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Checkpoint inhibitors: What's known (lessons learned) and What's new (perspectives)

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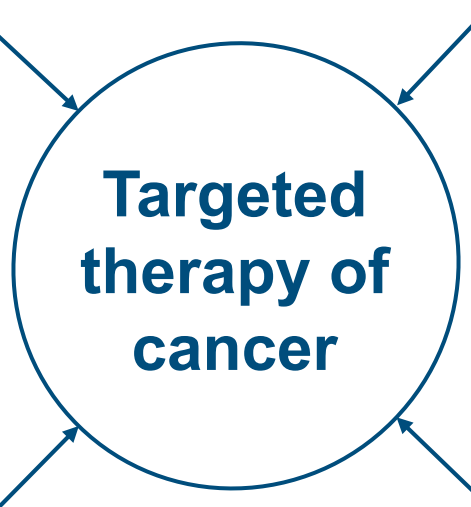
The partners of oncology progress

Biologists

- Hallmarks of cancer
- Driver targets
- Critical pathways

Sequencers

- Individual tumor genomic landscapes



Chemists

- Selective drugs to molecular aberration

Clinical researchers

- Innovative drug development methodology

A. Awada. Personal communication 2018.

Eight lessons learned from the development of dozens of molecular-targeted therapies (1)

- Treatment of unselected populations should be discouraged
- The identification of a driver genetic abnormality and the discovery of a selective agent are key
- ‘Rare’ tumors are ‘good’ niches for MTTs
- Discovery of the resistance mechanisms is a high priority

MTT, molecular-targeted therapy.
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Eight lessons learned from the development of dozens of molecular-targeted therapies (2)

- One gene may predict resistance, but no single gene, protein, or pathway can predict full efficacy
- Chemotherapy (also radiotherapy) remains important for synergy with targeted agents in selective settings
- Better outcomes are seen in the metastatic setting than in the adjuvant one
- Expected and unexpected side effects can arise from MTTs

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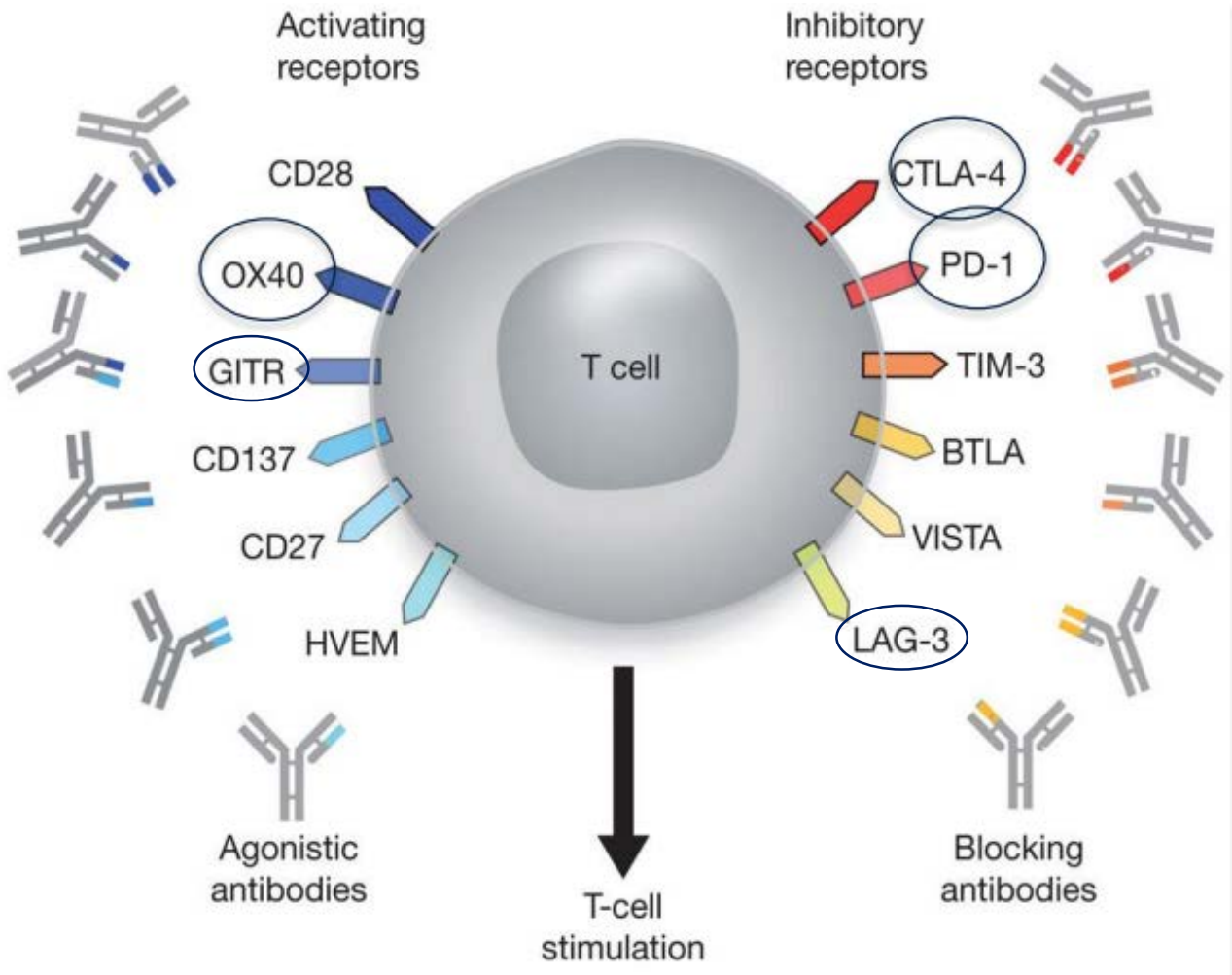
Activating and inhibitory receptors on T cells: basis of modern immunotherapy



Mellman et al. Nature 2011;480:480–9.

