

Use of Real Word Data to Complement Prospective Studies: Case Example in Alveolar Soft Parts Sarcoma and Epithelioid Sarcoma

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EMA and EORTC Soft Tissue and Bone Sarcoma Workshop

May 24, 2024

How Many Variable Confound a Clinical Trial

- Evofosfamide, Palifosfamide, Olaratumab, EORTC 62012, Aldox, GeDDiS
 - > 2000 randomized participants
 - > 40+ Disease Entities; Inter and Intra Subtype Variability
- Locally Advanced and Metastatic: Variations in clinical behavior
- Inappropriate Trial Designs and Outcomes (Overall Survival)
- 80-99 Sites Worldwide; 12+ countries

Variations in Practice and Referral Patterns; Subsequent lines of therapy for each disease

- Lack of contemporary data sets and accurate historical controls
- ? Scientific rationale – poor understanding of MOA
- Lack of biomarkers and correlative science
- ? Pharmacodynamics

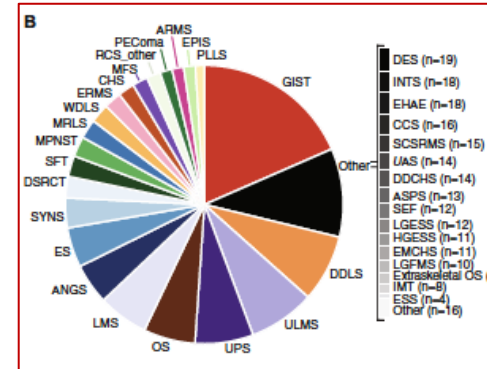
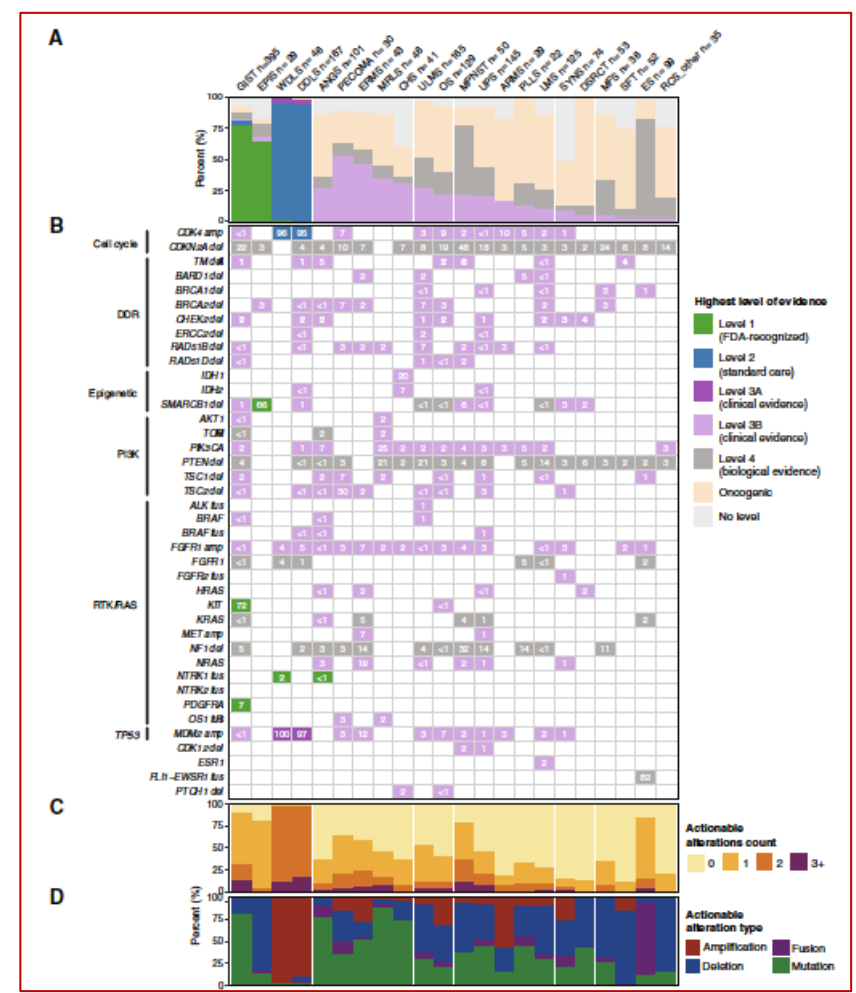
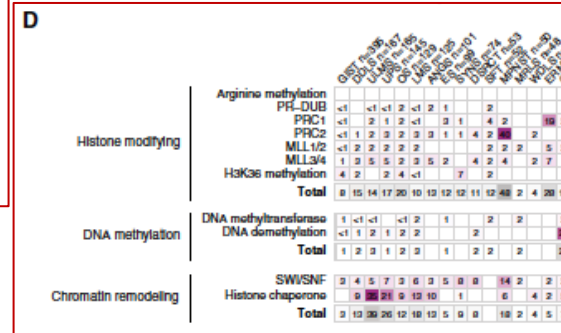
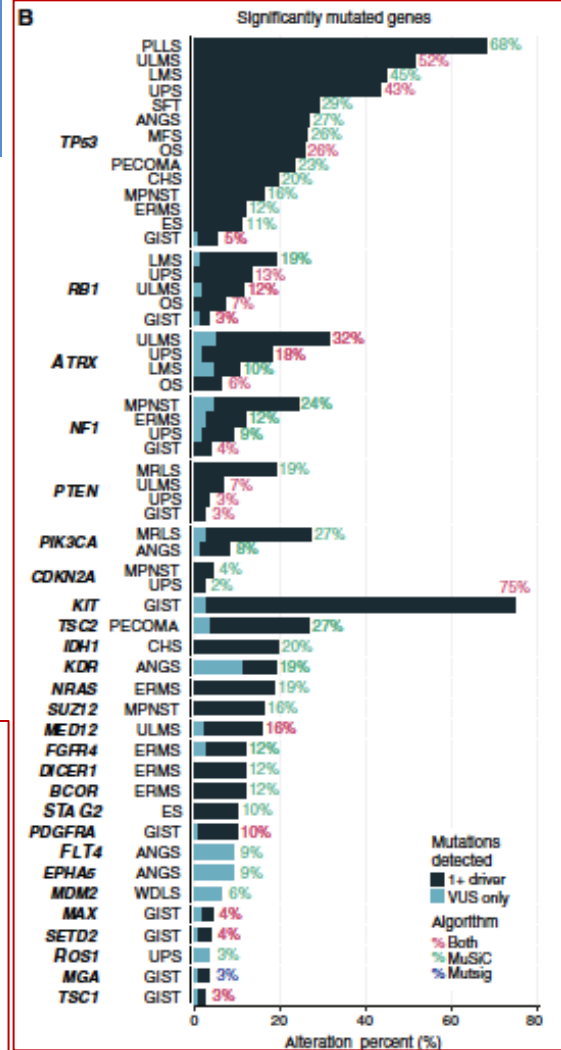
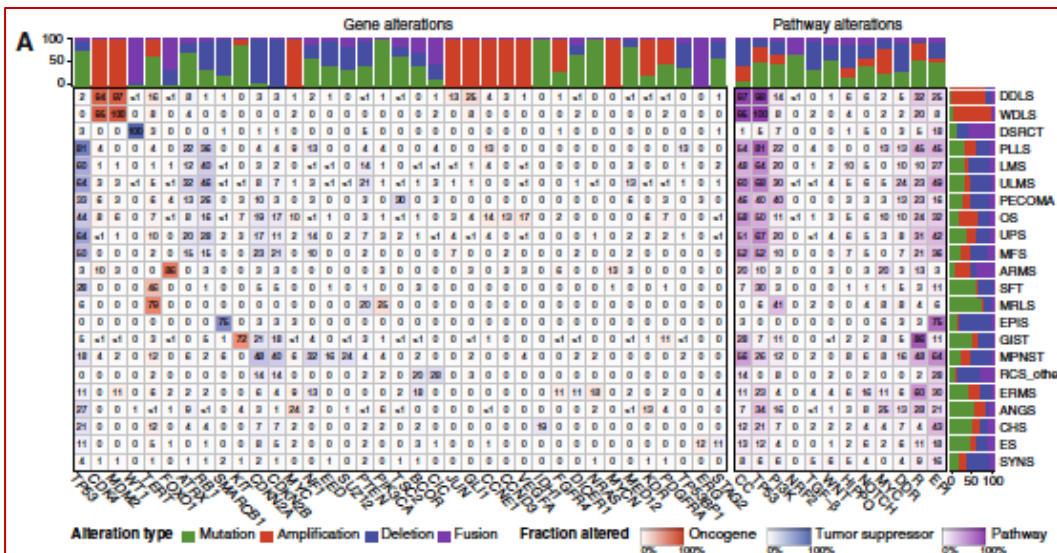
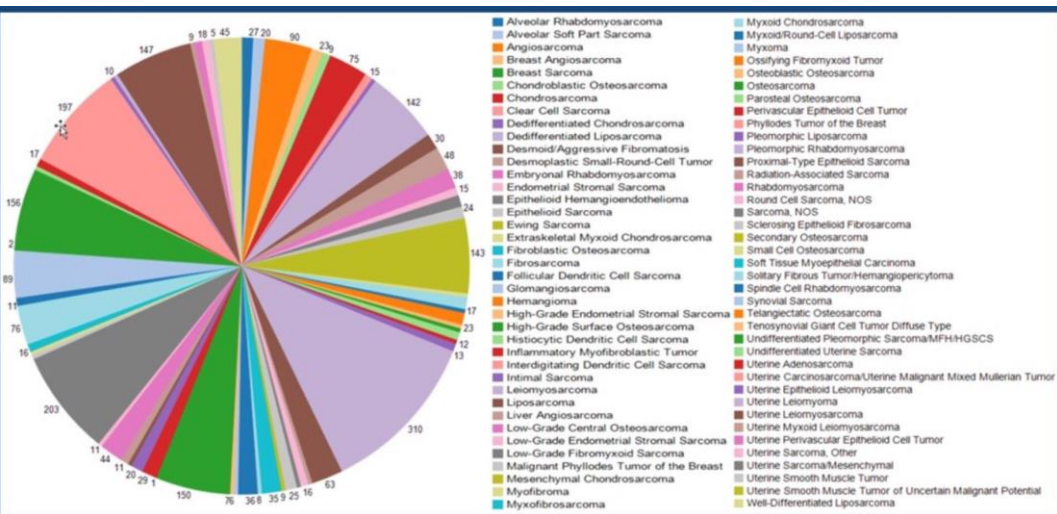
True numbers of
comparable diseases
(In P3; P2 vs P3)

