emerging perspectives

Fundamentals of Cancer

Module 3: Precision/Personalized Medicine and Oncology Endpoints

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BIO ONCOLOGY

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Module 3

PRECISION/PERSONALIZED MEDICINE AND ONCOLOGY ENDPOINTS

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Learning objectives

- Review the concept of personalized/precision medicine and explain the importance of biomarkers in the practice of this individualized approach to managing patients with cancer
- Discuss the importance of adaptive immunity in protecting the body against cancer and innovative strategies to increase T cell–mediated antitumor response
- Describe strategies to overcome or delay the development of resistance
- Review traditional approaches to clinical development, common trial endpoints, and recent developments

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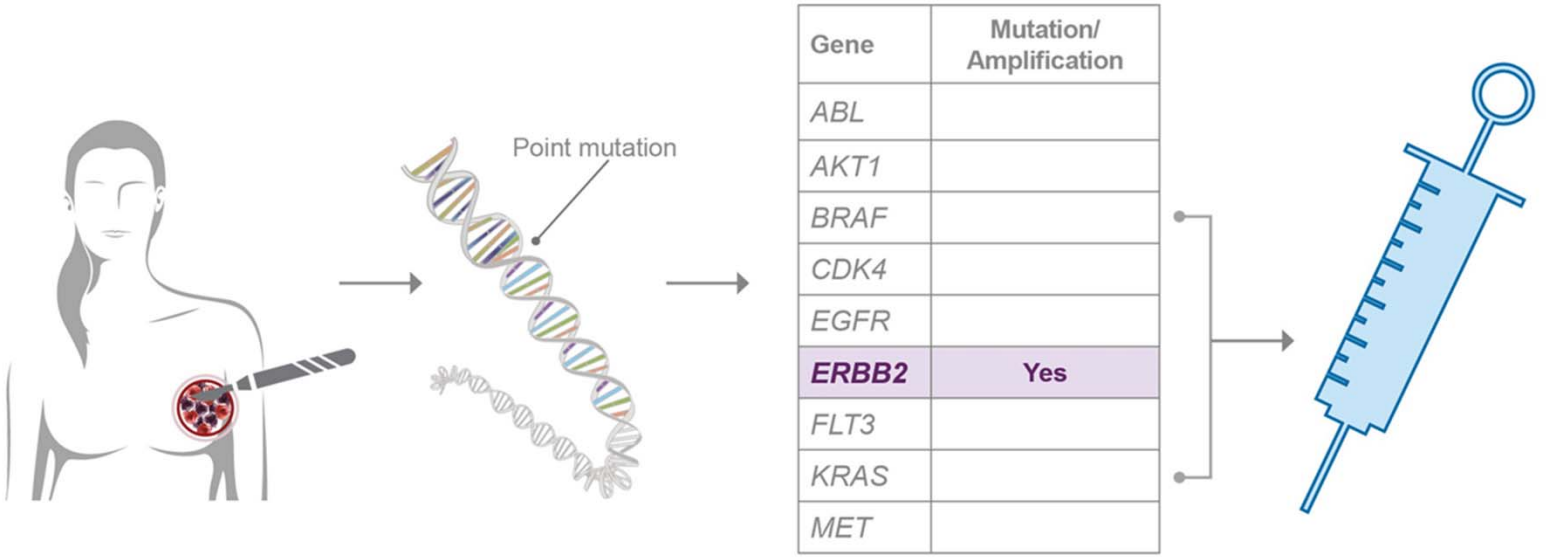
What is precision/personalized medicine?



- The ability to profile patients for a comprehensive set of clinically actionable genomic alterations defines personalized cancer medicine
- Advances in technology have enabled the identification of thousands of mutations in patient tumors, and these specific genetic variants can help in the development of personalized cancer treatments

ABL=Abelson murine leukemia viral oncogene homolog; CDK4=cyclin-dependent kinase 4; EGFR=epidermal growth factor receptor; ERBB2=v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; FLT3=FMS-like tyrosine kinase 3; KRAS=Kirsten rat sarcoma viral oncogene homolog.

MacConaill LE, Garraway LA. *J Clin Onc*. 2010;28:5219-5228.

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Biomarkers are key to driving personalized approaches to patient management

What is a biomarker?

A characteristic that is objectively measured and evaluated as an indicator of:

- Normal biologic processes
- Pathogenic processes
- Pharmacologic responses to a specific therapeutic intervention

Prognostic

Provides information about the patient's overall cancer outcome, regardless of therapy

Predictive

Provides information on the effect of a therapeutic intervention in a patient (eg, predicts response to a particular therapy)

Pharmacogenomic

Provides data on interindividual differences in the PK, PD, and toxicity of therapy

PD=pharmacodynamics; PK=pharmacokinetics.

Oldenhuis CN, et al. *Eur J Cancer*. 2008;44:946-953. Ventola CL. *P T*. 2013,38:545-560.

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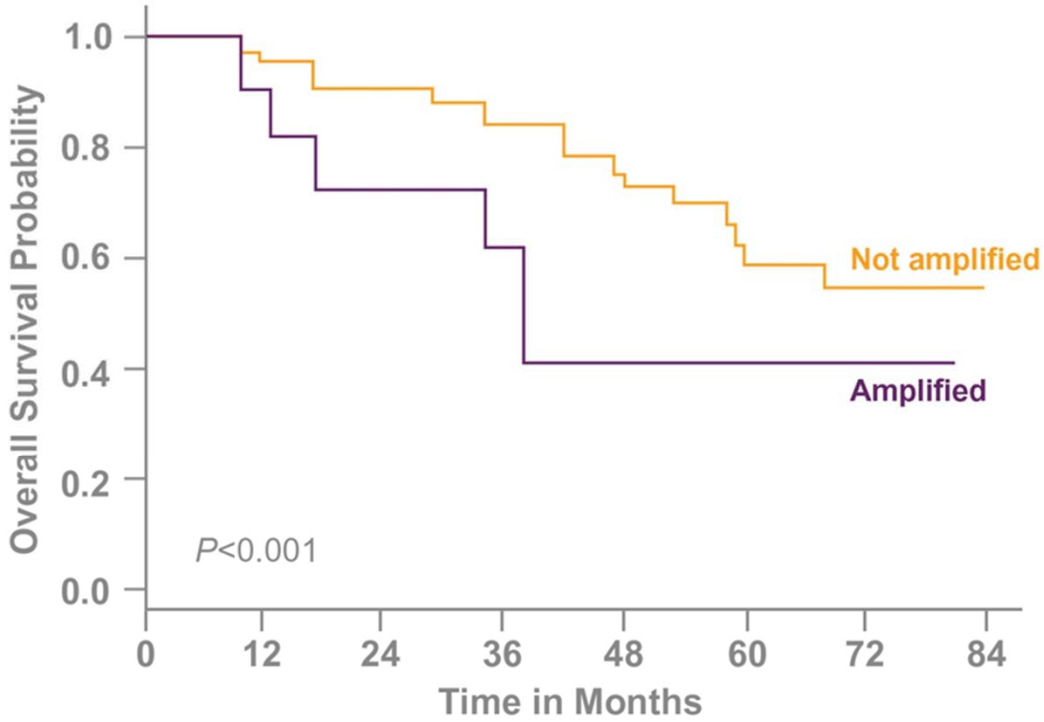
Examples of clinically relevant biomarkers: *HER2* can be used as a predictive or prognostic biomarker in breast cancer



Analyses were performed on 86 primary breast cancer samples from node-positive patients.

- Prognostic: In patients with breast cancer, *HER2* amplification is associated with shorter overall survival
- Predictive: Patients with *HER2*-amplified breast cancer are more likely to respond to *HER2*-targeted agents

HER2=human epidermal growth factor receptor 2.

Cianfrocca M, Goldsterin LJ. *Oncologist*. 2004;9:606-616. Slamon DJ, et al. *Science*.1987;235:177-182.
From Slamon et al. *Science* 235:177 (1987) . Reprinted with permission from AAAS.

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Examples of FDA-recognized clinically relevant biomarkers

Hematologic disease

- KIT D816V mutation
- Del(17p)
- BCR-ABL1 expression/mutations
- *PML-RAR* translocation; t(15;17)
- *FIP1L1-PDGFRA* (del 4q12)
- *PDGFRB* rearrangements
- Del(5q)
- *Tp53* deletion

Gastric

- *HER2* amplification/overexpression
- *c-Kit expression*

Solid tumors

- dMMR/MSI-H*

Non-small cell lung cancer

- *EGFR* expression
- *ALK* expression/gene rearrangement
- *EGFR* exon 19 deletion
- EGFR T790M mutation
- EGFR L858R mutation
- *EGFR* exon 20 insertions
- EGFR G719X mutation
- EGFR S768I mutation
- EGFR L861Q mutation
- PD-L1
- ROS1
- BRAF V600E

Melanoma

- BRAF V600E/K mutation

Breast cancer

- ER expression
- PR expression
- *HER2* amplification/overexpression
- *BRCA1* and *BRCA2*

Colorectal cancer

- *KRAS* and *NRAS* mutations*
- *BRAF* mutations
- EGFR expression*
- DPYD deficiency
- *UGT1A1*28* allele

Ovarian

- *BRCA1* and *BRCA2*

*Approved as complementary and/or companion diagnostic by the FDA as of February 2018.