Lesson 1: Checkpoint inhibitors are so far approved in several solid tumors or histologically agnostic tumors, but there are more to come…

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Approved immune checkpoint inhibitors in solid tumors

- Melanoma: nivolumab ± ipilimumab, pembrolizumab (1st line)
- NSCLC: pembrolizumab ± chemotherapy (1st line PD-L1 ≥ 50%)
- NSCLC (sq. and non-sq.): nivolumab, pembrolizumab and atezolizumab (chemo pretreated)
- RCC:* nivolumab (prior TKIs); nivolumab + ipilimumab (1st line)
- Bladder: several checkpoint inhibitors
- Head and neck: pembrolizumab, nivolumab…
- Merkel cell carcinoma: avelumab
- MSI tumors:* pembrolizumab, nivolumab

Slide shows a mixture of EMA and FDA approvals

and more to come…

*Only FDA approved at present.
EMA, European Medicines Agency; FDA, Food and Drug Administration; MSI, microsatellite instability; NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; sq., squamous; TKI, tyrosine kinase inhibitor.
A. Awada. Personal communication 2018.

Lesson 2: Solid tumors do not respond equally to checkpoint inhibitors

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Efficacy of checkpoint inhibitors in different solid tumors: virus-induced tumors as an example

Tumor (virus)	ORR (%)	Disease control rate (%)
Hepatocellular (HBV, HCV)	14–17	68
Cervix (HPV)	13	25
Merkel (polyomavirus)	30	41
Anal (HPV, HIV)	27	70
Head and neck/nasopharyngeal (EBV)	11–18/26	15–36
Gastric/GEJ (EBV)	9–26	29–38

Question: How can we improve efficacy? Combinations? …

EBV, Epstein–Barr virus; GEJ, gastroesophageal junction; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; ORR, objective response rate.
ESMO/ASCO 2016, 2017 and 2018.

Limited efficacy so far of single-agent checkpoint inhibitors in other solid tumors

Tumor	ORR (%)	Disease control rate (%)
Prostate[1]	13	NA
Ovarian	11–15	NA
TNBC	9–19	31–46
ER+ BC	3–12	28
Neuroendocrine	6–12 (lung 20%)	60–88
Biliary tract cancers	6–18	NA

Question: How to transform cold tumors to hot tumors?

BC, breast cancer; ER, estogen receptor; NA, not available; TNBC, triple-negative breast cancer.
ESMO/ASCO 2016, 2017 and 2018. 1. Hansen et al. Presented at ESMO 2016; Abstract 725PD.

Lesson 3: Combinations based on immunotherapies: huge potential and setting/tumor dependency

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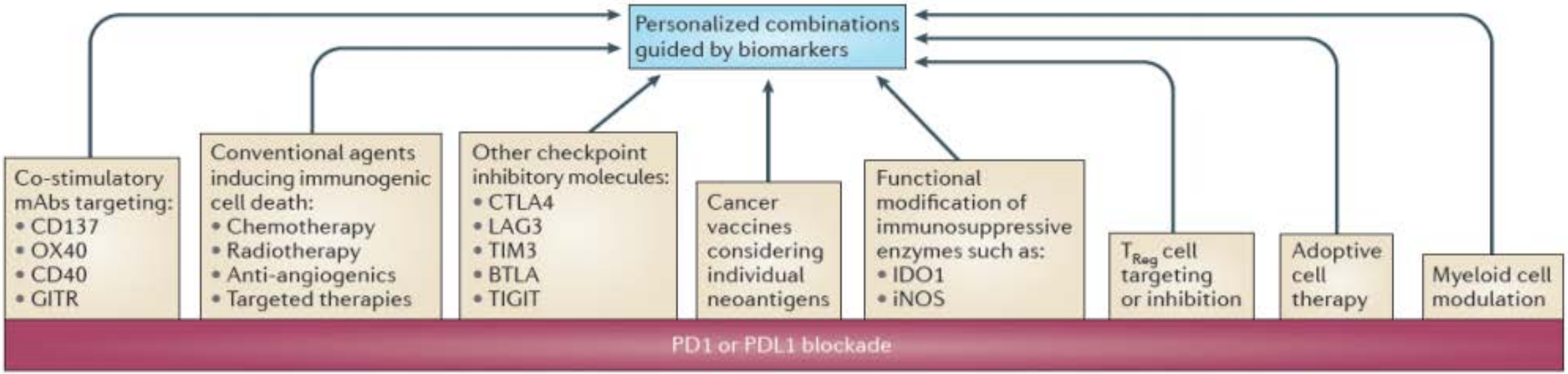
Combination therapy based on immunotherapies: a means to overcome resistance!



BTLA, B- and T-lymphocyte attenuator; CTLA4, cytotoxic T lymphocyte-associated antigen 4; GITR, glucocorticoid-induced TNFR-related protein; IDO1, indoleamine 2, 3-dioxygenase 1; iNOS, inducible nitric oxide synthase; LAG3, lymphocyte-activation protein 3; mAb, monoclonal antibody; PD1, programmed cell death 1; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; TIM3, T cell immunoglobulin mucin 3; T_{reg}, regulatory T cell.

