Tumor Agnostic Therapies and Clinical Trial Design

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Disclosures

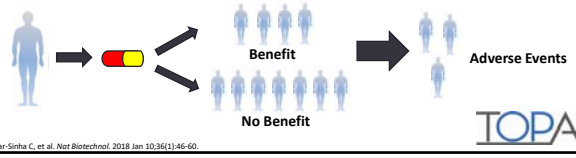
- Current employment: Xcenda

Objectives

- Recognize the barriers for development of tumor agnostic therapies
- Discuss clinical trial design as it pertains to tumor agnostic therapies and how these trials differ from typical clinical trial designs in oncology
- Identify the FDA-approved tumor agnostic therapies and potential tumor agnostic therapies in the drug development pipeline

Cancer Treatment Background

- The mechanisms underlying cancer have been investigated for >100 years
- Clinical management of cancer remains rooted in treatments such as surgery, radiation, and chemotherapy to stop uncontrolled cellular proliferation



Kumar-Sinha C, et al. *Nat Biotechnol*. 2018 Jan 10;36(1):46-60.

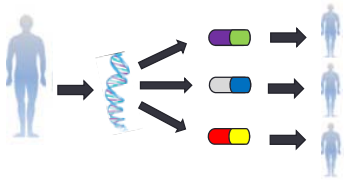
Paradigm Shift in Cancer Therapy

- Morphological and histopathological methods are largely used to diagnose patients and estimate prognosis
  - Treatment selection historically relied on tumor site, histology, tumor stage, and prior response to therapy
- Cancer development is now understood to be driven by genomic alterations

Yates LR, et al. *Ann Oncol*. 2018 Jan 1;29(1):30-35.
American Cancer Society. Questions people ask about cancer. January 4, 2018. https://www.cancer.org/cancer/cancer-basics/questions-people-ask-about-cancer.html. Accessed February 27, 2018.
Kumar-Sinha C, et al. *Nat Biotechnol*. 2018 Jan 10;36(1):46-60.

Precision Medicine

- A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease



National Cancer Institute. Precision Medicine in Cancer Treatment. October 3, 2017. https://www.cancer.gov/about-cancer/treatment/types/precision-medicine. Accessed April 13, 2018.

Paradigm Shift in Cancer Therapy

- Recent studies have shown as high as 30% to 40% of patients who undergo tumor genomic profiling have an actionable alteration that can be matched to an approved targeted therapy
- Precision medicine has been shown to improve outcomes in patients with actionable alterations for which there is targeted therapy available as compared with standard of care therapy or best supportive care

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Haslem DS, et al. *J Oncol Pract*. 2017 Feb;13(2):e108-e119.
Marquart J, et al. *JAMA Oncol*. 2018 Aug 1;4(8):1093-1098.
Massard C, et al. *Cancer Discov*. 2017;7(6):586-595.
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Schwaederle MC, et al. *J Clin Oncol*. 2016;34(15_suppl):11520-11520.

Improved Outcomes with Precision Medicine

Trial	Study Design	Endpoints	Patient Population	Results
MOSCATO 01	Single-center, single-arm, open-label in patients receiving genomically targeted therapy	PFS2/PFS1 ratio	N=199 advanced "hard-to-treat" solid cancers	PFS2/PFS1 ratio > 1.3 in 33% of evaluable patients
InterMountain Healthcare Group	Retrospective analysis comparing targeted therapy vs historical controls (SoC chemotherapy or BSC)	PFS	N=36 advanced solid cancers	Average PFS 22.9 weeks vs 12.0 weeks (HR 0.47; 95% CI: 0.29, 0.75)
Meta-analysis of Phase 1 Trials	Meta-analysis comparing precision medicine-based treatment selection strategy vs SoC chemotherapy	ORR PFS	N=13,203 refractory malignancies	ORR 30.6% vs 4.9% (*P*<0.0001) PFS 5.7 months vs 2.95 months (*P*=0.0002)

Key: BSC – best supportive care; ORR – objective response rate; PFS – progression-free survival; PFS1 – progression-free survival on first-line therapy; PFS2 – progression-free survival on second-line therapy; SoC – standard of care.

