Imunoterapia no tratamento do câncer de mama avançado - Dados atuais e perspectivas

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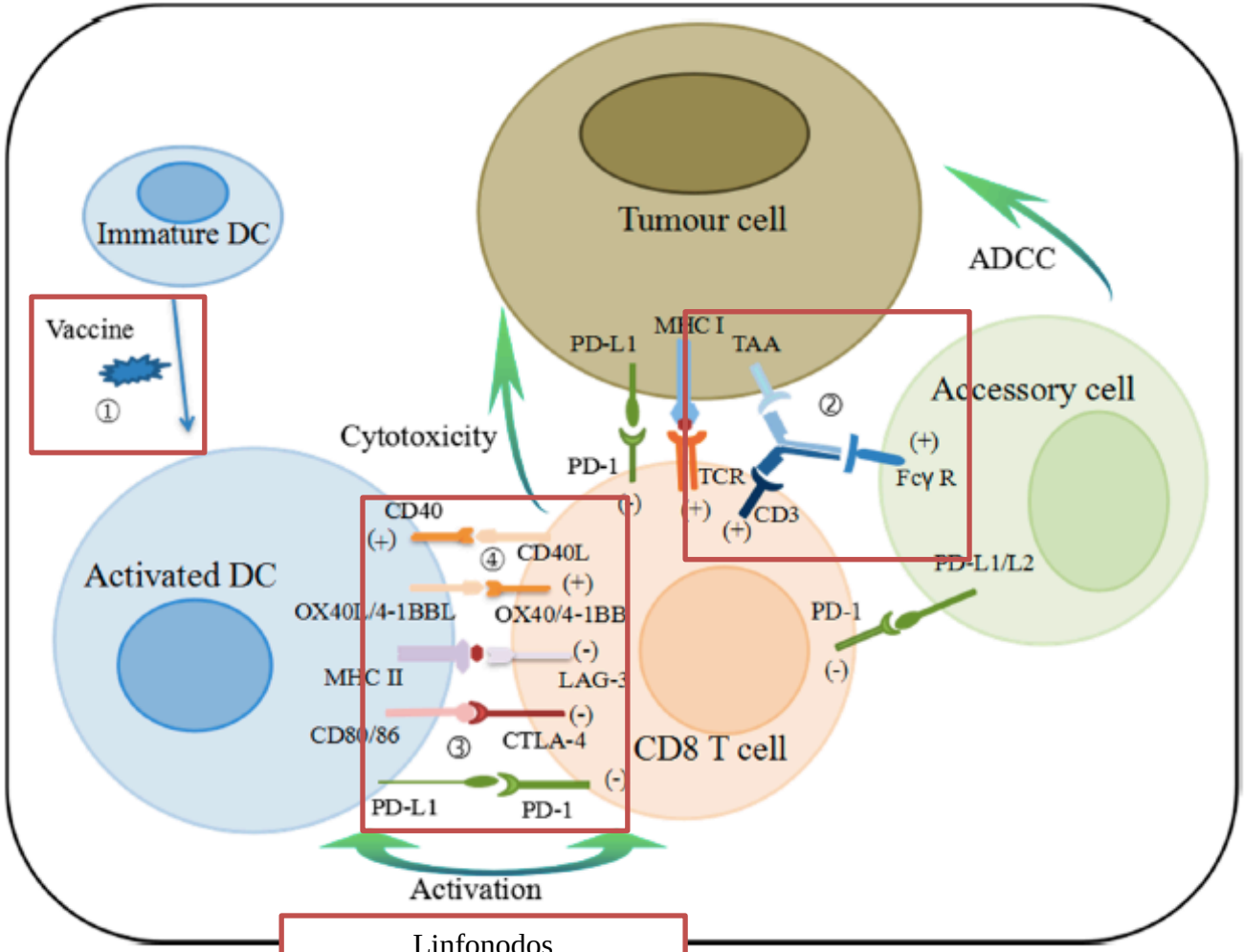
Imunoterapia - Mecanismo de Ação

HOSPITAL SANTA LÚCIA



Linfonodos
Resposta imune adaptativa

Int J Environ Res Public Health. 2017 Jan 12;14(1)