ABL1=Abelson murine leukemia viral oncogene homolog 1; ALK=anaplastic lymphoma kinase; BCR=B-cell receptor; BRCA1/2=breast cancer susceptibility gene 1/2; c-KIT=proto-oncogene receptor tyrosine kinase c; dMMR=mismatch repair deficient; DPYD=dihydropyrimidine dehydrogenase; EGFR=epidermal growth factor receptor; ER=estrogen receptor; FIP1L1-PDGFRA=FIP1-like-1–platelet-derived growth factor receptor-alpha; HER2=human epidermal growth factor receptor-2; KRAS=Kirsten rat sarcoma; MSI-H=microsatellite instability high; NRAS=neuroblastoma rat sarcoma; PDGFRA/B=platelet-derived growth factor receptor A/B; PD-L1=programmed death-ligand 1; PML=promyelocytic leukemia protein; PR=progesterone receptor; RAR=retinoic acid receptor; ROS1=c-ros oncogene 1; Tp53=tumor suppressor 53.

US Food and Drug Administration. http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm. Accessed February 8, 2018.

US Food and Drug Administration. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm. Accessed February 8, 2018.

US Food and Drug Administration. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm330711.htm. Accessed February 8, 2018.

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PERSONALIZED APPROACH TO ELICIT T CELL–MEDIATED ANTITUMOR IMMUNITY

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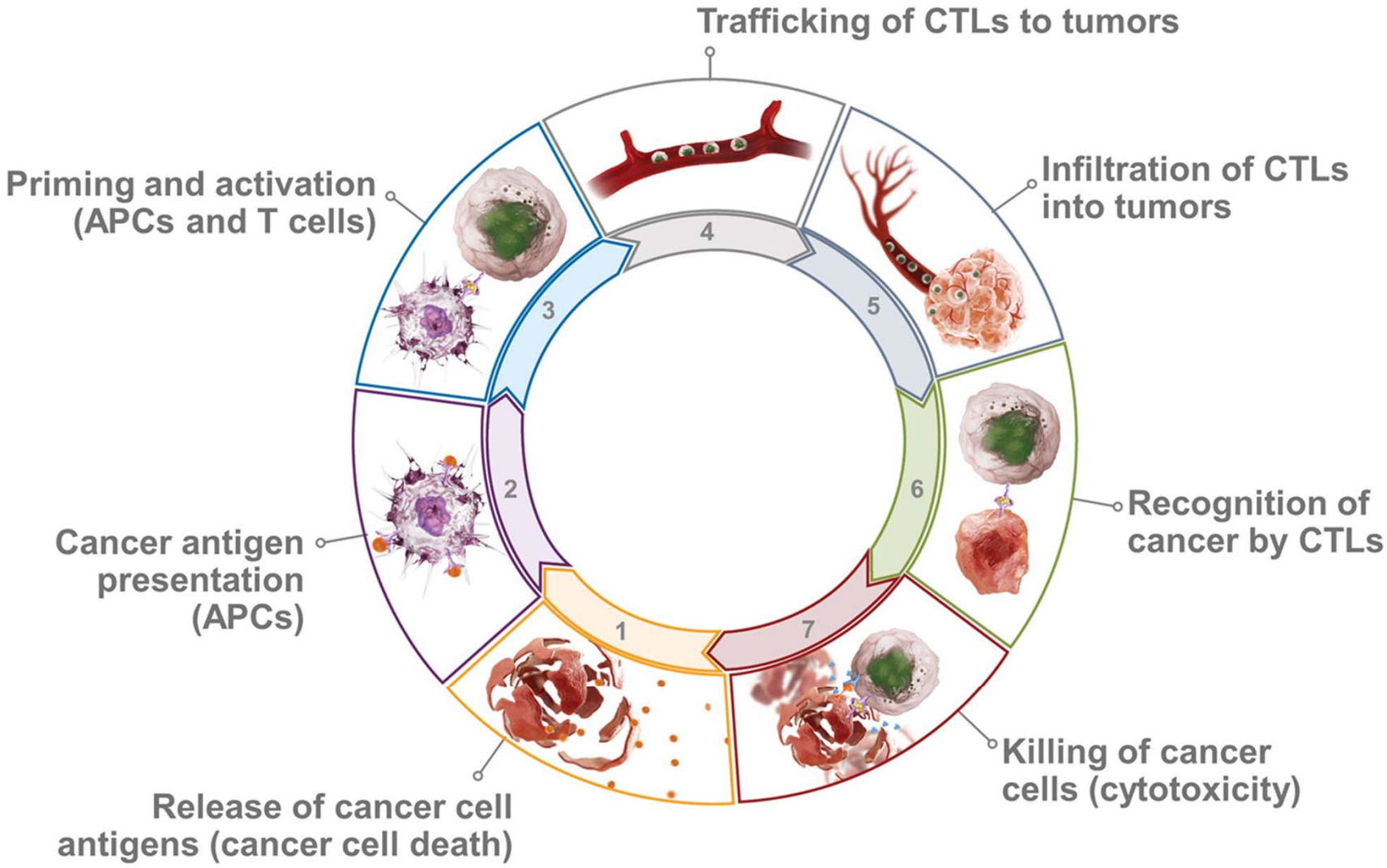
Cytotoxic T cells play an important role in protecting the body against cancer



APC=antigen presenting cell; BC=breast cancer; CTL=cytotoxic T lymphocytes.
Chen D, Mellman I. *Immunity*. 2013;39:1-10.
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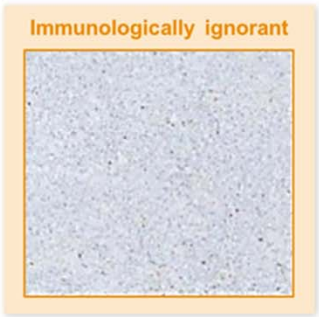
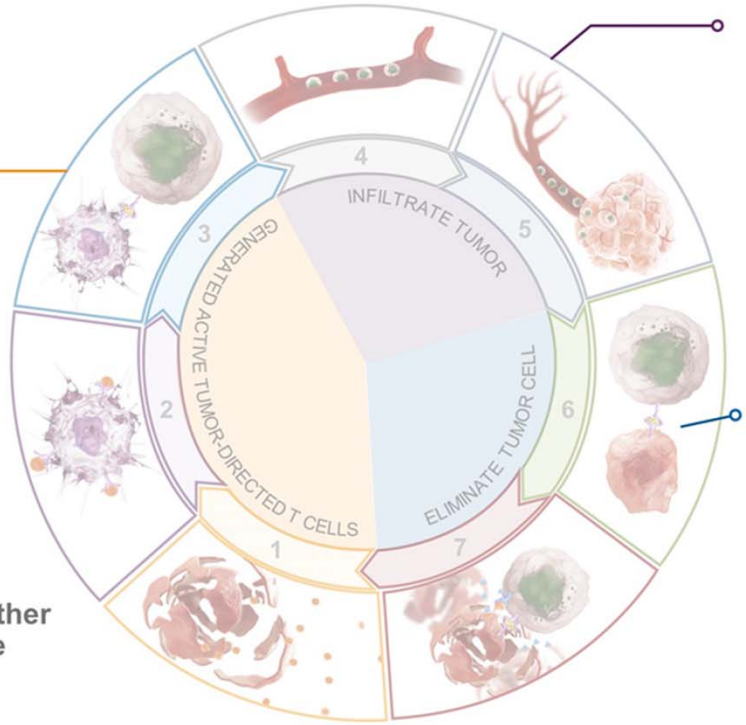
Tumors can be classified into immune phenotypes based on their mechanisms of evading T cell–mediated antitumor immunity



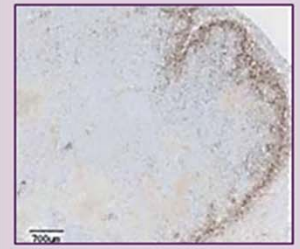
Immune desert[a]

- Low MHC I
- Highly proliferative
- **Characterized by the paucity of T cells in either the parenchyma or the stroma of the tumor**



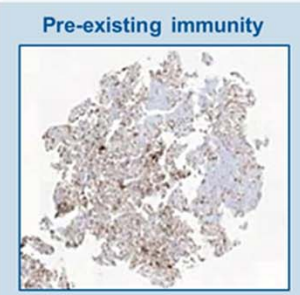
Immune excluded[b]

- Immune reactive stroma
- Angiogenesis
- **Characterized by abundance of immune cells, but these do not penetrate the tumor**



Inflamed[c]

- High TIL/CD8+ T cells
- High IFN-γ
- High PD-L1
- High mutational burden
- **Presence of pre-existing antitumor response, but was arrested**



Specific immune phenotypes are associated with different mechanisms of immune escape from immune surveillance and may have a significant impact on the clinical development of immunotherapeutic agents.

[a]Immune desert: Failure can occur in step 1, 2, or 3 of the CIC.

[b]Immune excluded: Failure can occur in step 4 or 5 of the CIC.

[c]Inflamed: Failure can occur in step 6 or 7 of the CIC.

CIC=cancer-immunity cycle; IFN-γ=interferon-gamma; MHC I=major histocompatibility complex class I; PD-L1=programmed death-ligand 1; TIL=tumor-infiltrating lymphocytes.