Haslem DS, et al. *J Oncol Pract*. 2017 Feb;13(2):e108-e119.
Massard C, et al. *Cancer Discov*. 2017;7(6):586-595.
Schwaederle MC, et al. *J Clin Oncol*. 2016;34(15_suppl):11520-11520.

Precision Medicine and Tumor Agnostic Cancer Therapy

- Tumor agnostic therapy: targeting oncogenic drivers regardless of tissue histology
  - Aim is to provide patients with a therapeutic intervention that is expected to provide a clinical benefit based upon the specific molecular or cellular features of the tumor
- Next generation sequencing has only recently revealed the presence of oncogenic drivers across a wide range of tumor histologies

Yates LR, et al. *Ann Oncol*. 2018 Jan 1;29(1):30-35.
Lartigue J. http://www.onclive.com/publications/oncology-live/2017/vol-18-no-15/trk-inhibitors-advance-rapidly-in-tumoragnostic-paradigm, Accessed January 29, 2018.

Barriers to Development of Tumor Agnostic Cancer Therapy

Finding Appropriate Patients for Tumor Agnostic Therapy

- Testing for genomic alterations has become a routine part of clinical oncology care
- Molecular testing has become both quicker and less costly
- Testing methodologies include: next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcription-polymerase chain reaction (RT-PCR)

Jarvis LM. *Chemical & Engineering News*. 2017;95(27):26-30.
Schram AM, et al. Nat Rev Clin Oncol. 2017 Dec;14(12):735-748.

Molecular Testing for Genomic Alterations

	NGS	RT-PCR	FISH	IHC
Strengths	• Can detect known and novel genetic alterations in DNA / RNA • Detects many genetic alterations using 1 sample	• Can detect genetic abnormalities in RNA	• Can detect certain genomic alterations in DNA / RNA • Typically quicker turnaround time vs NGS and RT-PCR	• Can detect protein expression that may be attributable to a genetic alteration • Typically lowest cost and quickest turnaround time
Limitations	• Slower turnaround time • Higher cost	• Slower turnaround time vs FISH or IHC	• Only alterations affecting the labeled region can be studied and detected • Various types of probes available	• Specificity (using protein expression as a surrogate for genetic alterations could lead to false-positives) • Separate assays require separate samples

Key: DNA – deoxyribonucleic acid; FISH – fluorescence it situ hybridization; IHC – immunohistochemistry; NGS – next generation sequencing; RNA – ribonucleic acid; RT-PCR – reverse transcription polymerase chain reaction.

National Cancer Institute. Cancer Genetics Overview (PDQ®)—Health Professional Version. Clinical sequencing. https://www.cancer.gov/about-cancer/causes-prevention/genetics/overview-pdqhsection/_2594. Accessed September 5, 2018.
National Cancer Institute. Dictionary of Genetic Terms. Definition of Next-generation Sequencing. https://www.cancer.gov/publications/dictionaries/genetics-dictionary?cdrid=763024. Accessed September 5, 2018.
Hechtman JF, et al. *Am Surg Pathol*. 2017;41(11):547-1551.
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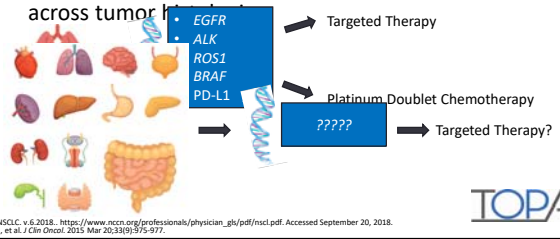
Brenca M, et al. *J Pathol*. 2016;238(4):543-549.

Finding Appropriate Patients for Tumor Agnostic Therapy

- Historically, genomic alterations were known and tested for within certain tumor histologies
- Many genomic alterations are rare and are found across tumor histologies



NCCN. NSCLC. v.6.2018.. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed September 20, 2018.
Redig AJ, et al. *J Clin Oncol.* 2015 Mar 20;33(9):975-977.

Finding Appropriate Patients for Tumor Agnostic Therapy – Is NGS the Answer?

- NGS technology is able to simultaneously identify multiple genomic alterations in a single tumor tissue sample
  - Approximately 90% of tumor tissues were successfully sequenced and 83% of these samples were identified to have ≥1 mutation
- NGS panels typically include only selected exons and few introns from known cancer-associated genes
  - Potential to fail to detect the presence of novel alterations

Tan O, et al. Clin Genet. 2018 Mar;93(3):533-544.
Schram AM, et al. Nat Rev Clin Oncol. 2017 Dec;14(12):735-748.