Estudos clínicos finalizados de imunoterapia em câncer de mama

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Phase	Breast Cancer Subtype	*n*	Study	Immune-Related Response	Clinical Benefit
			Vaccines		
I/II	HER2⁺ BC	195	E75 + GM-CSF	All patients developed a DTH response to E75 after vaccination, and that DTH reactions were dose dependent	Toxicities were mild; improved 5-year DFS
II	Early stage BC	206	AE37 + GM-CSF	Increase in DTH response to AE37, decrease in $CD4^+CD25^{high}$ $CD127^{low}$ regulatory T-cells	A reduction in recurrence
I/II	Stage IV HER2⁺ MBC	22	HER2 vaccine + Trastuzumab	Increase the HER2-specific immune responses	Well tolerated
I	HER2⁺ BC (trastuzumab-refractory)	12	HER2 vaccine + Lapatinib	Anti-HER2-specific antibodies and HER2-specific T-cells were induced in 100% and 8% of patients respectively	Well tolerated; no objective clinical responses
III	MBC	1208	Theratope + Endocrine	Antibody response to theratope	Longer TTP and OS than control group
I	MBC	12	PANVAC	Limited tumor burden, better CD4 response or higher number of CEA specific T-cells appeared to benefit from this vaccine	33% SD and 8% CR
I	HER2⁺ MBC	18	Lapuleucel-T	Significant HER2-specific T-cell proliferation	Without grade 3 or 4 adverse events; 5.5% PR, 16.6% experienced SD lasting >1 years
II	MBC	26	P53 DC vaccine	The efficacy was associated with tumor p53 expression, p53 specific T-cells and serum YKL-40 and IL-6 levels	8/19 evaluable patients attained SD
			BsAbs		
I	HER2⁺ MBC	15	Ertumaxomab	A strong T helper cell type 1-associated immune response	Most drug-related adverse events were mild; The ORR was 33%
I	MBC	23	Anti-CD3/anti-HER2 BsAb armed ATC along with low-dose IL-2 and GM-CSF	Induce both PBMC specific anti-SK-BR-3 and innate immune responses	No dose-limiting toxicities was observed; 59.1% evaluable patients had SD or better, and the median OS was 36.2 months
			CTLA-4		
I	MBC	26	Tremelimumab + Exemestane	Treatment was associated with increased peripheral $CD4^+$ and $CD8^+$ T-cells expressing ICOS and a marked increase in the ratio of $ICOS^+$ T-cells to $FoxP3^+$ regulatory T-cells.	Tolerable, and 42% patients experienced SD lasting ≥12 weeks.

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Phase	Breast Cancer Subtype	*n*	Study	Immune-Related Response	Clinical Benefit
				PD-1/PD-L1	
I	PD-L1+ mTNBC	32	Pembrolizumab	NR	15.6% experienced at least one drug-related serious adverse event; 16.1% PR, 9.7% SD
I	PD-L1+ TNBC	21	Atezolizumab	Treatment was associated with increased plasma cytokine concentrations and proliferating CD8 cells	24% ORs, 29% patients had PFS of 24 weeks or longer; several adverse reactions
I	mTNBC	11	Atezolizumab + Nab-paclitaxel	NR	Tolerable, 4 PRs and 1 SD
I	Locally MBC	168	Avelumab	NR	Among all patients with PD-L1 expressing, 33.3% (4 of 12) had PRs.
				LAG-3	
I/II	MBC	30	IMP321 + paclitaxel	Increase the number of activated APC, percentage of NK and long-lived cytotoxic effector-memory CD8 T-cells	ORR was 50%, and clinical benefit was noted in 90% in 6 months with no clinically significant IMP321-related adverse events
				OX40	
I	Advanced cancer (refractory to conventional therapy)	30	9B12	Immunologic effects were increased including proliferation of circulation CD4 and CD8 T-cells, responses to recall and naive reporter antigens, and endogenous tumor-specific immune responses	Induced the regression of at least one metastatic lesion in 40% patients

Int J Environ Res Public Health. 2017 Jan 12;14(1)

Triplo Negativo

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- Maior instabilidade cromossômica
- Maior número de mutações → Formação de mais antígenos
- Maior expressão de PD-L1 (20-30%)
- Maior infiltração por TILs

Mol Cancer Ther. 2007;6(7):2065-2072 ; J Clin Oncol. 2013;31:(suppl; abstr 521) ; Neoplasia 8:190, 2006