Hegde PS, et al. *Clin Cancer Res*. 2016;22:1865-1874. Kim JM, Chen DS. *Ann Oncol*. 2016;27:1492-1504. Chen DS, Mellman I. *Nature*. 2017;541:321-330.

Reprinted with permission from Elsevier.

Adapted from *Clinical Cancer Research*, 2016, 22/8, 1865-1874, Hegde PS, Karanikas V, Evers S, The where, the when, and the how of immune monitoring for cancer immunotherapies in the era of checkpoint inhibition, with permission from AACR.

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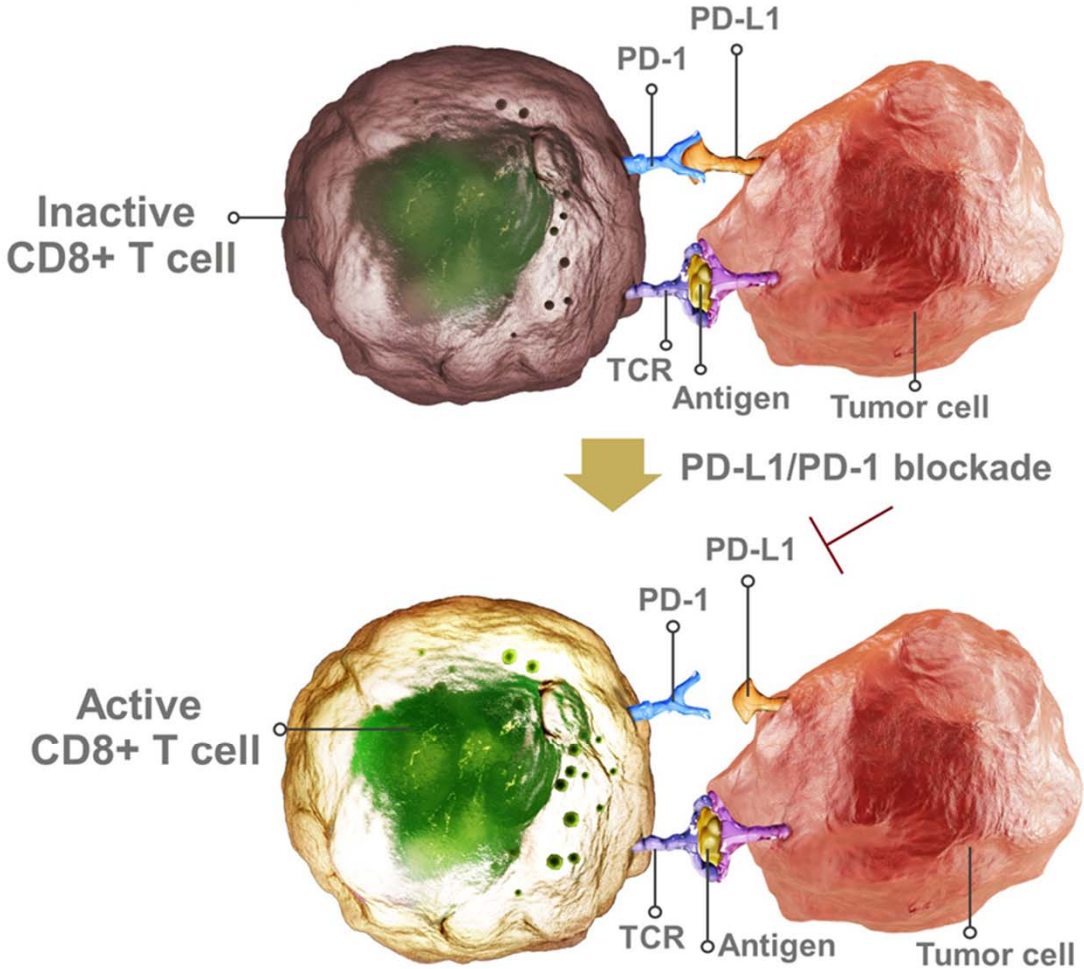
Innovative approaches to elicit T cell–mediated immunity: Disrupting immune checkpoint interaction

Potential approach to increase T cell–mediated immunity in tumors with the inflamed immune phenotype: targeting PD-L1



PD-1=programmed death-1; PD-L1=programmed death-ligand 1; TCR=T-cell receptor.

Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264. Chen D, Mellman I. *Immunity*. 2013;39:1-10.

Adapted by permission from Springer Nature: *Nature Reviews Cancer* The blockade of immune checkpoints in cancer immunotherapy, Pardoll DM, © 2012.

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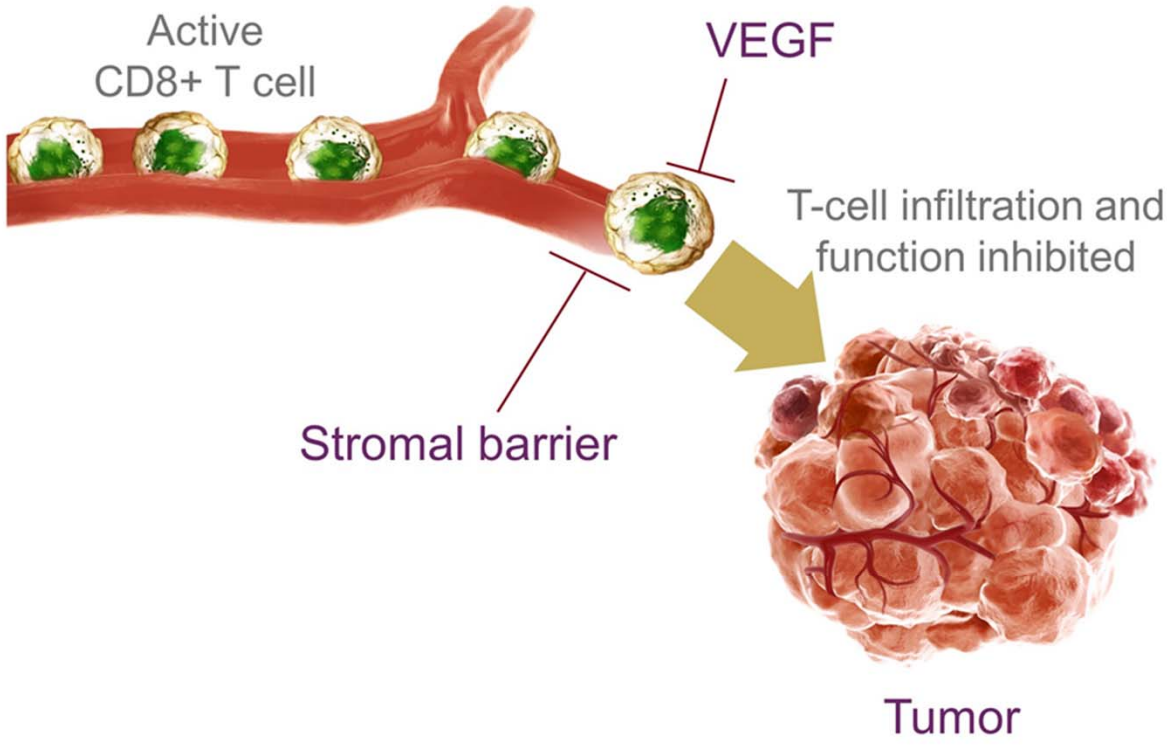
Innovative approaches to elicit T cell–mediated immunity: Targeting barriers to T-cell trafficking and infiltration

Potential approach to increase T cell–mediated immunity in tumors with the excluded immune phenotype: targeting VEGF



VEGF=vascular endothelial growth factor.

Mauge L, et al. *Front Oncol.* 2014;4:1-10.