Studying different
populations of those
diseases in P1 → P2 → P3



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How Have We Adapted?



Ultra-Rare Sarcomas: A Consensus Paper From the Connective Tissue Oncology Society Community of Experts on the Incidence Threshold and the List of Entities

Cancer
August 15, 2021

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Ultra Rare Sarcomas

Understanding Ultra Rare Cancers

- Often new disease entities, recently genetically defined
- Natural history of the disease poorly understood/defined
- Genomic and clinical variability not described
- Clinical needs patient population need to be defined/measured
- Meaningful clinical and research outcome measures
- Unique features drug/technology need to be understood
- Unknown response or usage patterns for repurposed drugs

URSWG – Ultra Rare Sarcoma Working Group ≤1/1,000,000 (>70 Bone and Soft Tissue Sarcomas)

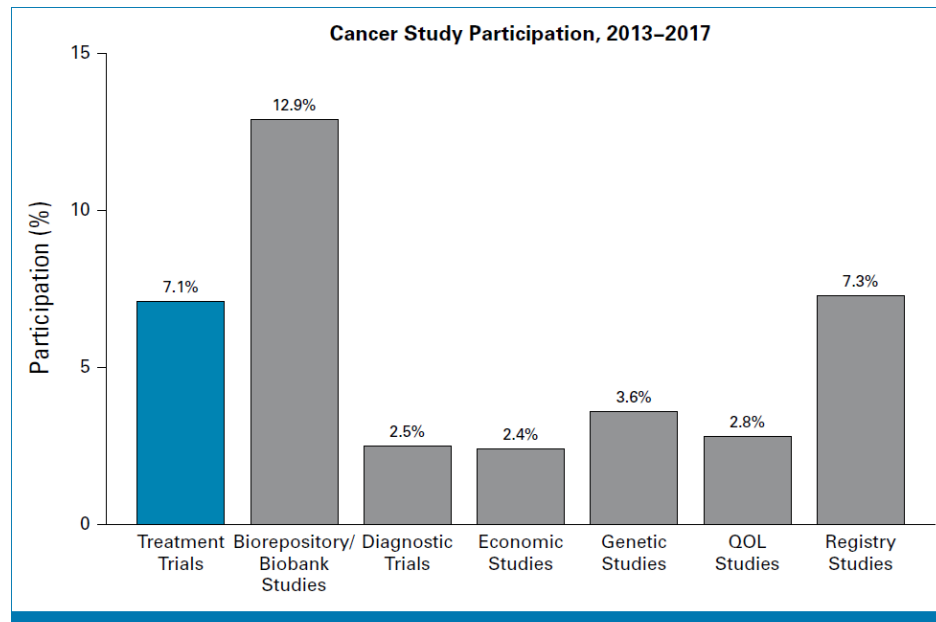


FIG 2. Estimated cancer study participation by type of study, 2013-2017. The estimate for treatment trial enrollment is highlighted in blue. QOL, quality-of-life.