Atezolizumab + Nab-Paclitaxel in Metastatic TNBC: Phase Ib Study Design

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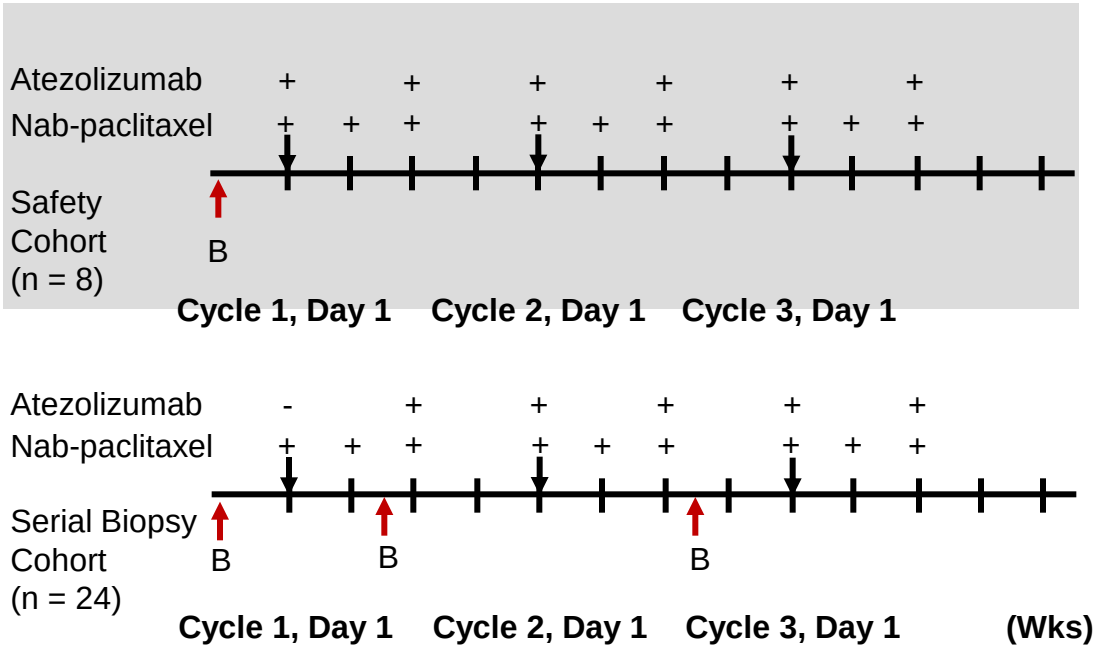
- GP28328: a multicenter, multicohort phase Ib study; arm F includes pts with TNBC (metastatic or unresectable, locally advanced)[1,2]

Pts with TNBC ≤ 2 previous systemic cytotoxics, ECOG PS 0/1, no CNS cancer or untreated/active CNS metastases, available tumor sample →



Atezolizumab (800 mg) + nab-paclitaxel (125 mg/m²), as long as clinical benefit received; nab-paclitaxel for at least 4 cycles, unless disease progression or unacceptable toxicity; if discontinued, atezolizumab as monotherapy

- Primary endpoint: safety and tolerability
- Secondary endpoints: response per RECIST v1.1 (ORR, DoR, PFS) and immune-modified response criteria; pharmacokinetics; biomarker analyses

1. Adams S, et al. ASCO 2016. Abstract 1009.
2. ClinicalTrials.gov. NCT01633970.

Atezolizumab + Nab-Paclitaxel in mTNBC

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- Tempo mediano de seguimento : 6.1m
- Duração mediano da exposição: 5.4m (0-17m) para atezolizumab; 4.2m (0-12m) for nab-paclitaxel
- Sem mortes relacionadas ao tratamento

Treatment-Related AE (Grade 3/4 AEs Occurring in ≥ 1% of Pts), %	Pts (N = 32)	
	All Grades	Grade ≥ 3
All	100	69
Neutropenia/decreased neutrophil count	66	46
Thrombocytopenia and decreased platelet count	16	9
Diarrhea	41	6
Anemia	22	6
Decreased white blood cell count	9	6

Adams S, et al. ASCO 2016. Abstract 1009.

Atezolizumab + Nab-Paclitaxel in mTNBC

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Atezolizumab-Related AE (Any Grade AE in ≥ 10% of Pts), %	Pts (N = 32)	
	All Grades	Grade ≥ 3
Fatigue	34	--
Neutropenia/decreased neutrophil count	28	9
Pyrexia	25	--
Diarrhea	19	3
Peripheral neuropathy	19	--
Nausea	16	--
Alopecia	13	--
Headache	13	--
Pruritus	13	--

Adams S, et al. ASCO 2016. Abstract 1009.

Atezolizumab + Nab-Paclitaxel in mTNBC:

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Best Overall Response	First Line (n = 13)	Second Line (n = 9)	Third Line+ (n = 10)	All (N = 32)
Confirmed ORR, % (95% CI)	46 (19-75)	22 (3-60)	40 (12-74)	**38** (21-56)
CR, %	8	0	0	3
PR, %	38	**22**	**40**	34
SD, %	38	67	30	44
PD, %	15	0	30	16
Missing or NE, %	0	11	0	3
Median DoR, mos (range)	NE (2.9 to 11.5+)	NE (9.1 to 13.1+)	NE (1.9+ to 5.6+)	

- Atezolizumabe - 12 respondedores, 6 (50%) continuavam em uso;
- Sem diferenças de resposta pela expressão de PD-L1

Adams S, et al. ASCO 2016. Abstract 1009.