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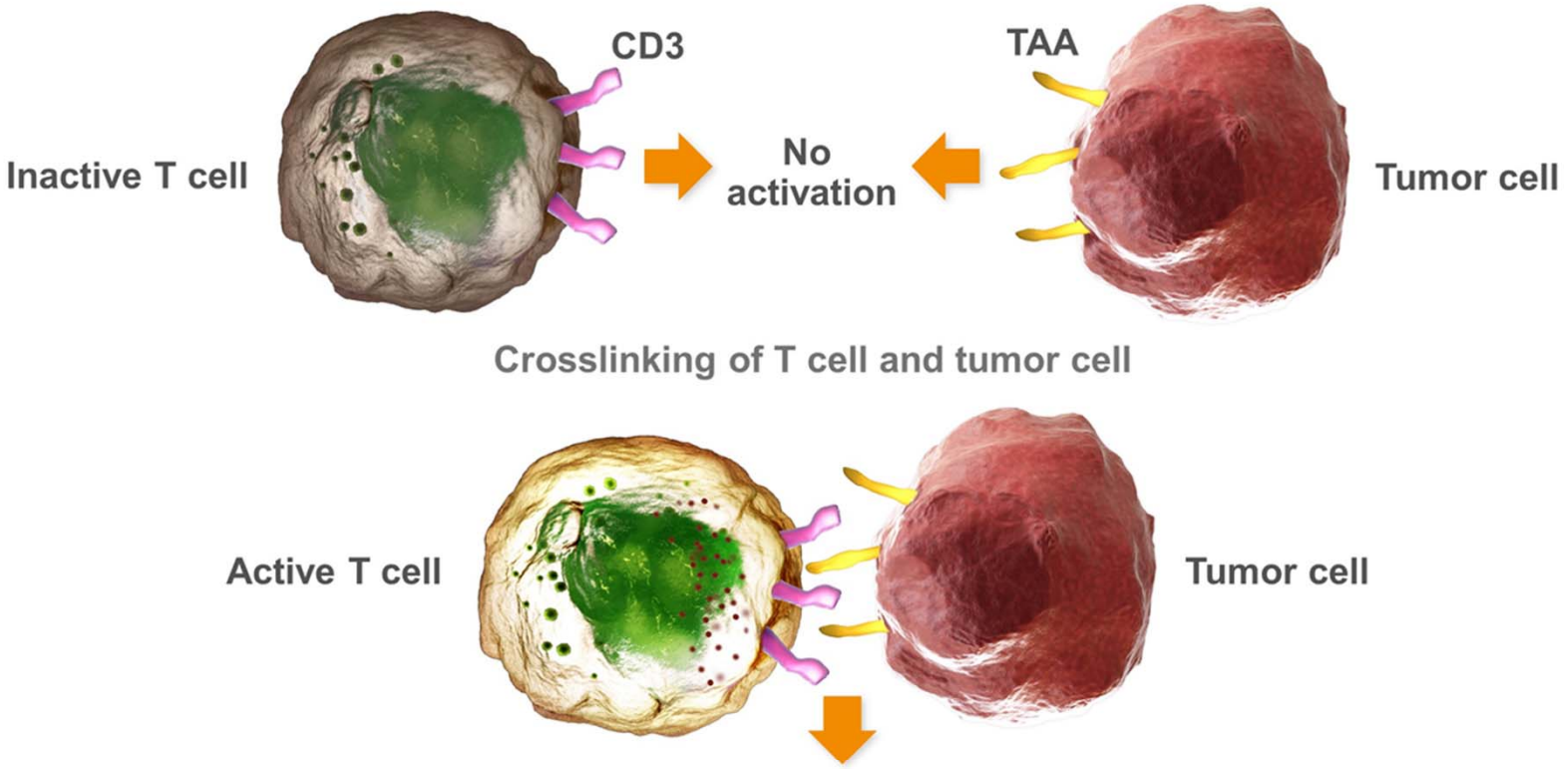
Innovative approaches to elicit T cell–mediated immunity: Crosslinking of cytotoxic T cell to tumor cell

Potential approach to increase T cell–mediated immunity in tumors with the desert-immune phenotype



One approach is based on the recognition of tumor surface antigens and the simultaneous binding of the CD3ε chain (a component of the TCR complex) on T cells. This coordinated event may trigger the activation of cytotoxic and helper T cells leading to intratumoral T-cell accumulation, T-cell proliferation, cytokine production, and T cell–mediated immunity.

TAA=tumor-associated antigen; TCR=T-cell receptor.

Bacac M, et al. *Clin Cancer Res*. 2016;22:3286-3297.

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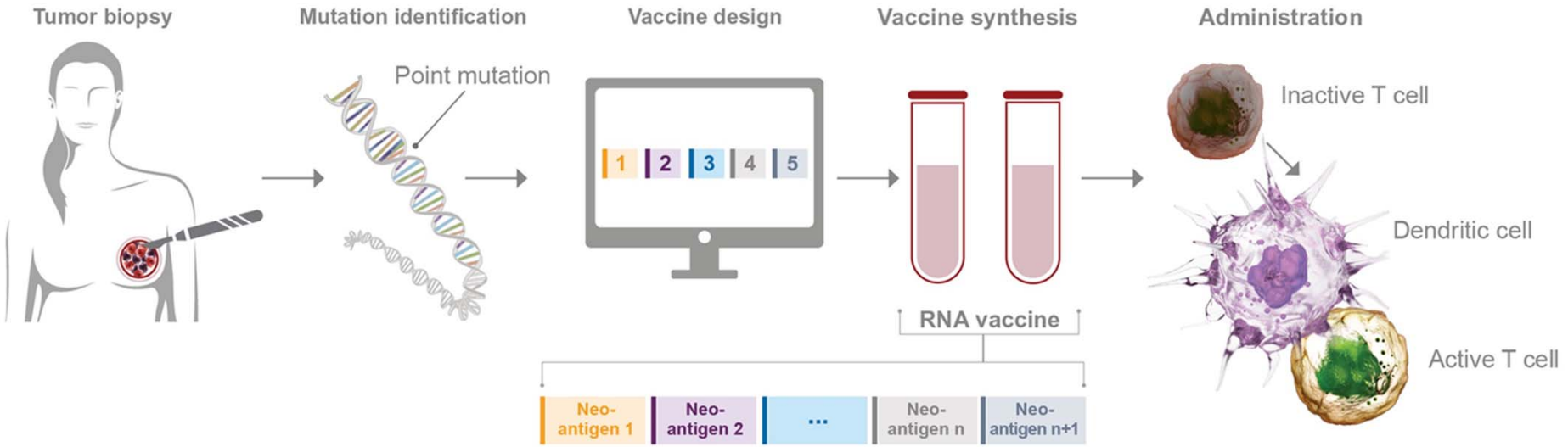
Emerging approaches to elicit T cell–mediated immunity: Personalized cancer vaccines

Potential approach to increase T cell–mediated immunity in tumors with the desert-immune phenotype



- Only a small fraction of cancer mutations induce spontaneous immune responses in the tumor-bearing host, thus limiting the effectiveness of immunotherapy to tumors with a high mutational load
- Targeting unique individual cancer mutations by RNA neo-epitope vaccines may allow the mobilization of T-cell immunity against tumors harboring these specific mutations in a patient

Sahin U, et al. *Nature*. 2017; 547:222-226. Vormehr M, et al. *J Immunol Res*. 2015;2015:595363.

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MULTI-PATHWAY APPROACH TO DELAY OR OVERCOME RESISTANCE

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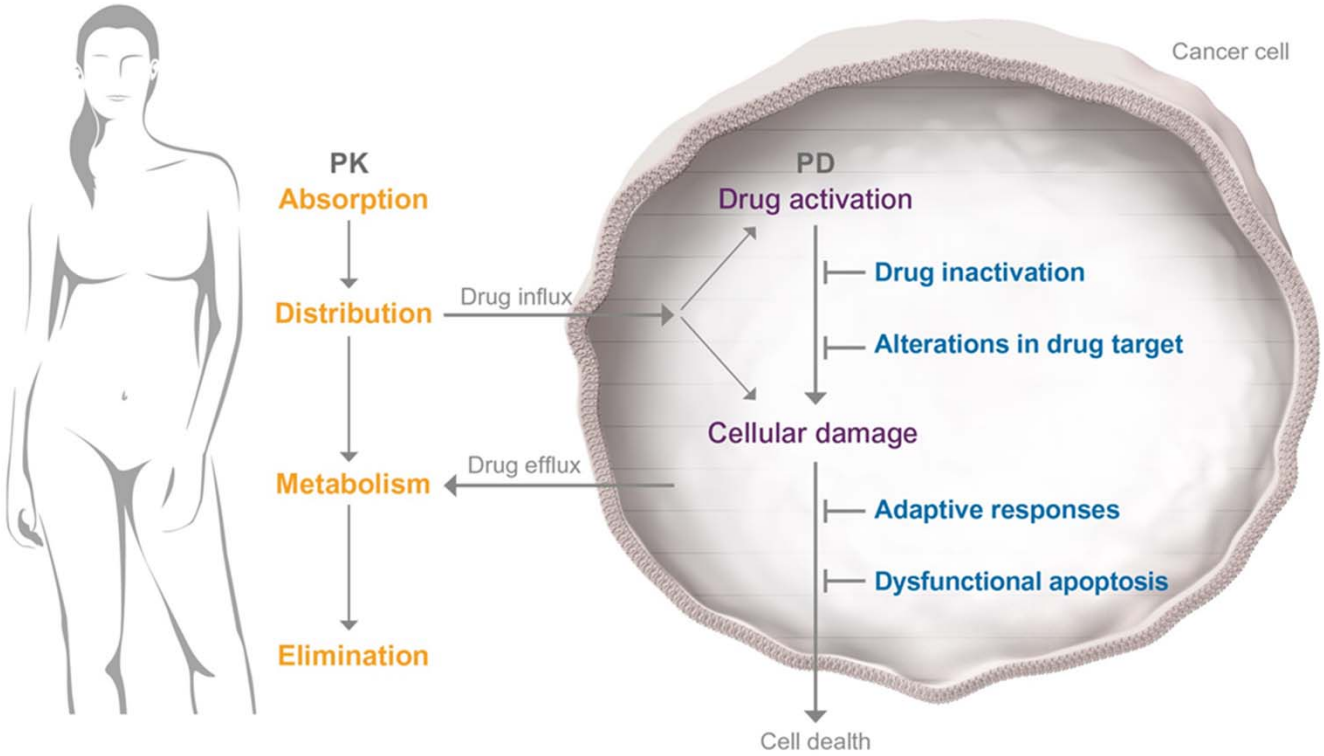
There are multiple resistance mechanisms to anticancer therapy regimens



- Drug resistance limits the effectiveness of current cancer therapies
- Absorption, distribution, metabolism, and elimination (ADME) are drug properties that limit the amount of drug that reaches the tumor
- Various drug resistance mechanisms can operate at the cellular level, such as increased drug efflux, mutations of the drug target, DNA damage repair, activation of alternative signaling pathways, and evasion of cellular death

PD=pharmacodynamics; PK=pharmacokinetics.
Holohan C, et al. *Nat Rev*. 2013;13:714-726.
Adapted by permission from Springer Nature: *Nature Reviews Cancer* Cancer drug resistance: an evolving paradigm, Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG, © 2013.