Melero et al. Nat Rev Cancer 2015;15:457–72.

Examples of checkpoint inhibitors Combinations + other molecular-targeted agents or chemotherapy

- Checkpoint inhibitors + VEGF(R) inhibitors
- Checkpoint inhibitors + chemotherapy agents

VEGF(R), vascular endothelial growth factor (receptor).
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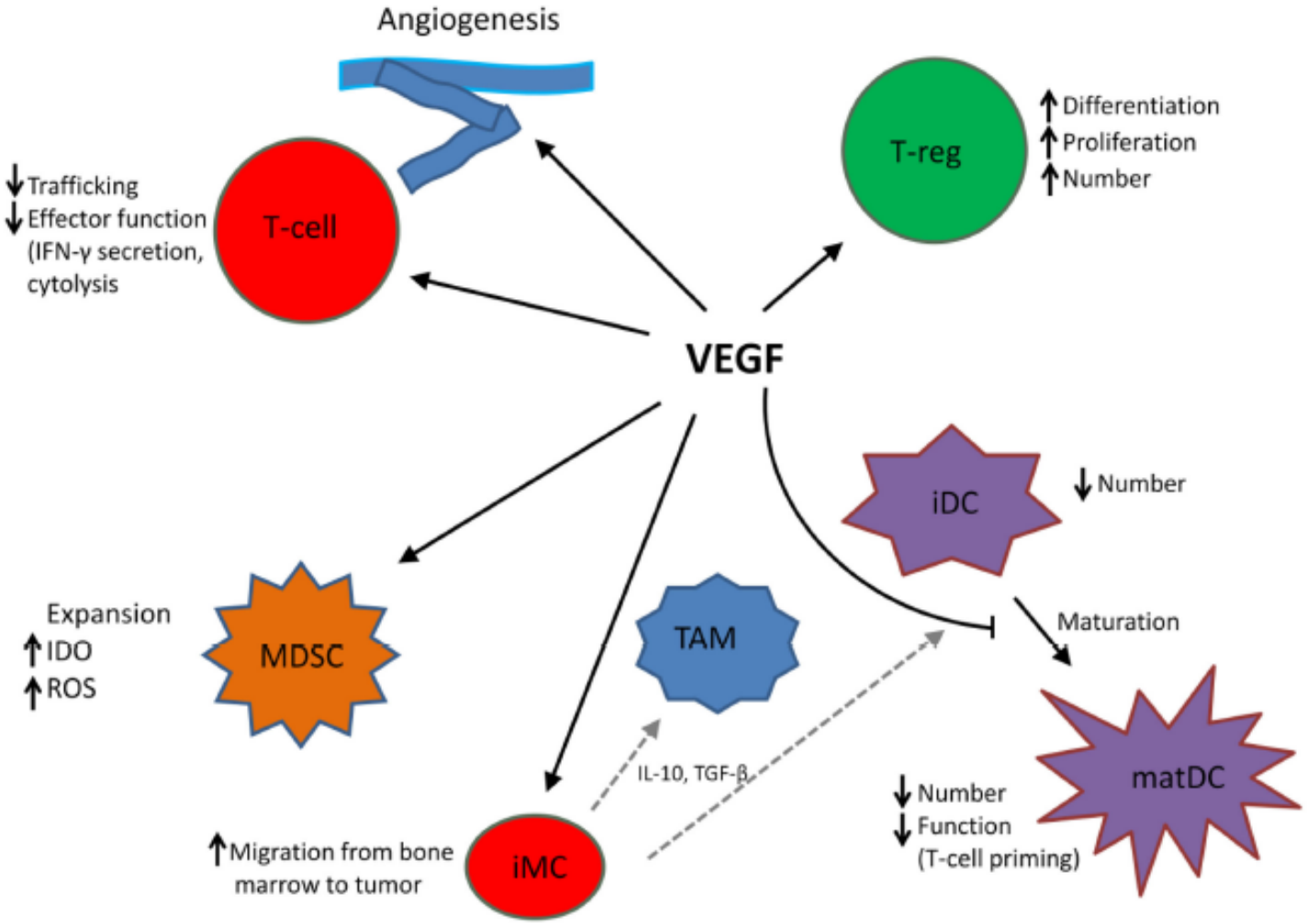
Angiogenesis (VEGF) leads to an immunosuppressive tumor microenvironment



iDC, immature dendritic cell; IFN, interferon; IL, interleukin; iMC, immature myeloid cell; matDC, mature dendritic cell; MDSC, myeloid-derived suppressor cell; ROS, reactive oxygen species; TAM, tumor-associated macrophage; TGF, transforming growth factor.
Ott et al. Front Oncol 2015;5:202.

Selected studies of CPIs + VEGF-targeted therapies in renal cell carcinoma

Agents	No. of patients (line)	ORR, %	DCR, %
Atezolizumab + bevacizumab	454 (1st)	43% (PDL1+)	–
Nivolumab + sunitinib	33 (1st)	51	81
Nivolumab + pazopanib	20 (1st)	45	80
Tremelimumab + sunitinib	21 (1st or 2nd)	43	76
Pembrolizumab + bevacizumab	14 (2nd)	71	NA
Pembrolizumab + lenvatinib	30	63	NA
Pembrolizumab + axitinib	52 (1st)	71	90

CPI, checkpoint inhibitor; DCR, disease control rate.
Kusak et al. Angiogenesis 2017;20:205–15.