KEYNOTE-086 – Pembrolizumabe em mTNBC – Cohort A

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- International, multicohort phase II study

mTNBC pts who progressed on ≥ 1 prior systemic therapy; ECOG PS 0-1; LDH < 2.5 x ULN; tumor biopsy sample available for PD-L1 evaluation (N = 170)

→ Pembrolizumab 200 mg IV Q3W (N = 170)

→ *For 2 yrs or until PD, unacceptable toxicity, consent withdrawal, or investigator decision*

Endpoints

- Primary: ORR in overall, PD-L1+ pts; safety
- Secondary: DoR, DCR, PFS, OS in overall, PD-L1+ pts

Assessments

- Tumor imaging: every 9 wks for 1 yr, then every 12 wks
- Response: RECIST v1.1 by ICR
- PD-L1 positive: CPS ≥ 1% by IHC at central lab

Adams S, et al. ASCO 2017. Abstract 1008.

KEYNOTE-086 - Pembrolizumabe em mTNBC

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Characteristic	All Pts (N = 170*)	PD-L1 Positive (n = 105)	PD-L1 Negative (n = 64)
Median age, yrs (range)	53.5 (28-85)	53.0 (30-85)	55.0 (28-80)
Female, %	100	100	100
ECOG PS 1, %	47.1	51.4	40.6
LDH > 1 x ULN	51.2	48.6	56.2
Postmenopausal, %	82.4	81.0	84.4
Visceral ± nonvisceral disease, %			
Prior taxane, anthracycline, %	95.9	97.1	93.8
Prior (neo)adjuvant therapy, %	83.5	81.9	85.9
Prior lines of therapy, %			
▪ 1	31.2	34.3	26.6
▪ 2	25.3	25.7	23.4
▪ ≥ 3	43.5	40.0	50.0

Adams S, et al. ASCO 2017. Abstract 1008.

KEYNOTE-086: Pembrolizumabe em mTNBC

HOSPITAL SANTA LÚCIA

Response*	All Pts (N = 170†)	PD-L1 Positive (n = 105)	PD-L1 Negative (n = 64)
ORR, % (95% CI)	4.7 (2.3-9.2)	4.8 (1.8-10.9)	4.7 (1.1-13.4)
DCR,‡ % (95% CI)	7.6 (4.4-12.7)	9.5 (5.1-16.8)	4.7 (1.1-13.4)
Best overall response, %			
▪ CR	0.6	1.0	0
▪ PR	4.1	3.8	4.7
▪ SD	20.6	21.0	18.8
▪ PD	60.6	62.9	57.8
Median TTR, mos (range)	3.0 (1.9-8.1)	--	--
Median DoR, mos (range)	6.3 (1.2+ to 10.3+)	--	--

Adams S, et al. ASCO 2017. Abstract 1008.

KEYNOTE-086 - Pembrolizumabe em mTNBC

HOSPITAL SANTA LÚCIA

Outcome	All Pts (N = 170)	PD-L1 Positive (n = 105)	PD-L1 Negative (n = 64)
PFS			
▪ Median, mos (95% CI)	2.0 (1.9-2.0)	2.0 (1.9-2.1)	1.9 (1.6-2.0)
▪ Events, n	148	90	57
▪ 3-mo rate, %	25.5	24.2	26.6
▪ 6-mo rate, %	12.3	13.2	11.1
OS			
▪ Median, mos (95% CI)	8.9 (7.2-11.2)	8.3 (6.9-10.5)	10.0 (6.2-NR)
▪ Events, n	90	58	32
▪ 6-mo rate, %	69.0	71.0	65.4
▪ 9-mo rate, %	49.8	47.5	52.6

Adams S, et al. ASCO 2017. Abstract 1008.

KEYNOTE-086 - Pembrolizumabe em mTNBC

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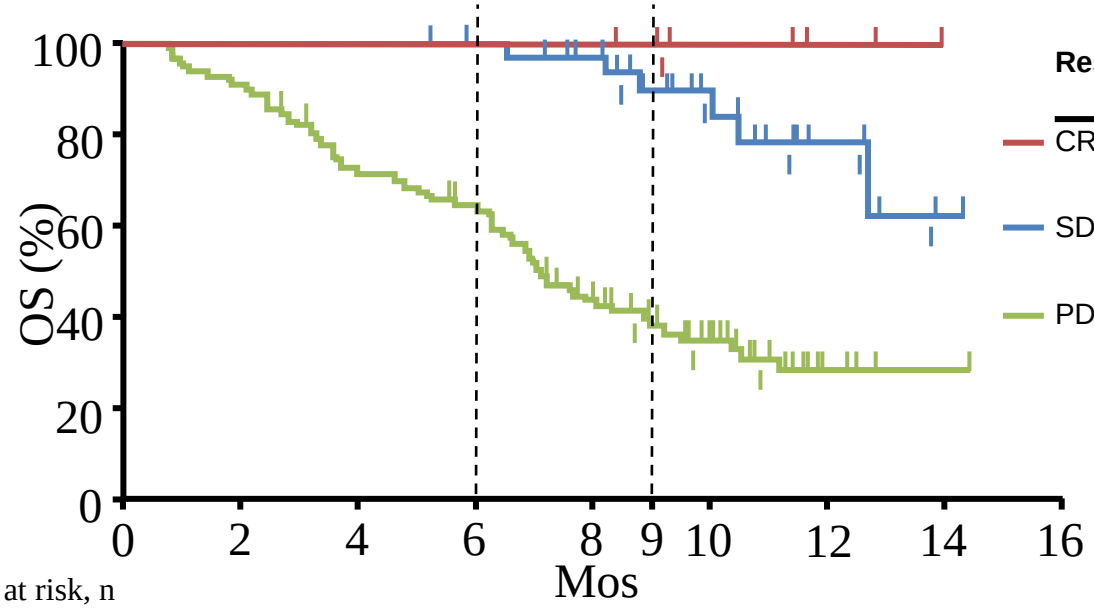
- Sem mortes relacionados ao tratamento
- Descontinuação do tratamento – 4,1% (efeitos colaterais) e 1.2% (eventos imuno-relacionados)

