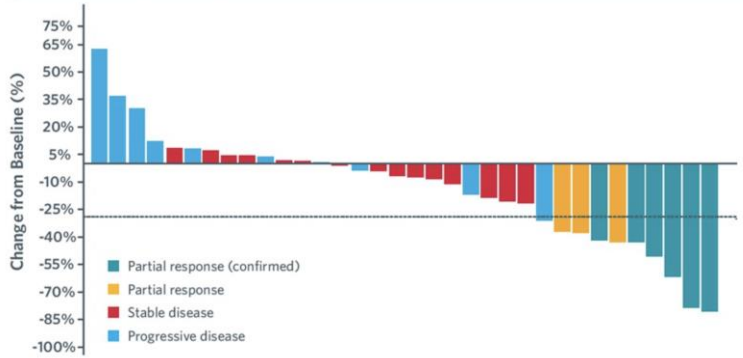
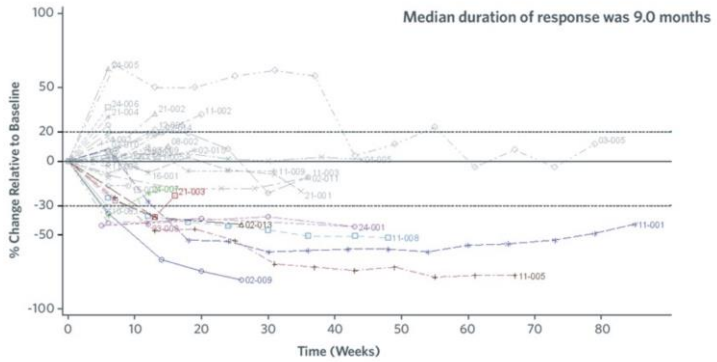


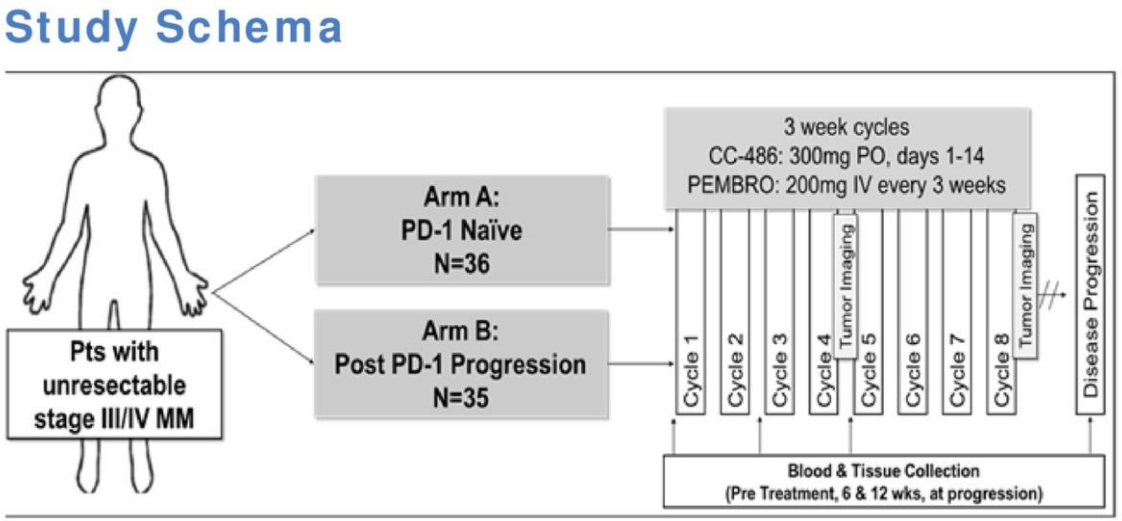

Figure 4. **Change in Tumor Size from Baseline Over Time.** Durable responses were observed.




Agarwala et al. ASCO 2019

# Tratamentos experimentais: hipometilantes

- Estudo fase 2: azacitadina + pembro




| Best Overall Response | Arm A (N=12) # (%) | Arm B (N=11) # (%) |
|---|---|---|
| | | |
| Complete response | 0 | 0 |
| Partial response | 5 (50%) | 0 |
| Stable disease | 0 | 2 (20%) |
| Progressive disease | 5 (50%) | 8 (80%) |
| Not evaluable | 2 | 1 |
| Overall response rate (CR+PR) | 5 (50%) | 0 |
| Clinical benefit rate (CR+PR+SD) | 5 (50%) | 2 (20%) |