Checkpoint inhibitors + chemotherapy

- ESMO LBA1_PR. IMpassion130: atezolizumab + nab-paclitaxel first-line improved OS in PD-L1+ TNBC[1]
- ESMO LBA8_PR. Pembrolizumab ± PF improved OS vs PF + cetuximab in recurrent/metastatic head and neck cancer (PD-L1+)[2]
- CheckMate 227,[3] IMpower 150[4] and 131[5], KEYNOTE-189[6] and 407[7]: five studies showed benefit in 1st-line NSCLC

OS, overall survival; PF, platinum-based chemotherapy.

1. Schmid et al. Presented at ESMO 2018; Abstract LBA1_PR. 2. Burtness et al. Presented at ESMO 2018; Abstract LBA8_PR. 3. Hellmann et al. N Engl J Med 2018;378:2093–104. 4. Socinski et al. N Engl J Med 2017;378:2288–2301. 5. Jotte et al. Presented at ASCO 2018; Abstract LBA9000. 6. Gandhi et al. N Engl J Med 2018;378:2078–92. 7. Paz-Ares et al. N Engl J Med 2018;379:2040–51.

Checkpoint inhibitors + other immunotherapy approaches

- Ipilimumab (CTLA4) + nivolumab (PD-1)
- Durvalumab (PD-L1) + MEDI 0680 (PD-1)
- Pembrolizumab (PD1) + epacadostat (IDO)*
- Nivolumab (PD-1) + BMS-986016 (LAG3)
- Nivolumab (PD-1) + mogamulizumab (CCR4)
- Nivolumab (PD-1) + ISA101 (vaccine)

*Negative results in melanoma.[1]
CCR, CC chemokine receptor 4.
1. Long et al. Presented at ASCO 2018; Abstract 108.

Ipilimumab (CTLA4) + nivolumab (PD-1) in solid cancers

Ref.	Tumor type, line of therapy (no. of pts)	ORR, %	DCR, %
Lenz et al. ESMO 2018[1]	CRC (MSI-H or dMMR), 1st line	60 (CR 7%)	NA
Janjigian et al. ASCO 2017[2]	Upper GI	23–40 (PD-L1 ≥ 1%) 0–22 (PD-L1 < 1%)	NA
Antonia et al. Lancet Oncol 2016[3]	SCLC, ≥ 1 line (115)	21	40
Zalcman et al. ESMO 2017[4]	Mesothelioma, > 1 line	28	50
Hellmann et al. Lancet Oncol 2017[5]	NSCLC, 1st line (77)	43	68
ESMO 2017, LBA5[6]	RCC, 1st line	42	–
Wolchok et al. N Eng J Med 2017[7]	Melanoma, 1st line (314)	58	70

ASCO, American Society of Clinical Oncology; CR, complete response; CRC, colorectal cancer; dMMR, defective DNA mismatch repair; ESMO, European Society for Medical Oncology; GI, gastrointestinal; MSI-H, high microsatellite instability; SCLC, small-cell lung cancer.

1. Lenz et al. Presented at ESMO 2018; Abstract LBA18_PR. 2. Janjigian et al. Presented at ASCO 2017; Abstract 4014. 3. Antonia et al. Lancet Oncol 2016;17:299–308. 4. Zalcman et al. Presented at ESMO 2017; Abstract LBA58_PR.
5. Hellmann et al. Lancet Oncol 2017;18:31–41. 6. Escudier et al. Presented at ESMO 2017; Abstract LBA5. 7. Wolchok et al. N Engl J Med 2017;377:1345–56.

Lesson 4: Emerging data in the (neo)adjuvant/ consolidation settings are very encouraging (compared with other targeted agents)

- Melanoma (adjuvant): ipilimumab, nivolumab, pembrolizumab
- NSCLC (maintenance): durvalumab (PD-L1+)
- Neoadjuvant: lung (nivolumab pCR: 45%), MCC, TNBC (+ chemo), bladder (pembrolizumab pCR 42%), colon (dMMR)

MCC, Merkel-cell carcinoma; pCR, pathologic complete response.
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Lesson 5: CPIs are active in melanoma brain metastases

What about other solid tumors?

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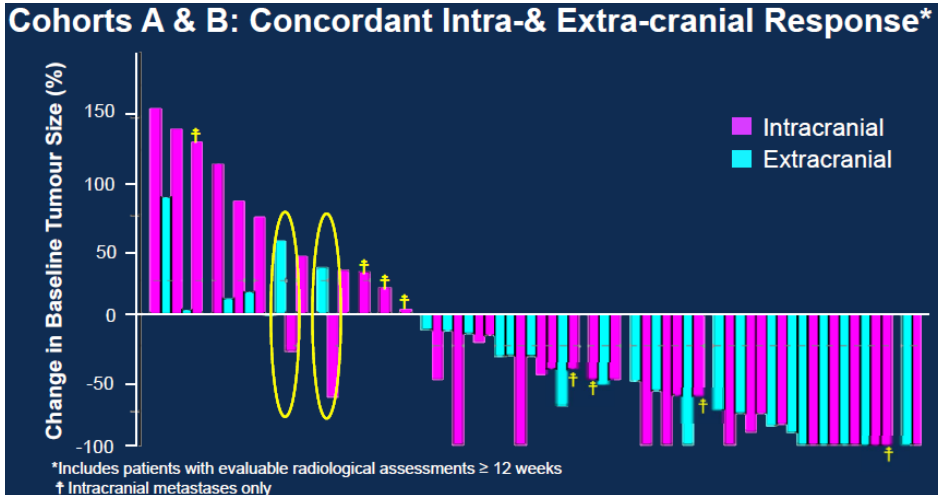
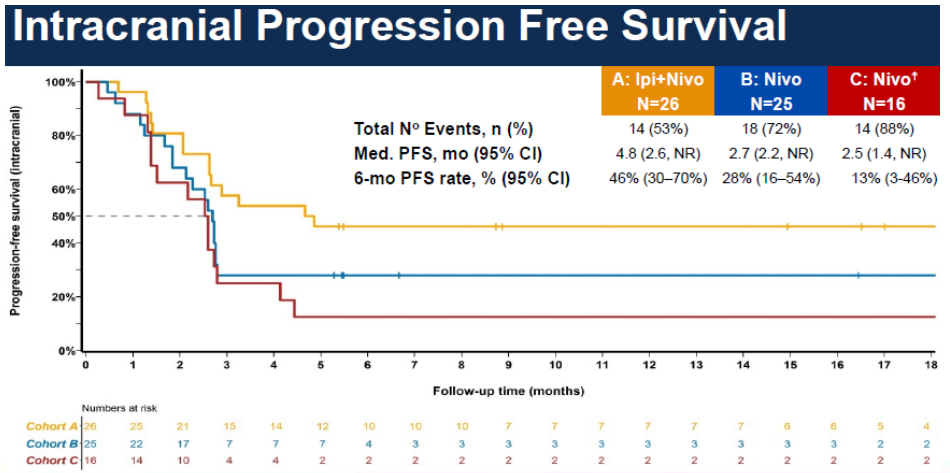
Prospective phase II clinical trials of ipilimumab + nivolumab in locally untreated melanoma brain metastases presented at ASCO 2017[1,2]