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Due to the emergence of drug-resistant clones, responses to single-agent therapy can be short-lived

- Tumor heterogeneity can be intratumor or intertumor
- Genetic differences between malignant cells and selective pressure drive genetic heterogeneity and clonal evolution
- Intratumor heterogeneity can be observed in breast cancer cells in the form of 2 distinct or intermixed clones exhibiting different patterns of *HER2* gene amplification and overexpression

HER2=human epidermal growth factor receptor 2.

Landau DA, et al. *Leukemia*. 2014;28:34-43. Ng CK, et al. *Genome Biology*. 2015;16:1-21.

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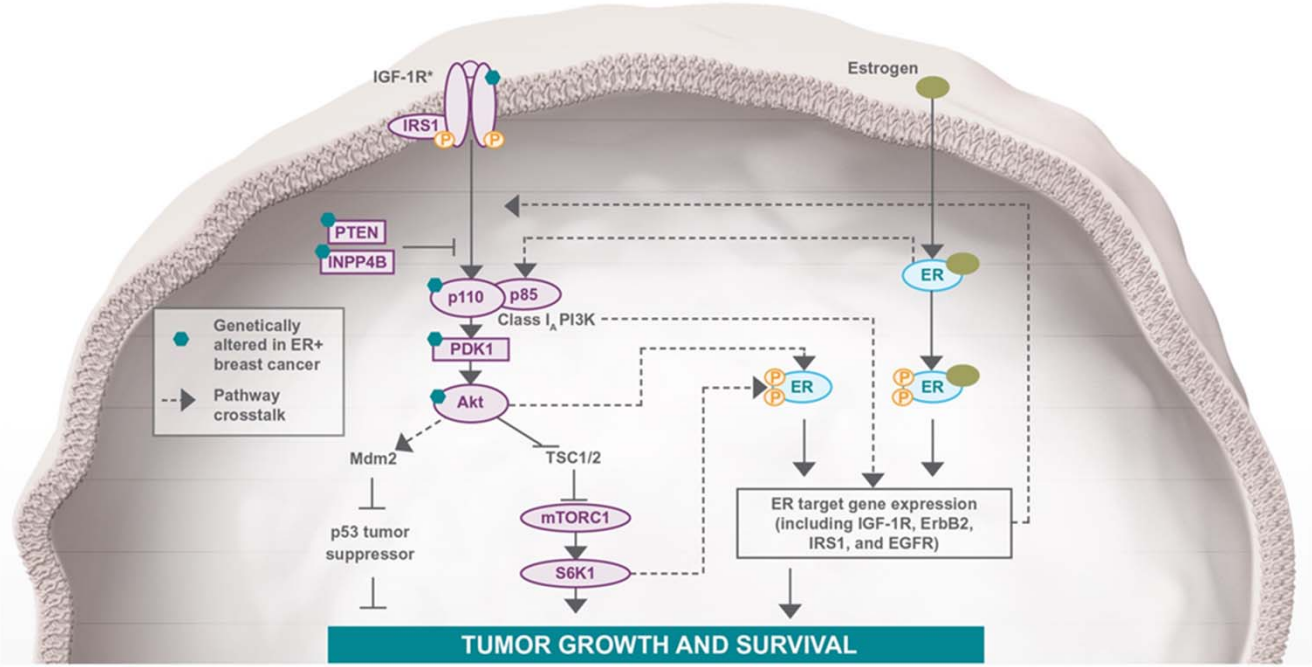
Crosstalk between different signaling pathways may lead to the development of resistance



- The ER pathway is important in the development of hormone receptor–positive breast cancer
- Targeting the ER pathway in hormone receptor–positive tumors would be expected to interfere with a key driver of breast cancer, but it doesn't always stop growth and proliferation or sometimes does so only temporarily
- Hyperactivation of the PI3K/Akt/mTOR pathway is implicated in the development of resistance to the inhibition of ER pathway

EGFR=epidermal growth factor receptor; ER=estrogen receptor; ErbB2=human epidermal growth factor receptor 2; IGF-1R=insulin-like growth factor 1 receptor; INPP4B=inositol polyphosphate 4-phosphatase type II; IRS1=insulin receptor substrate 1; Mdm2=mouse double minute 2 homolog; mTORC1=mammalian target of rapamycin complex 1; p53=tumor suppressor 53; p110=class I_A PI3K catalytic subunit; p85=class I_A PI3K catalytic subunit; PDK1=phosphoinositide dependent kinase-1; PI3K=phosphatidylinositol 3-kinase; PTEN=phosphatase and tensin homolog; S6K1=ribosomal protein S6 kinase beta-1; TSC1/2=tuberous sclerosis 1/2.

Ciruelos Gil EM. *Cancer Treat Rev*. 2014;40:862-847.
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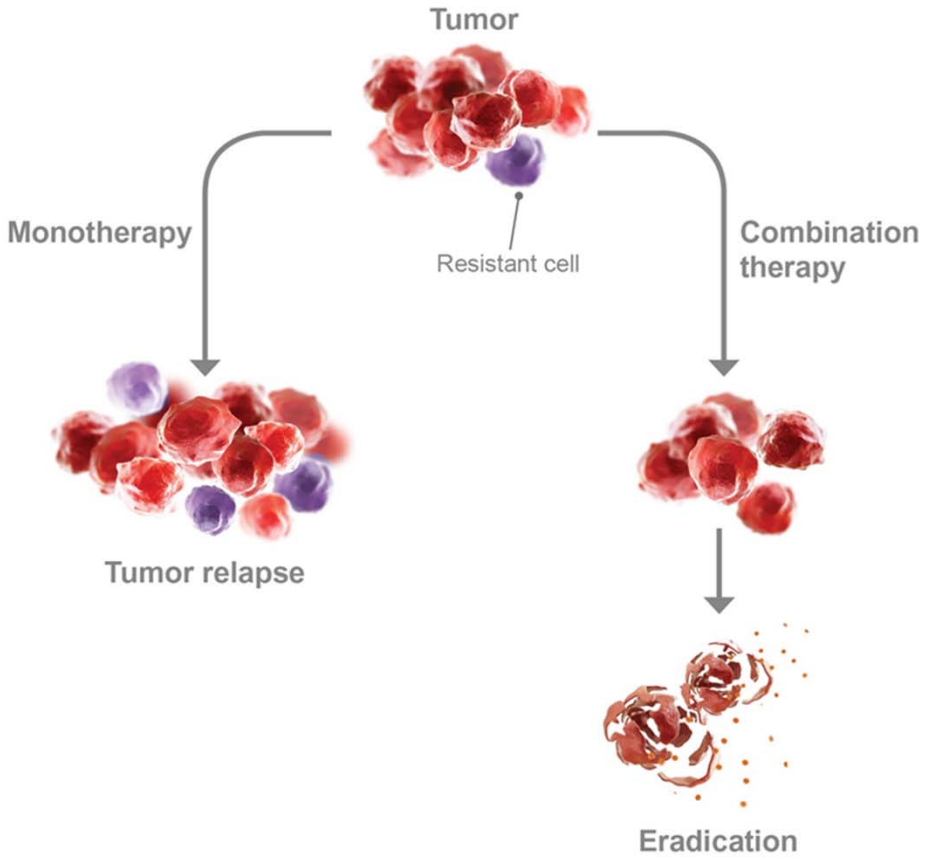
Combination therapy in cancer

- Combination therapy is a cornerstone of cancer therapy
  - Has the ability to target key pathways in a synergistic or an additive manner
  - Potentially reduces drug resistance



Mokhtari RB, et al. *Oncotarget*. 2017;8:38022-38043.
Figure adapted from Kaiser J. *Science* 2015;347:226-229.