Barriers to Development of Tumor Agnostic Cancer Therapy

Clinical Trial Design for Tumor Agnostic Therapies

- Randomized controlled trial (RCT) is the gold standard study design
  - Assesses the therapeutic efficacy of an experimental treatment or intervention as compared to a control group
- One major flaw of traditional study designs within oncology is clinical inefficiency
  - <5% of cancer patients are currently enrolled on clinical trials
    - Almost half of patients are excluded due to eligibility issues with trial exclusion criteria

Bogaerts J, et al. Eur J Cancer. 2015 Feb;51(3):271-281.
Hyman DM, et al. Cell. 2017 Feb 9;168(4):584-599.
Unger JM, et al. Am Soc Clin Oncol Educ Book. 2016;35:185-198.
Panageas KS. Expert Rev Clin Pharmacol. 2015;8(6):661-663.

Clinical Trial Design for Tumor Agnostic Therapies – Can We Use a RCT?

- Many genomic alterations are rare and are found across tumor histologies
  - The RCT design is not feasible for rare cancer populations due to limitations in the number of patients that can be enrolled

Redig AJ, et al. *J Clin Oncol.* 2015 Mar 20;33(9):975-977.
Panageas KS. Expert Rev Clin Pharmacol. 2015;8(6):661-663.

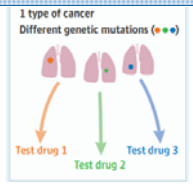
Clinical Trial Design for Tumor Agnostic Therapies

- Genetic alterations align themselves to single-arm trials as they are defined by a oncogenic driver that leads to a high sensitivity to a specific targeted therapy
- Many of these genomic alterations are also rare and occur at low incidences making the RCT design challenging

André F. *N Engl J Med.* 2018 Feb 22;378(8):763-765.

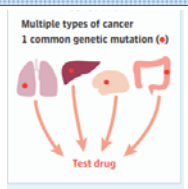
Clinical Trial Design for Tumor Agnostic Therapies – Novel Precision Medicine Trials

Umbrella Trial



- Possible to test and develop many potentially active drugs simultaneously

Basket Trial



- Identify small subgroups of a broad cancer population

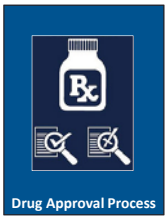
West HJ. *JAMA Oncol.* 2017 Mar 1;3(3):423.

Clinical Trial Design for Tumor Agnostic Therapies – Basket Trials

- Basket trials are used when actionable mutations are identified prospectively and patients are assigned in a nonrandomized, single-arm fashion to a specific targeted treatment
  - Built on the hypothesis that a molecular marker predicts response to targeted therapy independent of tumor histology
- Overarching goal of the tumor-agnostic approach is to increase efficiency in drug development and expedite treatment options for patients

Redig AJ, et al. *J Clin Oncol.* 2015 Mar 20;33(9):975-977.
Jarvis LM. *Chemical & Engineering News.* 2017;95(27):26-30.

Barriers to Development of Tumor Agnostic Cancer Therapy



Drug Approval Process for Tumor Agnostic Therapy

FDA U.S. FOOD & DRUG ADMINISTRATION

- "For regular approval, it is critical that the applicant show direct evidence of clinical benefit or improvement in an established surrogate for clinical benefit"
  - In oncology, survival improvement is considered an appropriate measure of clinical benefit

U.S. Department of Health and Human Services: Food and Drug Administration. May 2007. https://www.fda.gov/downloads/drugsGuidanceComplianceRegulatoryInformation/Guidance/UCM071590.pdf. Accessed August 15, 2018.

Drug Approval Process for Tumor Agnostic Therapy

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes non-cancer deaths • Time
Symptoms Endpoints (patient reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments

U.S. Department of Health and Human Services: Food and Drug Administration. May 2007. https://www.fda.gov/downloads/drugsGuidanceComplianceRegulatoryInformation/Guidance/UCM071590.pdf. Accessed August 15, 2018.