Study	Therapy, Cohorts	Tot. No.	ORR IC %	ORR EC %	Gr3/4 AE%	Discontinuation due to AE
CMate 204	Ipi/nivo	75	**55**	**49**	52	31
ABC	A: Ipi/nivo	26	**42***	**48**	46	27
	B: Nivo	25	**20***	**30**	24	4
	C: Nivo	16	**6**	**25**	19	6





AE, adverse event; CI, confidence interval; EC, extracranial; Gr, grade; IC, intracranial; ipi, ipilimumab; nivo, nivolumab; NR, not reached; PFS, progression-free survival.

1. Tawbi et al. Presented at ASCO 2017; Abstract 9507. 2. Long et al. Presented at ASCO 2017; Abstract 9508.

Lesson 6: Resistance will emerge sooner or later. Understanding the mechanisms is key

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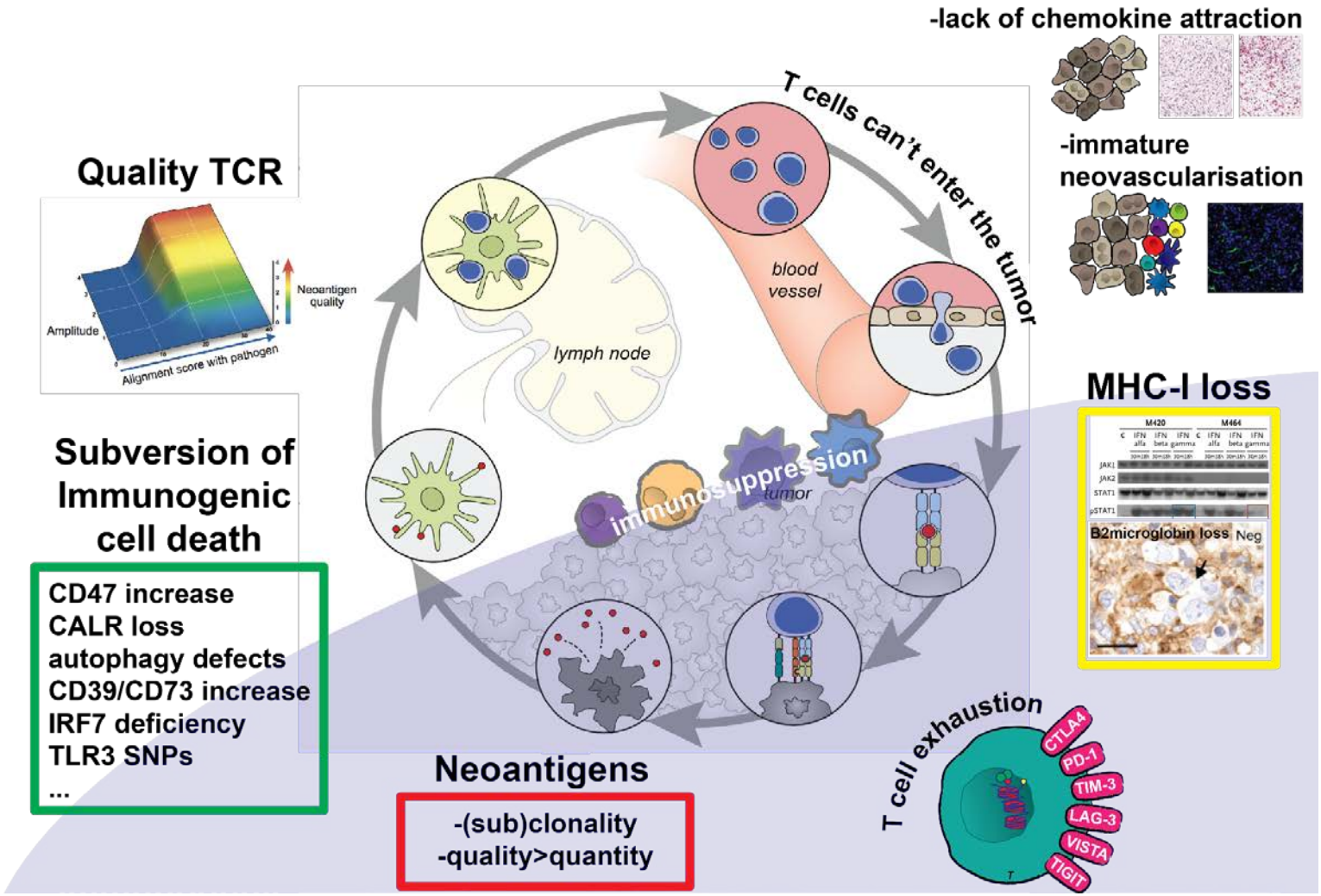
Resistance mechanisms are multifactorial