AEs in ≥ 5% of Pts, %	Any Grade (N = 170)	Grade 3/4 (N = 170)
Treatment related	60.0	12.4
▪ Fatigue	20.6	0.6
▪ Nausea	10.6	0.6
▪ Decreased appetite	7.6	0
▪ Hypothyroidism	7.6	0
▪ Diarrhea	7.1	1.8
▪ Asthenia	6.5	0
▪ Arthralgia	5.9	0
▪ Pruritus	5.9	0
Immune mediated	18.8	1.2
▪ Hypothyroidism	11.2	0
▪ Hyperthyroidism	4.7	0
▪ Pneumonitis	3.5	0.6

Adams S, et al. ASCO 2017. Abstract 1008.

KEYNOTE-086 - Pembrolizumabe em mTNBC



Pts at risk, n									
CR or PR	8	8	8	8	8	4	2	0	0
SD	35	35	35	33	29	16	7	1	0
PD	103	94	72	63	39	20	4	1	0

Response	Events/Pt, n/n	mPFS, Mos (95% CI)	6-Mo PFS, %	9-Mo PFS, %
CR or PR	0/8	Not reached (NR-NR)	100	100
SD	6/35	7.1 (6.3-8.8)	100	89.6
PD	66/103	Not reached (12.7-NR)	64.6	39.0

Coorte B → TR 23%

Adams S, et al. ASCO 2017. Abstract 1008.

KEYNOTE-086: sTIL Level Variation by Pt Cohort, Timing, and Site of Biopsy Sample

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	Combined (n = 193)	Cohort A (n = 147)	Cohort B (n = 46)	P Value (A vs B)
Median sTIL, % (IQR)	5 (3-20)	5 (1-10)	17.5 (5-61.25)	< .001

	LN (n = 39)	Lung (n = 16)	Breast (n = 51)	Liver (n = 25)	Skin (n = 17)	Chest Wall (n = 25)	Other (n = 20)	P Value
Median sTIL, % (IQR)	10 (5-50)	12.5 (5-36)	10 (5-30)	5 (3-25)	3 (1-10)	5 (1-8.5)	5 (1.25-13.75)	.003

Loi S, et al. ESMO 2017. Abstract LBA13.

KEYNOTE-086: sTIL Level Variation by Pt Cohort, Timing, and Site of Biopsy Sample

HOSPITAL SANTA LÚCIA

	Median sTIL, % (IQR)	P Value
Combined cohorts ▪ Responder (n = 18) ▪ Nonresponder (n = 175)	 37.5 (8.75-66.25) 5 (2-15)	< .001
Cohort A ▪ Responder (n = 7) ▪ Nonresponder (n = 140)	 10 (5-30) 5 (1-10)	.062
Cohort B ▪ Responder (n = 11) ▪ Nonresponder (n = 35)	 50 (35-70) 15 (5-40)	.009

Loi S, et al. ESMO 2017. Abstract LBA13.

Phase II TONIC: Nivolumab After Induction Radiotherapy or Low-Dose Chemo in mTNBC