Drug Approval Process for Tumor Agnostic Therapy

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Objective Response Rate	Surrogate for accelerated approval or regular approval	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier in smaller studies compared with survival • Effect attributable to drug, not natural history	• Not a direct measure of benefit • Not a comprehensive measure of drug activity • Only a subset of patient who benefit
Complete Response	Surrogate for accelerated approval or regular approval	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable CR can represent clinical benefit • Assessed earlier in smaller studies compared with survival	• Not a direct measure of benefit • Not a comprehensive measure of drug activity • Small subset of patients with benefit

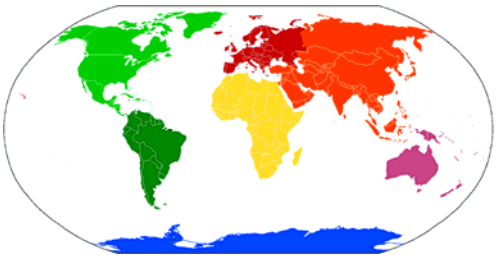
U.S. Department of Health and Human Services: Food and Drug Administration. May 2007. https://www.fda.gov/downloads/drugsGuidanceComplianceRegulatoryInformation/Guidance/UCM071590.pdf. Accessed August 15, 2018.

Drug Approval Process for Tumor Agnostic Therapy

- In settings where there is no available therapy and where major tumor regressions can be presumed to be attributed to the tested drug, the FDA has sometimes supported objective response rate (ORR) and response duration observed in single-arm studies as substantial evidence supporting accelerated approval

U.S. Department of Health and Human Services: Food and Drug Administration. May 2007. https://www.fda.gov/downloads/drugsGuidanceComplianceRegulatoryInformation/Guidance/UCM071590.pdf. Accessed August 15, 2018.

Drug Approval Process for Tumor Agnostic Therapy



Clinical Development of Tumor Agnostic Therapies

FDA Approved Tumor Agnostic Therapy

KEYTRUDA® (pembrolizumab) Injection 100 mg

- Pembrolizumab was the first therapy to receive a tumor agnostic approval from the FDA
  - Treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mis-match repair deficient (dMMR) solid tumors

Keytruda (pembrolizumab). Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2018.

Pembrolizumab for MSI-H and dMMR Solid Tumors

Trial	Design and Patient Population	N	Dose	Prior Therapy
KEYNOTE-016	Prospective Patients with CRC and other tumors	28 CRC 30 non-CRC	10 mg/kg q 2 weeks	CRC: ≥2 prior regimens Non-CRC: ≥1 prior regimen
KEYNOTE-164	Prospective CRC	61	200 mg q 3 weeks	Prior 5FU, oxaliplatin, and irinotecan ± anti-VEGF/EGFR mAb
KEYNOTE-012	Retrospective PD-L1 positive gastric, bladder, or TNBC	6	10 mg/kg q 2 weeks	≥1 prior regimen
KEYNOTE-028	Retrospective PD-L1 positive esophageal, biliary, breast, endometrial, CRC	5	10 mg/kg q 2 weeks	≥1 prior regimen
KEYNOTE-158	Prospective (retrospectively identified patients enrolled in specific rare tumor non-CRC cohorts	19	200 mg q 3 weeks	≥1 prior regimen

Key: 5FU – 5-fluorouracil; CRC – colorectal cancer; EGFR – epidermal growth factor receptor; kg – kilogram; mAb – monoclonal antibody; mg – milligram; PD-L1 – programmed death-ligand 1; TNBC – triple negative breast cancer; VEGF – vascular endothelial growth factor.

Keytruda (pembrolizumab). Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2018.

Pembrolizumab for MSI-H and dMMR Solid Tumors

- A total of 149 patients with MSI-H or dMMR cancers were identified across the five clinical trials

	N=149
Median age, years	55
ECOG PS, %	
0	36
1	64
Tumor type, %	
CRC	60
Other	40
Disease stage, %	
Locally advanced, unresectable	2
Metastatic	98
Median number of prior therapies	2

Key: CRC – colorectal cancer; ECOG – Eastern Cooperative Oncology Group; PS – performance status.

Keytruda (pembrolizumab). Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2018.