National Estimates of the Participation of Patients With Cancer in Clinical Research Studies Based on Commission on Cancer Accreditation Data

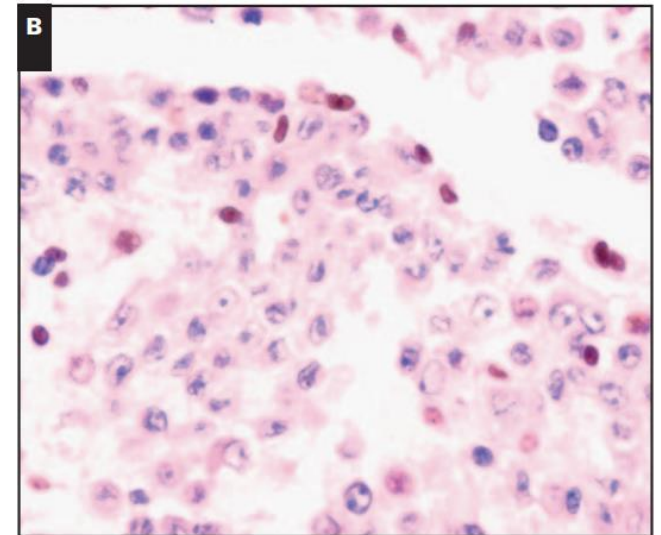
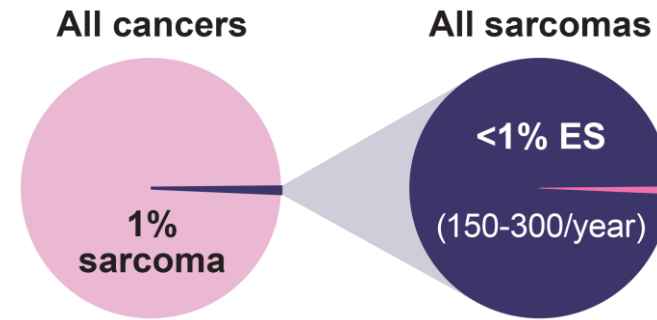
J Clin Oncol 00:1-10 Published April 2, 2024

Joseph M. Unger, PhD¹; Lawrence N. Shulman, MD²; Matthew A. Facktor, MD³; Heidi Nelson, MD⁴; and Mark E. Fleury, PhD⁵

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Epithelioid Sarcoma

- Affects men more than women
- Tend to occur in young adults
- 2 morphologically distinct subtypes
 - Classic (Distal) ES
 - Accounts for 2/3 of cases
 - Typically arises in the lower extremity, digits, or forearms
 - Painless, firm nodules/nonhealing ulcers
 - Higher propensity for local recurrence
 - Intransient Spread
 - Proximal ES
 - Proximal limbs/girdles/midline of the trunk
 - Tend to be deep, infiltrating soft-tissue masses
 - Behaves more aggressively, distant metastases