MHC, major histocompatibility complex; SNP, single nucleotide polymorphism; TCR, T-cell receptor.
Slide provided courtesy of S. Aspeslagh. Figure adapted from Chen & Mellman. Immunity 2013;39:1–10.

Lesson 7: Predictive biomarkers are present but not perfect

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Predictive biomarkers of checkpoint inhibitors under investigation

- **PD-L1 expression** (in tumor cells and/or tumor-infiltrating immune cells)

Overall, there is a correlation, but it is not perfect, and it is variable between drugs, antibodies used for staining, tumor types, and settings

- **Mutational load/neoantigens:** emerging biomarker (e.g. NSCLC, etc.)
- **Gene signature** (e.g. IFNγ signature)?
- **TILs/CD8+T cells** (T-cell clonality or fraction)?
- **CRP? LDH?**
- **Combination of biomarkers** (e.g. immunogram...)

CRP, C-reactive protein; LDH, lactate dehydrogenase; TIL, tumor-infiltrating lymphocyte.
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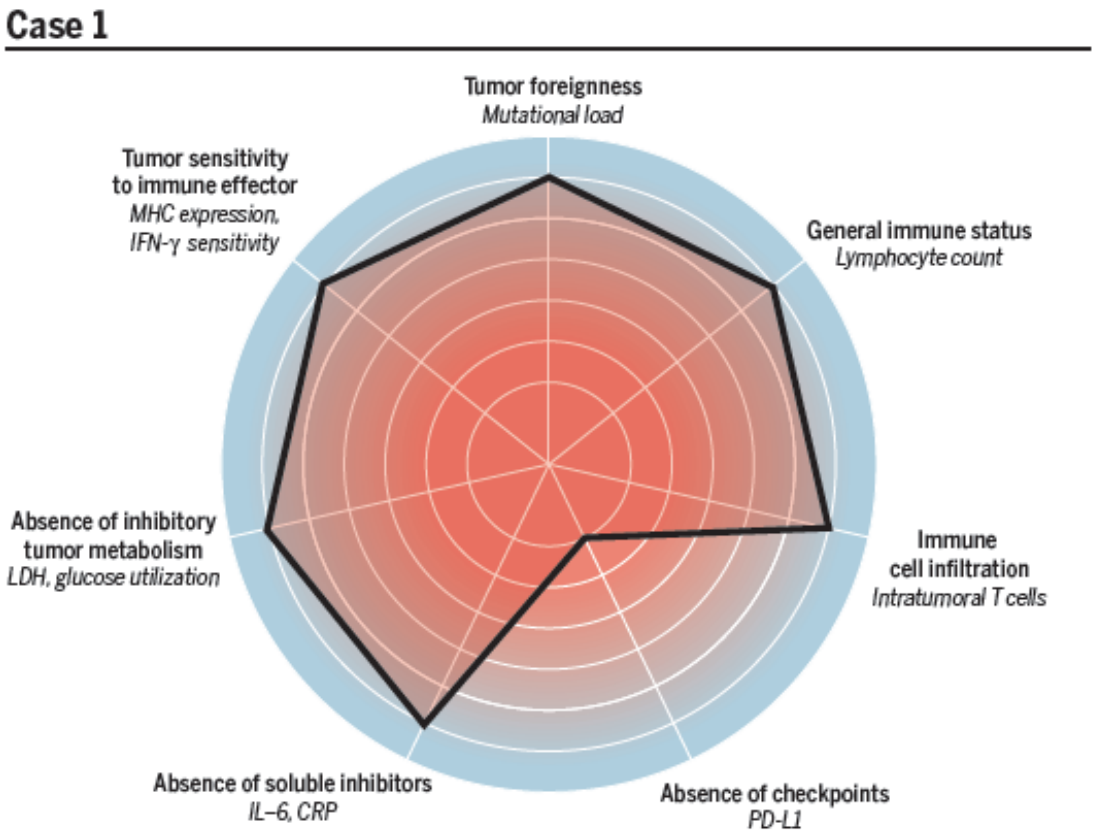
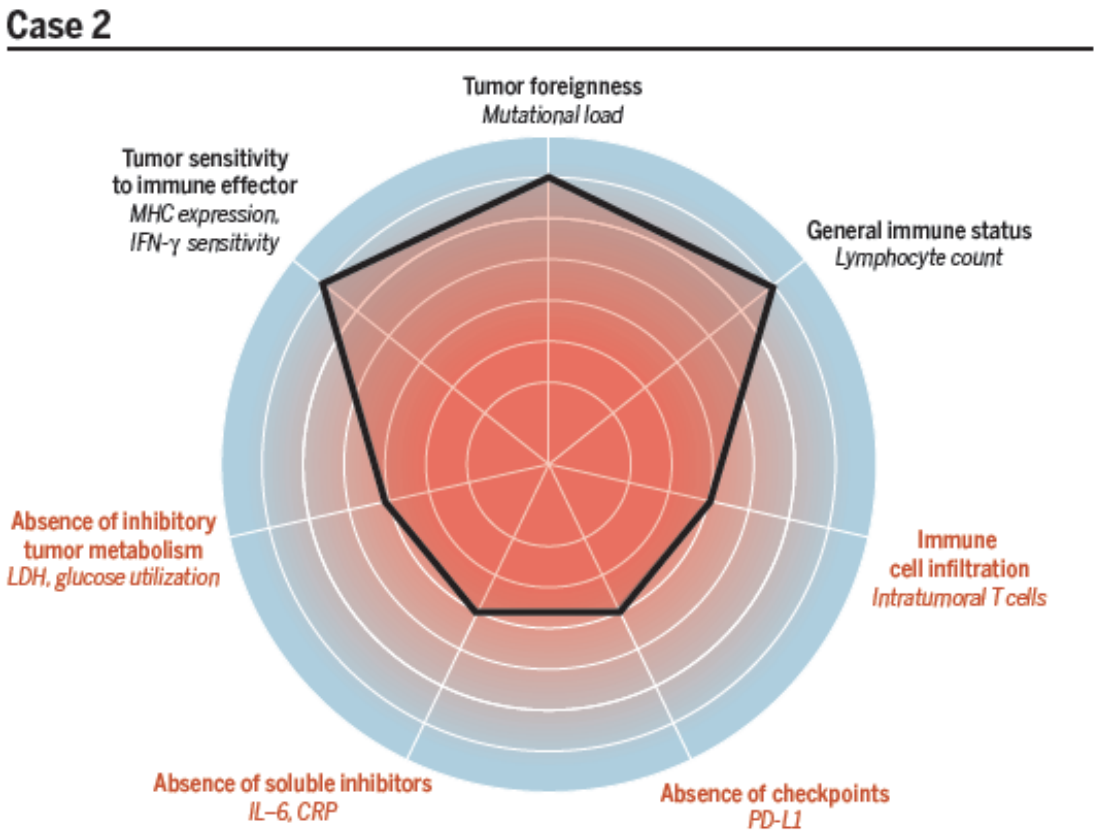
The cancer immunogram: value as a predictive tool to predict sensitivity/resistance to therapy?