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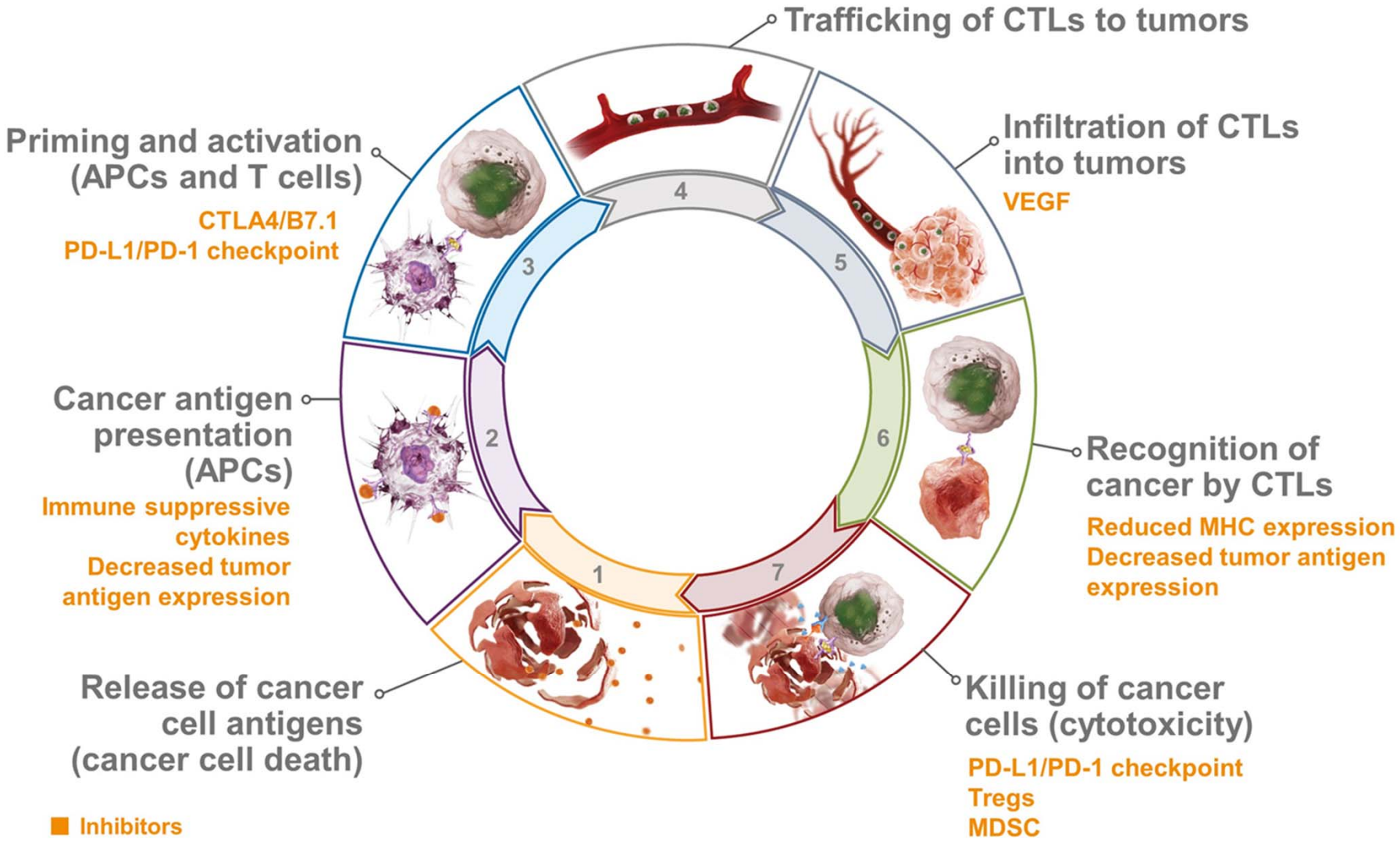
Multiple mechanisms of immune evasion can be targeted simultaneously in order to increase T cell–mediated antitumor response



APC=antigen-presenting cell; CTLA4=cytotoxic T-lymphocyte-associated antigen 4; CTLs=cytotoxic T lymphocytes; MDSC=myeloid-derived suppressor cell; MHC=major histocompatibility complex; PD-1=programmed death-1; PD-L1=programmed death-ligand 1; Treg=regulatory T cell; VEGF=vascular endothelial growth factor.

Chen DS, Mellman I. *Immunity*. 2013;30:1-10. Vinay DS, et al. *Semin Cancer Biol.* 2015;35(suppl):S185-S198.

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CURRENT APPROACHES TO CLINICAL TRIAL DESIGN AND COMMON ENDPOINTS

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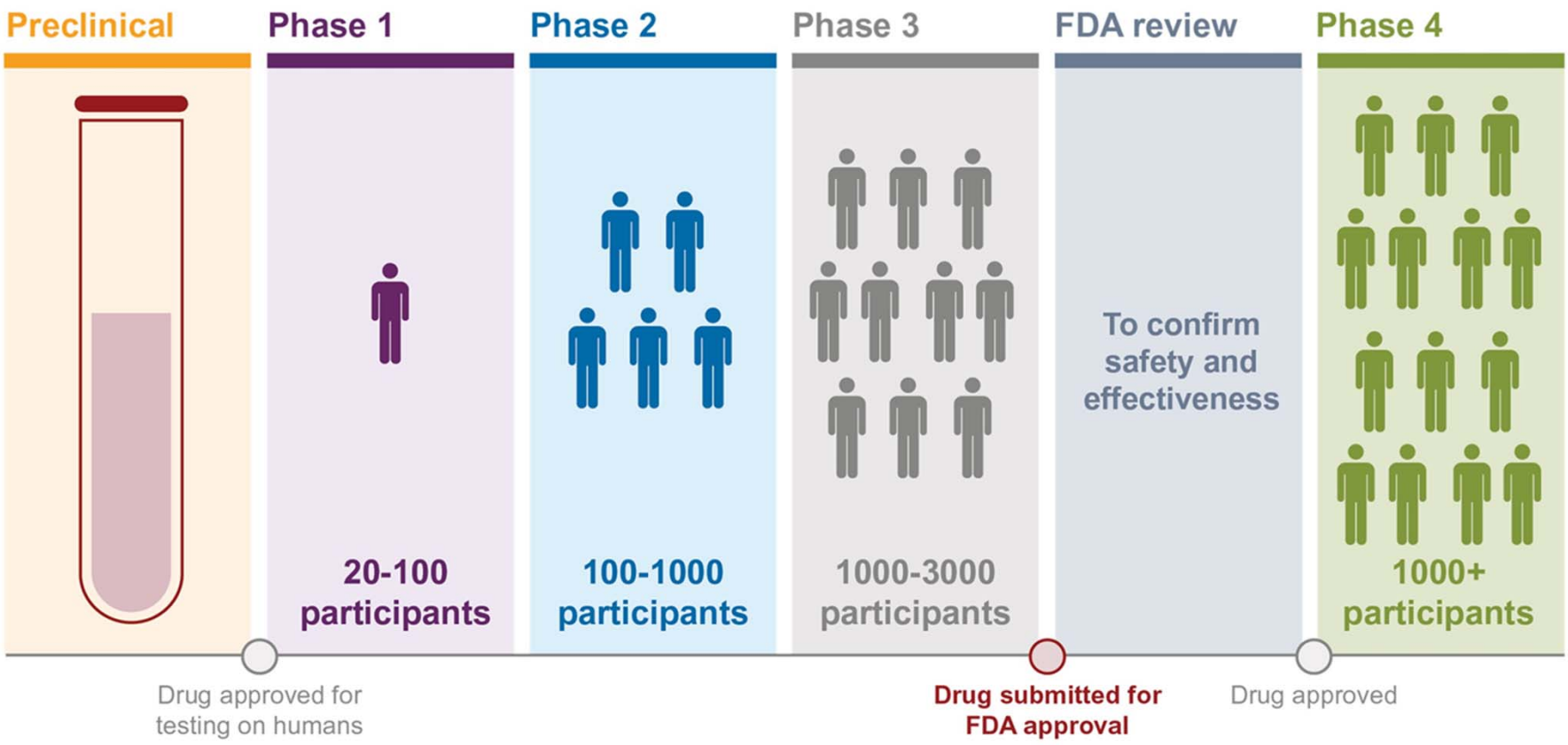
Overview of the clinical development of a drug



US Department of Health and Human Services. HIV/AIDS glossary: phase 3 trial. https://aidsinfo.nih.gov/understanding-hiv-aids/glossary/570/phase-3-trial. Accessed April 2, 2018.

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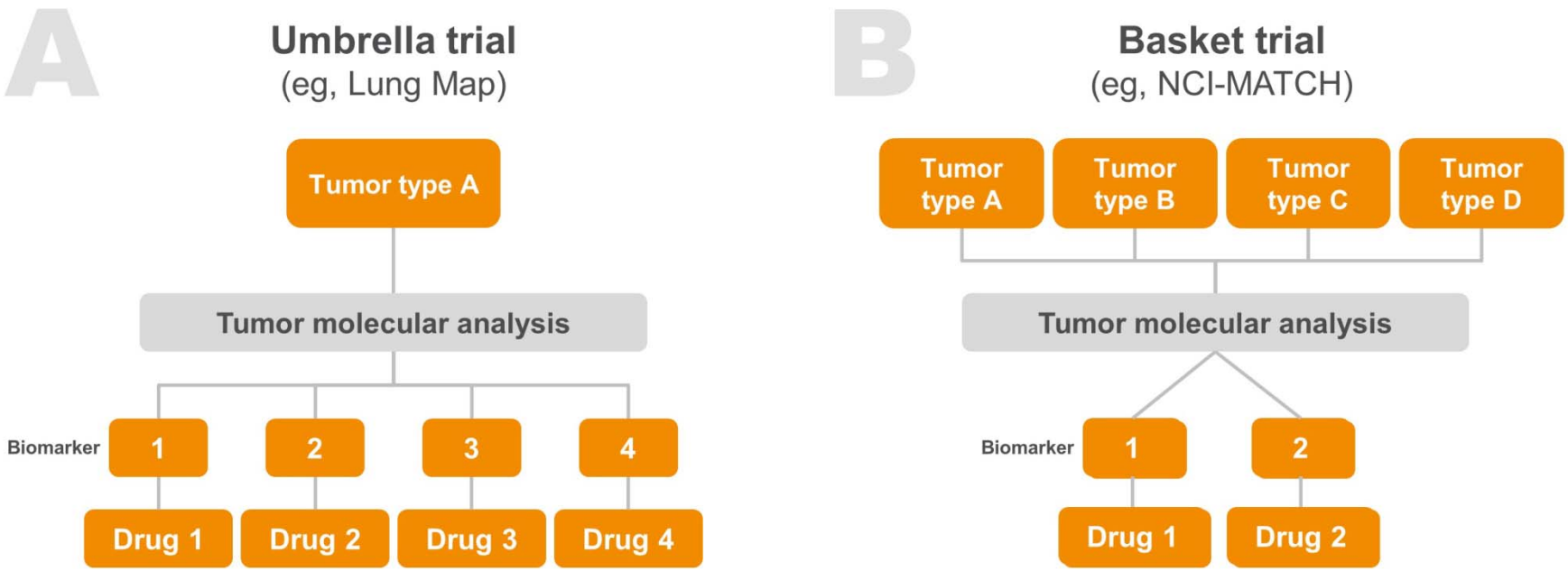
Biomarker-based trials and novel clinical trial designs can expedite the development of novel therapeutic agents