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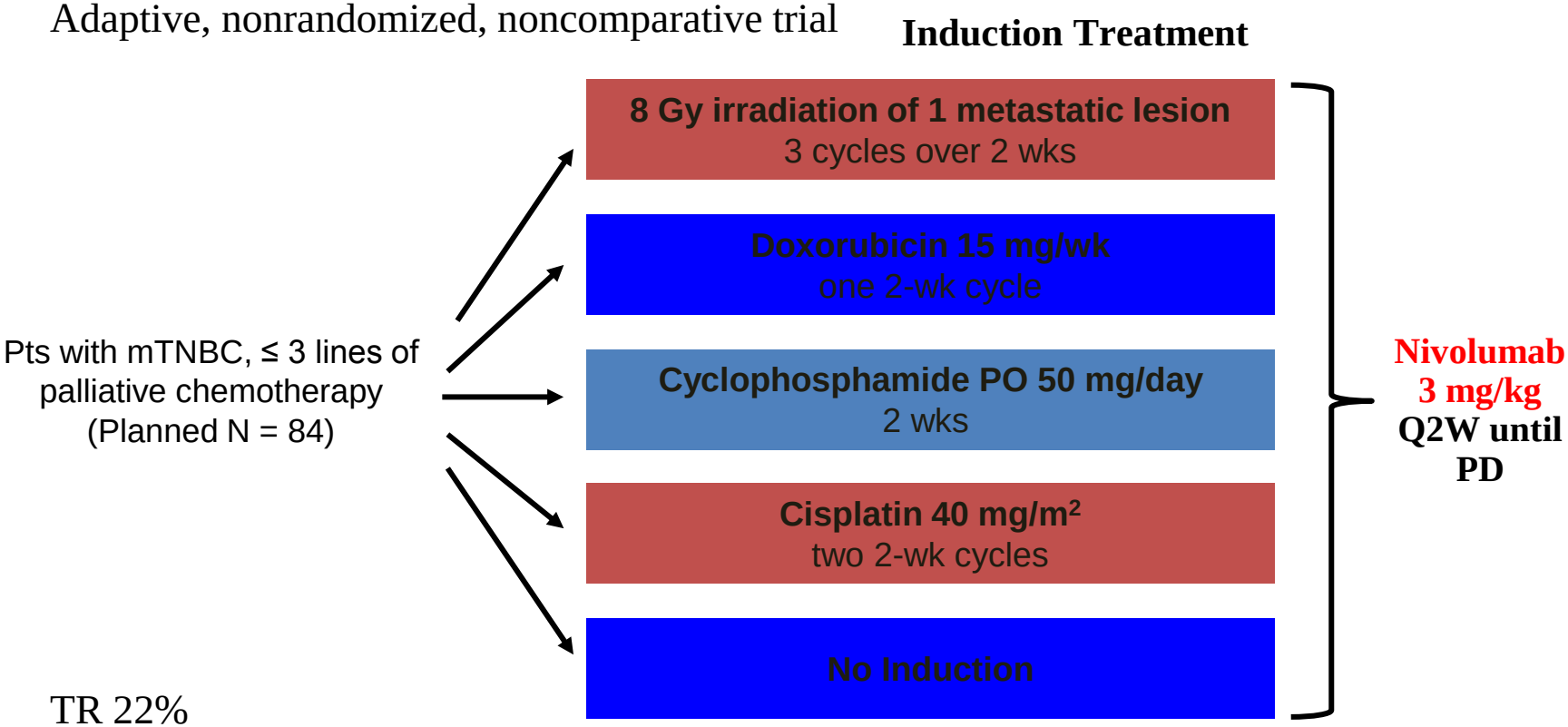
- Adaptive, nonrandomized, noncomparative trial



- TR 22%
  - Maior → infiltração de leucócitos / linfocitos TCD8
  - Indução cisplatina/doxorrubicina

- SLP: 3.4 months

Kok M, et al. ESMO 2017. Abstract LBA14. ClinicalTrials.gov. NCT02499367.

Avelumabe

HOSPITAL SANTA LÚCIA

- Estudo fase Ib (JAVELIN)
- Dose: 10mg/kg a cada 2 semanas
- Câncer de mama metastáticos: 168 pctes
  - 34% TNBC
- TR - PD-L1+: 44%

Melhor resposta global, %	Todos os pacientes (N = 168)	Pacientes com TNBC (N = 58)
Resposta Completa	**0,6%**	**0%**
Resposta Parcial	**4,2%**	**8,6%**
Doença Estável	23,3%	22,4%
Doença Progressiva	63,1%	65,5%
Não avaliado	8,9%	3,4%
Taxa de resposta objetiva (ORR)	4,8%	8,6%
DCR	28,0%	31,0%

Cancer Res. 2016, 76.

Epacadostate + Pembrolizumabe em tumores avançados

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- Inibidor IDO (enzima que induz tolerância imune)
- Estudo fase I/II
- Tumores de mama triplo negativo - n=39

TNBC, N = 39	
> 3 linhas anteriores	22 (56%)
ORR	4 (10%)
Taxa de controle de doença	14 (36%)
Eventos adversos grau 3 ou mais	5 (13%)

J Clin Oncol 35, 2017 (suppl; abstr 1103)