Blank et al. Science 2016;352:658–60.

Lesson 8: The pattern of tumor responses is different from that of other anticancer agents

- Timing of tumor response (early vs late)
- Duration of response (under or after stopping therapy)
- Pseudoprogression (rare outside melanoma)
- Hyperprogression (10–20%)

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Lesson 9: Survival is probably the best outcome in clinical trials (and not PFS!)

- Median survival time
- Percentage of surviving patients at different time points!

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Lesson 10: Side effects are mainly autoimmune diseases, which could, rarely, be fatal if not quickly and well managed

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Healthy organs affected by immune checkpoint blockade

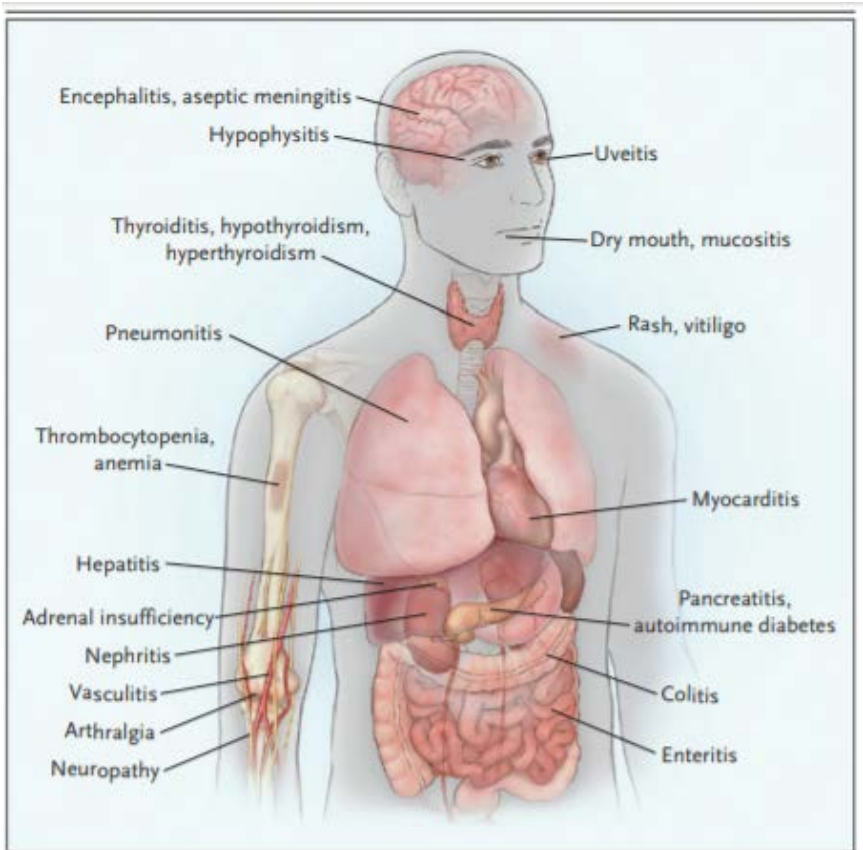

Figure 1. Organs Affected by Immune Checkpoint Blockade.
Immune checkpoint blockade can result in inflammation of any organ. Shown are the most common immune-related adverse events that clinicians encounter in patients treated with immune checkpoint blockade.