NCI-MATCH=National Cancer Institute-Molecular Analysis for Therapy Choice.

Biankin AV, et al. *Nature.* 2015;526:361-370.

Adapted by permission from Springer Nature: *Nature* Patient-centric trials for therapeutic development in precision oncology, Biankin AV, Piantadosi S, Hollingsworth SJ, © 2015.

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Overview of key endpoints used in clinical trials

Endpoint	Definition	Application
Overall survival	Time from randomization to death from any cause	• Short-term patient survival • No further treatment available
Progression-free survival	Time from randomization to the first documentation of disease progression or death	• Tumors with high unmet medical need • Not useful when underlying disease makes it difficult to determine the cancer progression
Disease-free survival	Time from randomization to first documentation of relapse or death	• Useful when low toxicity is the goal after a patient is considered "treated" following surgical removal of a tumor
Objective response rate	Proportion of subjects confirmed to have complete or partial response	• Disease state that resists treatment and requires more than the normal course of treatment
Durable complete response	Durable complete regression of progressing disease	• Useful when no alternative treatment is available
Patient reported outcomes	Definition of endpoint depends upon patient population and stage of disease	• Used for some malignancies when no alternative therapy is available

Slabiak T. Clinical trial endpoints for oncology studies. Applied Clinical Trials website. http://www.appliedclinicaltrialsonline.com/clinical-trial-endpoints-oncology-studies. Published April 2, 2012. Accessed May 1, 2018.

Table adapted from: Slabiak T. Clinical Trial Endpoints for Oncology Studies. In: http://www.appliedclinicaltrialsonline.com/clinical-trial-endpoints-oncology-studies. Accessed February 7, 2018.

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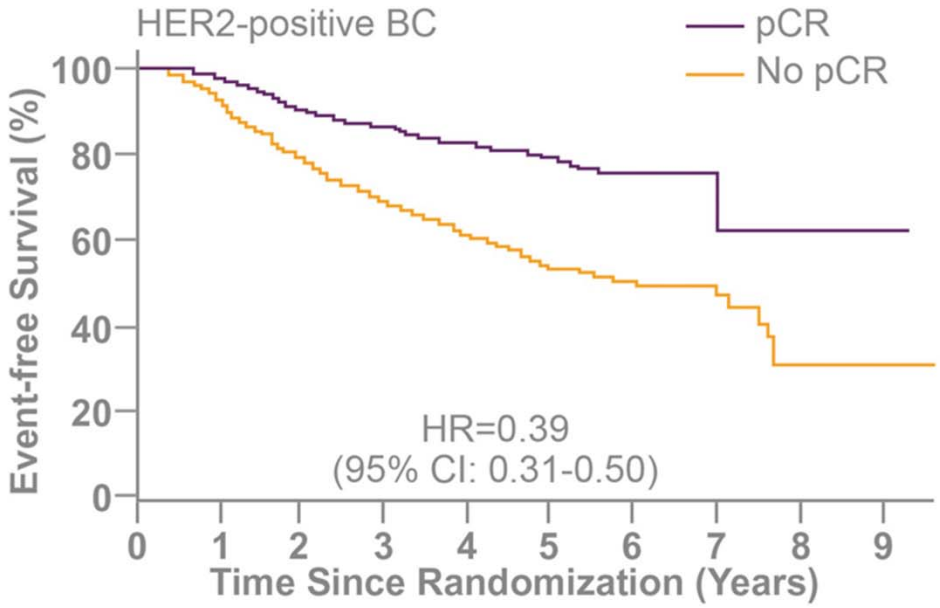
Pathologic complete response: An emerging clinical endpoint

This pooled analysis conducted by the FDA involved 11,955 patients from 12 international neoadjuvant trials treated with chemotherapy followed by surgery



A **pathologic** complete **response** is usually defined as the absence of residual invasive disease in the breast and the axillary lymph nodes at the completion of neoadjuvant treatment

BC=breast cancer; CI=confidence interval; HER2=human epidermal growth factor receptor 2; HR=hazard ratio; pCR=pathologic complete response.

Cortazar P, et al. *Lancet.* 2014;384:164-172.

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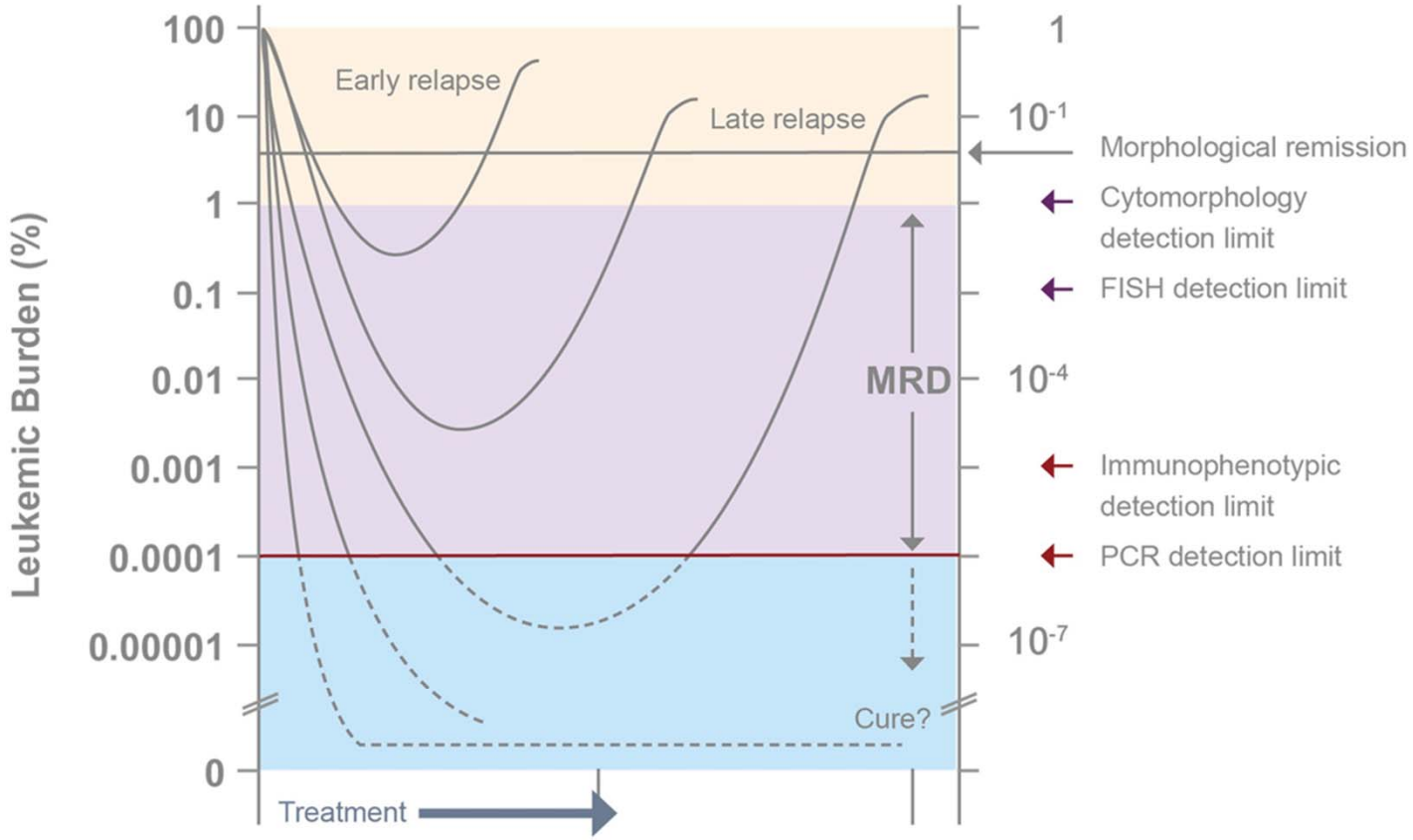
Minimal residual disease (MRD): An emerging clinical endpoint