Durvalumabe + Tremelimumabe x 4 → Durvalumabe 1a

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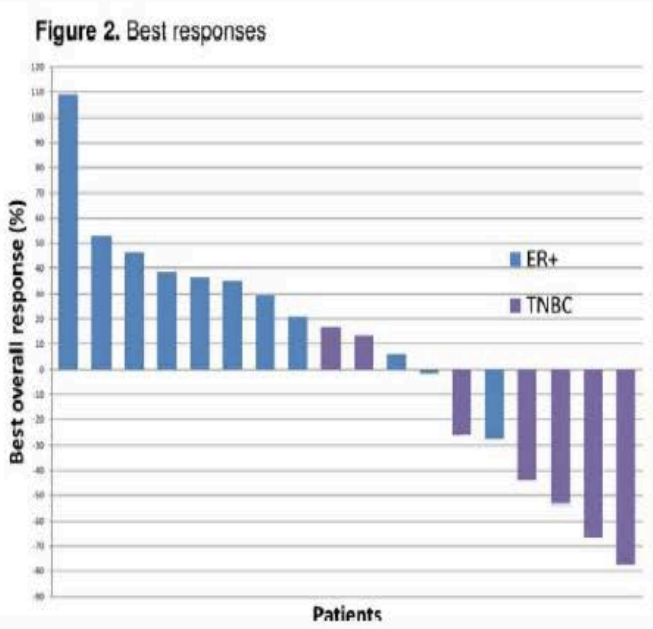
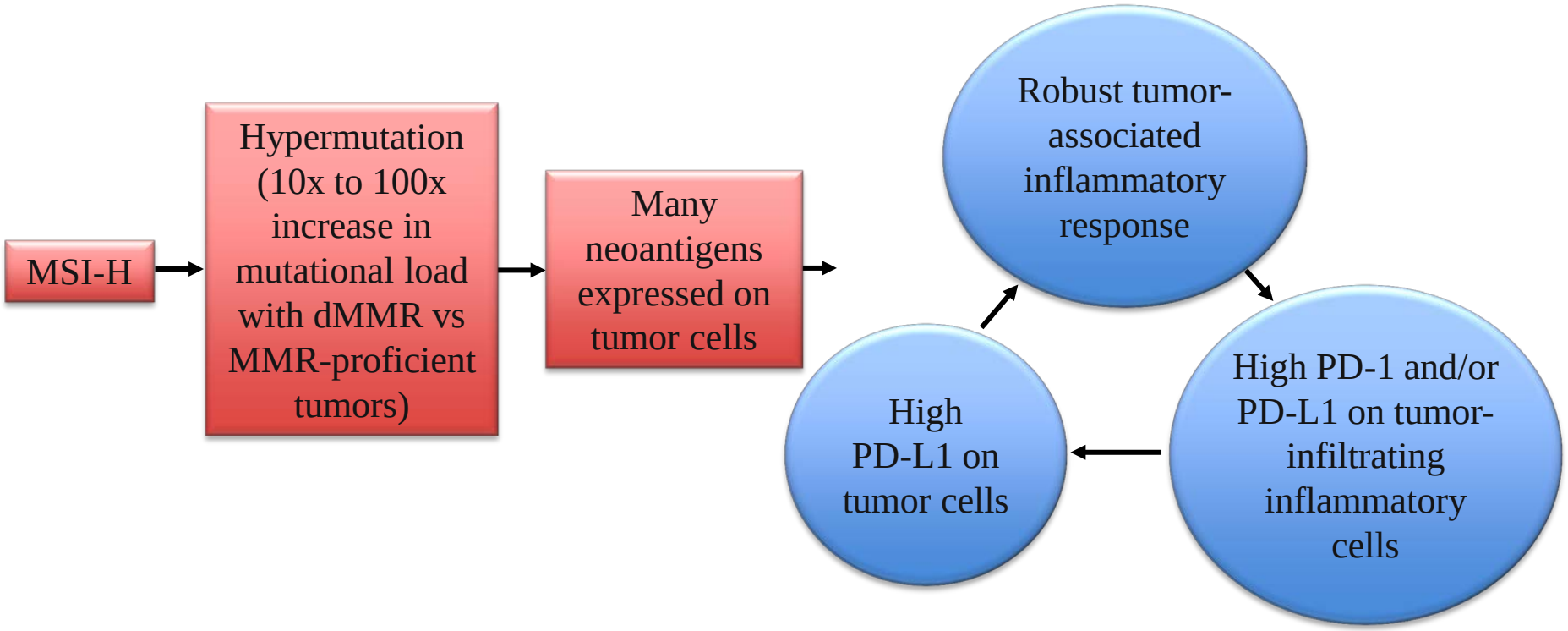
- Tumores triplo negativos e RE+

	All pts (n = 18)	TNBC (n = 7)	ER+ (n = 11)
PR	3	3	0
SD ≥6 months	1	1	0
PD	14	3*	11
ORR	17%	43%	0%

J Clin Oncol 35, 2017 (suppl; abstr 3052)



Instabilidade microsatélite



- Aprovação acelerada pelo FDA → Pembrolizumabe para tumores sólidos irressecáveis/metastáticos que progrediram e para os quais não há tratamentos satisfatórios

Le DT, et al. N Engl J Med. 2015;372:2509-2520.