Burton et al. ASCO 2019

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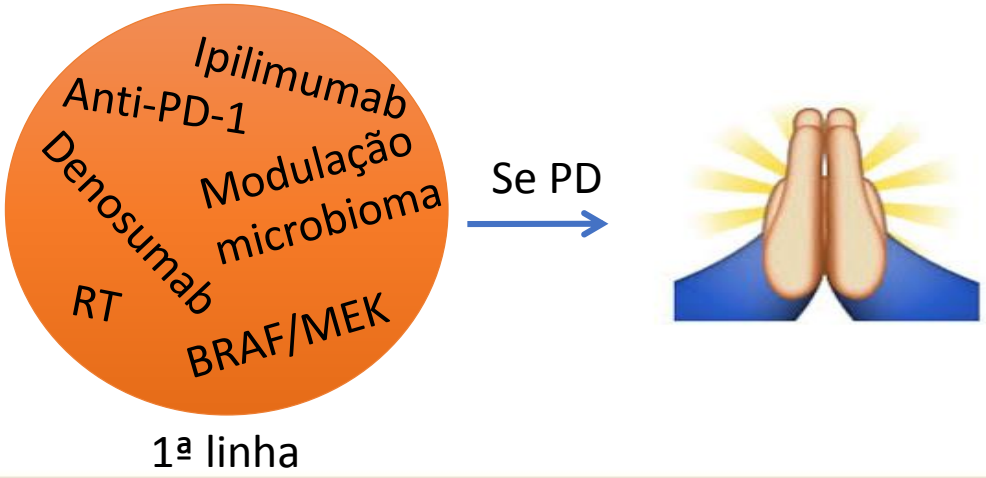
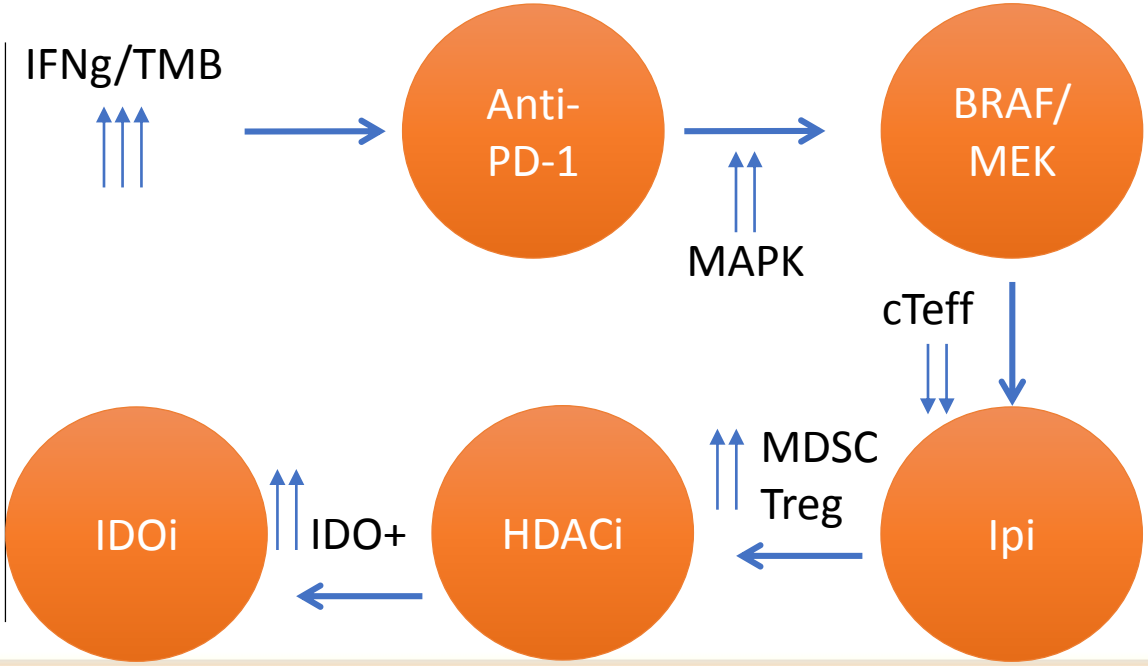
# Conclusões

- O tratamento com anti-PD-1 leva a respostas duradouras, mas 70% dos pacientes eventualmente apresentarão progressão de doença
- As opções após a falha de anti-PD-1 são escassas e de eficácia limitada
- Direções futuras:



HOSPITAL ISRAELITA
ALBERT EINSTEIN

# Obrigado!

VII SIMPÓSIO INTERNACIONAL DE Melanoma
HOTEL PULLMAN VILA OLÍMPIA
29 E 30 DE NOVEMBRO 2019

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