- MRD negativity is defined as less than 1 CLL cell per 10,000 benign leukocytes (10^{-4})



CLL=chronic lymphocytic leukemia; FISH=fluorescence in situ hybridization; PCR=polymerase chain reaction.
Böttcher S, et al. *Leukemia*. 2009;23:2007-2017. Szczepański T, et al. *Lancet Oncol*. 2001;2:409-417.
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Summary

- Because cancer is a complex and heterogeneous disease, constant innovation is required for effective management
- Innovative approaches that have evolved in the management of cancer include biomarker-based precision/personalized treatment, novel strategies to elicit T cell–mediated antitumor immunity, and simultaneous targeting of multiple pathways to overcome or delay the development of resistant disease
- The development of basket and umbrella clinical trial designs, the efforts in validating pCR and MRD as emerging clinical trial endpoints, and the assessment of irRC are additional recent developments to optimize cancer care

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APPENDIX

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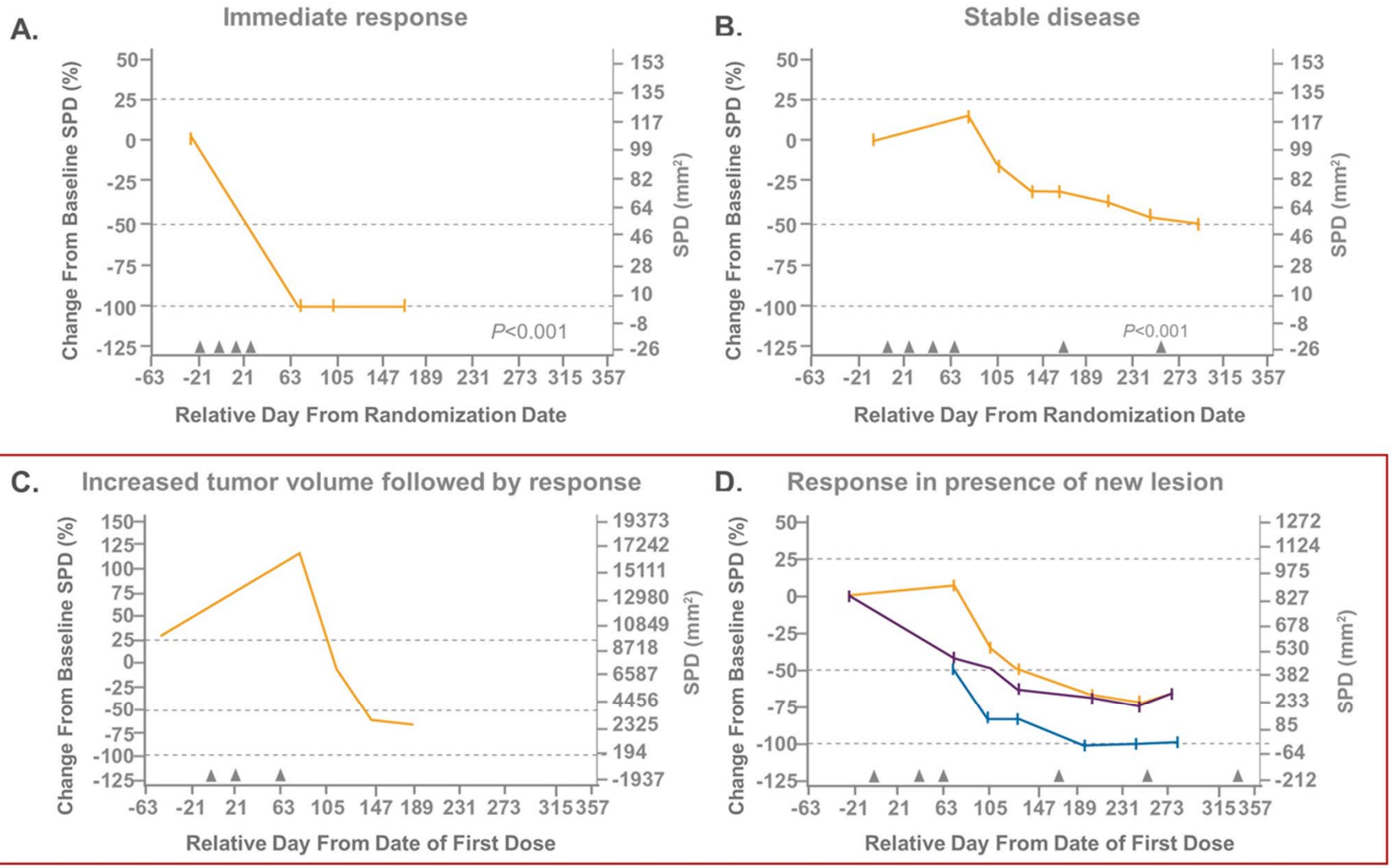
emerging perspectives

Novel patterns of response by irRC



irRC=immune-related response criteria; SPD=sum of the product of the greatest diameters.

Hoos A, et al. *J Natl Cancer Inst*. 2010;102:1388-1397. Wolchok J. *Clin Cancer Res*. 2009;15:7412-7420.

Hoos A, Eggermont AM, Janetzki S, et al, Improved endpoints for cancer immunotherapy trials, *Journal of the National Cancer Institute*, 2010, 102, 18, 1388-1397, by permission of Oxford University Press.

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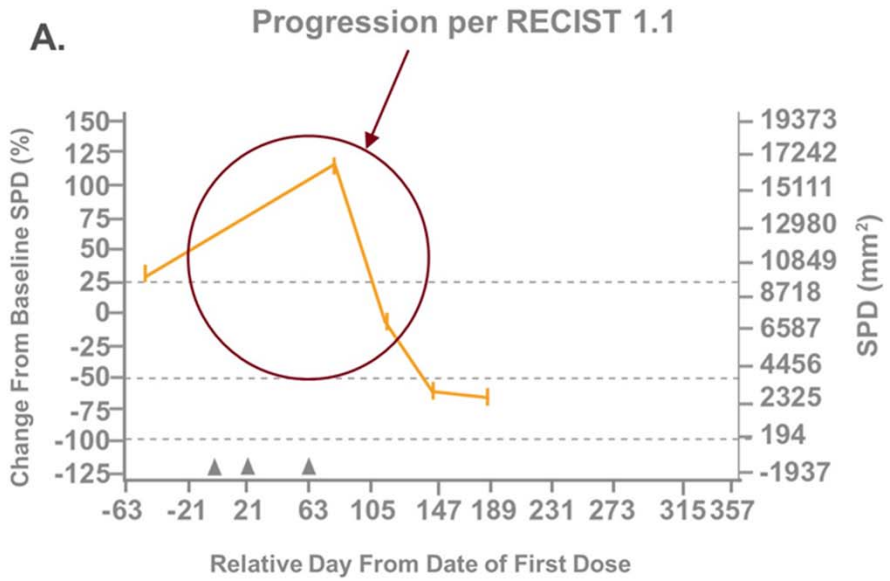
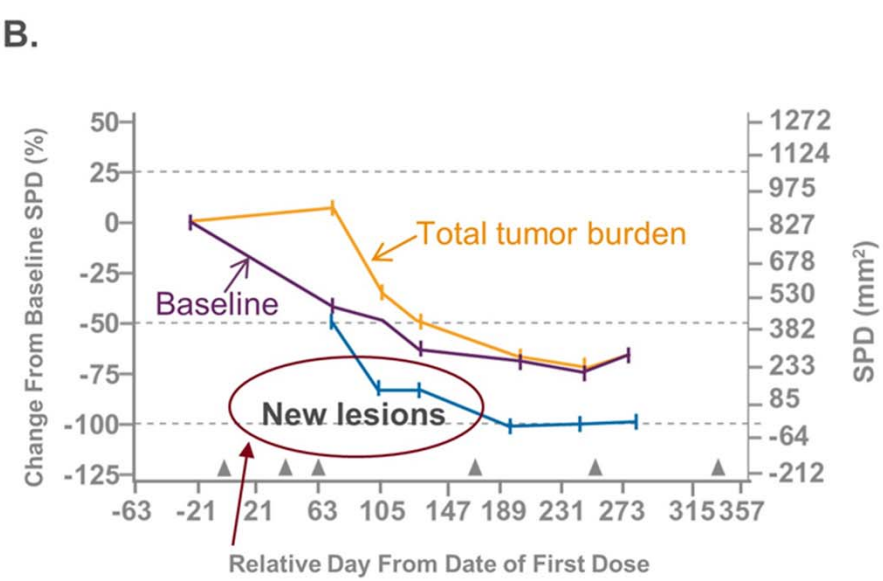
What are the most appropriate criteria for disease monitoring/assessment?





Progressive disease per RECIST 1.1

- Any new lesion
- ≥25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)

Progressive disease per irRC

- New measurable lesion incorporated into tumor burden*
- ≥25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart

*Tumor burden=SPD index lesions + SPD new measurable lesions.
irRC=immune-related response criteria; RECIST=Response Evaluation Criteria in Solid Tumors; SPD=sum of the product of the greatest diameters.
Hoos A, et al. *J Natl Cancer Inst*. 2010;102:1388-1397. Wolchok J. *Clin Cancer Res*. 2009;15:7412-7420.
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