Postow et al. N Engl J Med 2018;378:158–68.

Lesson 11: Some clinical answers but still a lot of challenging questions

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Immune checkpoint inhibitors: clinical research questions (1)

- Fully define spectrum of clinical activity; endpoints?
- Optimal doses/schedules/sequences and duration of therapy
- How to optimally manage the side effects and other events under treatment?

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Immune checkpoint inhibitors: clinical research questions (2)

- Role of the microbiome/use of antibiotics before or during therapy
- Benefit/risk in elderly patients/patients with organ grafts/patients with HIV
- Benefit/risk in patients with autoimmune diseases
- Efficacy in brain metastases (treatment or prevention)

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Lesson 12: Checkpoint inhibitors are not the only approach.

Other immuno-oncology approaches are emerging

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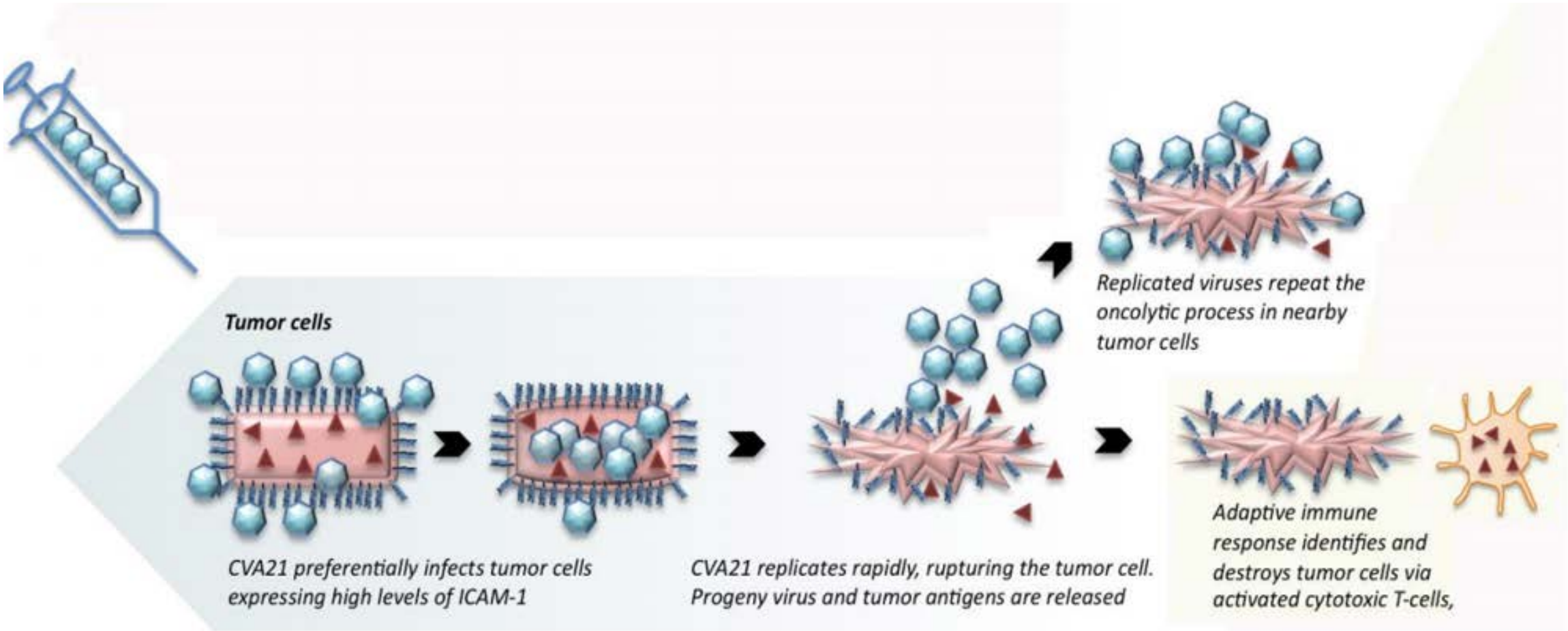
CAR-Ts CYAD-01 program at JB Institute

- CYAD-01: NKG2D receptor-based CAR-T targets
  - Eight stress ligands expressed across the hematologic/solid tumors
- CYAD-01: multiple administrations (safe) in ≠ solid tumors
- CYAD-01: combination with FOLFOX in CRC

CAR, chimeric antigen receptor; FOLFOX, folinic acid + fluorouracil + oxaliplatin; JB, Jules Bordet; NKG2D, natural killer group 2 member D.
A. Awada. Personal communication 2018.

Mode of action of oncolytic CVA21, an oncolytic virus



CVA21, coxsackievirus A21; ICAM-1, intercellular adhesion molecule 1.
Andtbacka et al. Presented at ASCO 2017; Abstract 3031.

Modern immunotherapy with CPIs has broken many dogmas in oncology… (1)

It is not true that

1. Immunotherapy does not work in bulky tumors
2. Immunotherapy works only in what were considered ‘immunologic tumors’, such as melanoma and RCC
3. Significant survival rates (cure?) are difficult to obtain in metastatic disease

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Modern immunotherapy with CPIs has broken many dogmas in oncology… (2)

It is not true that

4. Early progressive disease should trigger stopping the therapy (so what about pseudoprogression and late responses?)
5. Immunotherapy should not be combined with chemotherapy (and/or radiotherapy)
6. Our management of patients with cancer (mainly metastatic disease) is still minor

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But it is true that we are at the beginning, and we should continue to do hard but smart work to achieve more progress

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Thank you

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