Pembrolizumab for MSI-H and dMMR Solid Tumors

Endpoint	N=149
ORR (95% CI), %	39.6 (31.7, 47.9)
CR	7.4
PR	32.2
Median response duration (range), months	NR (1.6+, 22.7+)

Tumor Type	N	ORR (95% CI), %	DOR range, months
CRC	90	36 (26, 46)	1.6+, 22.7+
Endometrial	14	36 (13, 65)	4.2+, 17.3+
Biliary	11	27 (6, 61)	11.6+, 19.6+
Gastric or GE junction	9	56 (21, 86)	5.8+, 22.1+
Small intestine	8	38 (9, 76)	1.9+, 9.1+
Pancreatic	6	83 (36, 100)	2.6+, 9.2+
Breast	2	PR, PR	7.6, 15.9
Bladder	1	NE	
Esophageal	1	PR	18.2+
Sarcoma	1	PD	
Thyroid	1	NE	
Retroperitoneal adenocarcinoma	1	PR	7.5+
SCLC	1	CR	8.9+
RCC	1	PD	

Key: CI – confidence interval; CR – complete response; CRC – colorectal cancer; DOR – duration of response; GE – gastroesophageal; NE – not evaluable; NR – not reached; ORR – objective response rate; PD – progressive disease; PR – partial response; RCC – renal cell carcinoma; SCLC – small cell lung cancer.

Keytruda (pembrolizumab). Prescribing information. Whitehouse Station, NJ: Merck & Co., Inc.; August 2018.

Tumor Agnostic Therapies in the Pipeline

Agent	Company	Target	Indication	Status
Larotrectinib	Bayer / Loxo	TRK	Solid tumors with *NTRK* gene fusions	NDA
Entrectinib	Roche / Ignyta	TRK, ALK, ROS1	Solid tumors with *NTRK* gene fusions	Phase II
Merestinib	Eli Lilly	MET, TRK	Solid tumors with *NTRK* rearrangements	Phase II
Atezolizumab	Genentech / Roche	PD-L1	Solid tumors with MSI-H, high mutation burden, or alterations in DNA proofreading genes	Phase II
TPX-0005	TP Therapeutics	TRK, ALK, ROS1	Solid tumors with *NTRK*, *ALK*, and *ROS1* rearrangements	Phase I / II
LOXO-195	Loxo Oncology	TRK	Solid tumors with *NTRK* gene fusions, including those resistant to larotrectinib	Phase I / II

Key: ALK – anaplastic lymphoma kinase; MET - MNNG-HOS transforming receptor tyrosine kinase; NDA – new drug application; NTRK – neurotrophic tyrosine receptor kinase; PD-L1 – programmed death-ligand 1; ROS1 – receptor tyrosine kinase of the insulin receptor family; TRK – tropomyosin receptor kinase.

Garber K. *Nat Rev Drug Discov*. 2018 Apr;17(4):227-229.

Tumor Agnostic Therapies in the Pipeline

Agent	Company	Target	Indication	Status
LOXO-292	Loxo Oncology	RET	Solid tumors with *RET* rearrangements	Phase I
RXDX-105	Ignyta / Roche	RET	Solid tumors with *RET* fusions	Phase I
LY3300054	Eli Lilly	PD-L1	Monotherapy in MSI-H solid tumors; various combination criteria	Phase I
PLX8394	Plexxikon / Daiichi Sankyo	Mutant BRAF and WT CRAF	Solid tumors with *BRAF* mutation	Phase I / IIa
PLX9486	Plexxikon	KIT	Solid tumors with *KIT* mutations	Phase I / II

Key: BRAF – serine/threonine-protein kinase B-Raf; CRAF – serine/threonine-protein kinase C-Raf; KIT – receptor tyrosine kinase c-kit; MSI-H – microsatellite instability high; PD-L1 – programmed death-ligand 1; RET –rearranged during transfection ; WT – wild type.

Garber K. *Nat Rev Drug Discov*. 2018 Apr;17(4):227-229.

Conclusion

- Oncology is moving in the direction of precision medicine and tumor agnostic therapies
- There are many tumor agnostic therapies in the pipeline despite the hurdles to bring these to market
- Finding the appropriate patient population for use of these therapies in clinical practice presents a significant challenge

Tumor Agnostic Therapies and Clinical Trial Design

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