Frequency of MSI-High and dMMR in BC After Chemotherapy Treatment

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Chemotherapy Regimen	N	MSI-High, %	MSI-Low , %	Microsatellite Stable, %
Total	123	19	52	29
High FEC	68	28	54	18
Low FEC	31	13	58	29
AC	13	0	46	54
TC	3	0	67	33
Carbo/taxane	2	0	50	50
Epirubicin/taxane	1	0	0	100
HER2 inhibitor/taxane	4	0	0	100
Bev/taxane	1	0	0	100

Kamat N, et al. BMC Cancer. 2012;12:373.

Conclusão

- Câncer de mama pode ser imunogênico
  - Fatores pior prognóstico/ triplo negativo
  - Imunoterapia efetiva para uma minoria - respostas duradouras

- Pembrolizumabe – maior benefício
  - Primeira linha
  - Biomarcador – TIL's?
  - Instabilidade microssatélite

- Combinações?

- Estimular inclusão em ensaios clínicos

Estudo clínicos em andamento

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Trial ID	Phase	Breast Cancer Subtype	Primary Endpoint	Study
Vaccines				
NCT02427581	I	TNBC	Safety	Poly ICLC
NCT01730118	I	HER2$^+$ BC	Cardiac toxicity and anti-HER2 antibody concentration	Autologous Ad HER2 dendritic cell vaccine
NCT02018458	I/II	phase1: LA TNBC; phase 2: ER$^+$/HER2$^-$ BC	Safety	DC vaccination + Preoperative chemotherapy
NCT01570036	II	HER2$^+$ BC	DFS	E75 + Trastuzumab
NCT02061332	I/II	BC	Blood pressure, temperature, pulse	HER2 Pulsed Dendritic Cell Vaccine
NCT01376505	I	BC	Immune response and clinical benefit	HER2 vaccine
NCT02140996	I	BC	Safety and tolerability	Ad-sig-hMUC-1/ecdCD40L vector vaccine
BsAbs				
NCT01730612	I/II	HER2$^-$CEA$^+$ BC	Tumor targeting and signal/noise ratio	TF2 + 68 Ga-IMP-288
CTLA-4				
NCT02536794	II	HER2$^-$ BC	Response rate	MEDI4736 + Tremelimumab
NCT02381314	I	TNBC	Adverse event	MGA271 + Ipilimumab
PD-1				
NCT02661100	I/II	Advanced TNBC	DLT	Pembrolizumab + CDX-1401 + Poly ICLC
NCT02453620	I	HER2$^-$ BC	Adverse event	Entinostat + Ipilimumab + Nivolumab
NCT02129556	I/II	HER2$^+$BC (Trastuzumab-resistant)	DLT	Pembrolizumab
NCT02309177	I	BC	DLT, Safety, Grade 3 or 4 TEAE	Nab-Paclitaxel + Nivolumab + Gemcitabine + Carboplatin
NCT02404441	I/II	TNBC	DLT and ORR	PDR001
NCT02555657	III	TNBC	PFS and OS	Pembrolizumab + Capecitabine + Eribulin + Gemcitaine + Vinorelbine
PD-L1				
NCT02643303	I/II	BC	Phase 1 Safety and tolerability Phase 2 ORR, PFS, OS	Durvalumab + Tremelimumab + Poly ICLC
NCT02628132	I/II	TNBC	Adverse event	Paclitaxel + Durvalumab
NCT02685059	II	TNBC	pCR	Durvalumab + Placebo + nab-Paclitaxel + Epirubicin + Cyclophosphamide
NCT02725489	II/III	TNBC	Tolerability and adverse event	Vigil™ + Durvalumab
NCT02425891	III	Metastatic BC/TNBC	PFS and OS	Atezolizumab + Nab-Paclitaxel + Placebo
NCT02478099	II	TNBC	ORR	Atezolizumab
NCT02649686	I	HER2$^+$ Metastatic BC	Confirm phase II dose	Durvalumab + Trastuzumab
NCT02708680	I/II	Advanced TNBC	DLT, MTD and PFS	Entinostat + Atezolizumab
LAG-3				
NCT02614833	II	Stage IV BC	PFS	IMP321 + Placebo + Paclitaxel
OX40				
NCT01862900	I/II	Metastatic BC	DLT and safety profile	MEDI6469
4-1BB				
NCT02554812	II	TNBC	DLT and ORR	PF-05082566 + Avelumab

Int J Environ Res Public Health. 2017 Jan 12;14(1)

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*"O câncer está carregado de **imagens contemporâneas**: A célula é individualista, desesperada, inconformada. As metástases, um estado instável, sem âncoras... A **patologia do excesso**. Vive feroz, inventiva, territorial e defensivamente, como se nos ensinasse a dominar"*

Siddahartha Mukherjee, 2012

Obrigado!

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