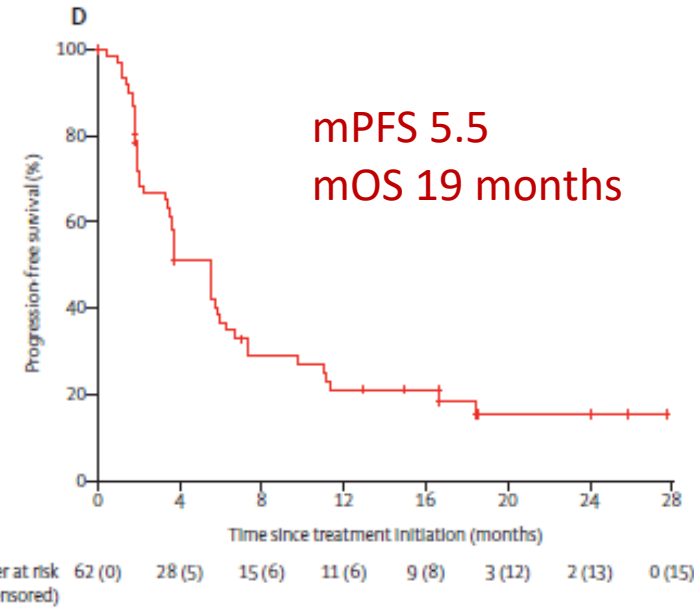
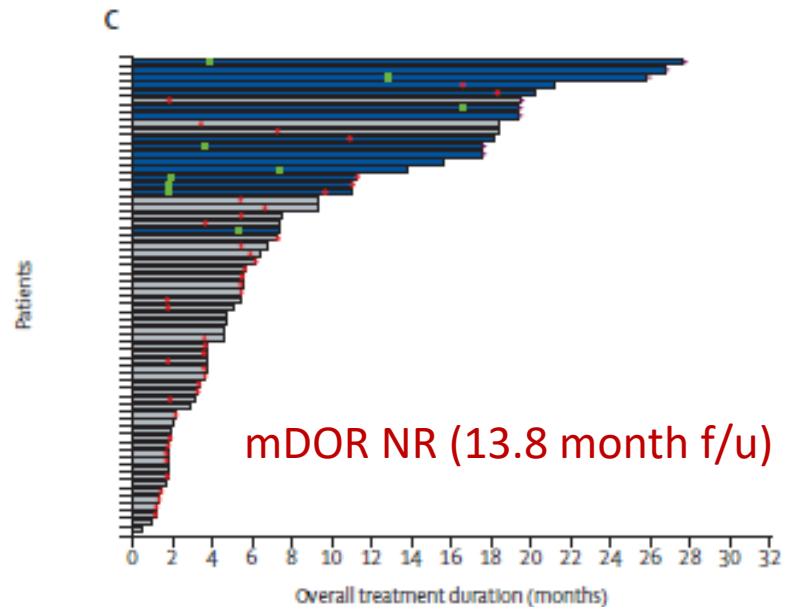
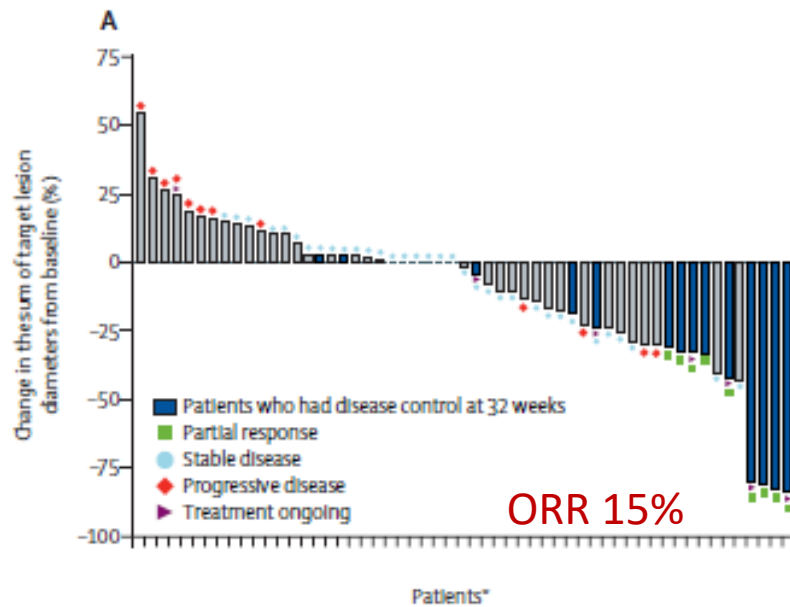


INI/SMARCB1 loss

Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study

Lancet Oncol 2020; 21: 1423-32

Mrinal Gounder, Patrick Schöffski, Robin L Jones, Mark Agulnik, Gregory M Cote, Victor M Villalobos, Steven Attia, Rashmi Chugh, Tom Wei-Wu Chen, Thierry Jahan, Elizabeth T Loggers, Abha Gupta, Antoine Italiano, George D Demetri, Ravin Ratan, Lara E Davis, Olivier Mir, Palma Dileo, Brian A Van Tine, Joseph G Pressey, Trupti Lingaraj, Anand Rajarethinam, Laura Sierra, Shefali Agarwal, Silvia Stacchiotti



FDA ODAC December 18, 2019
11-0 for Accelerated Approval

How Do We Use Tazemetostat?

A Phase 1b/3 trial of tazemetostat plus doxorubicin in the 1st line setting

- Confirmatory?
- Inform Clinical Practice and Usage?

Alveolar Soft Part Sarcoma

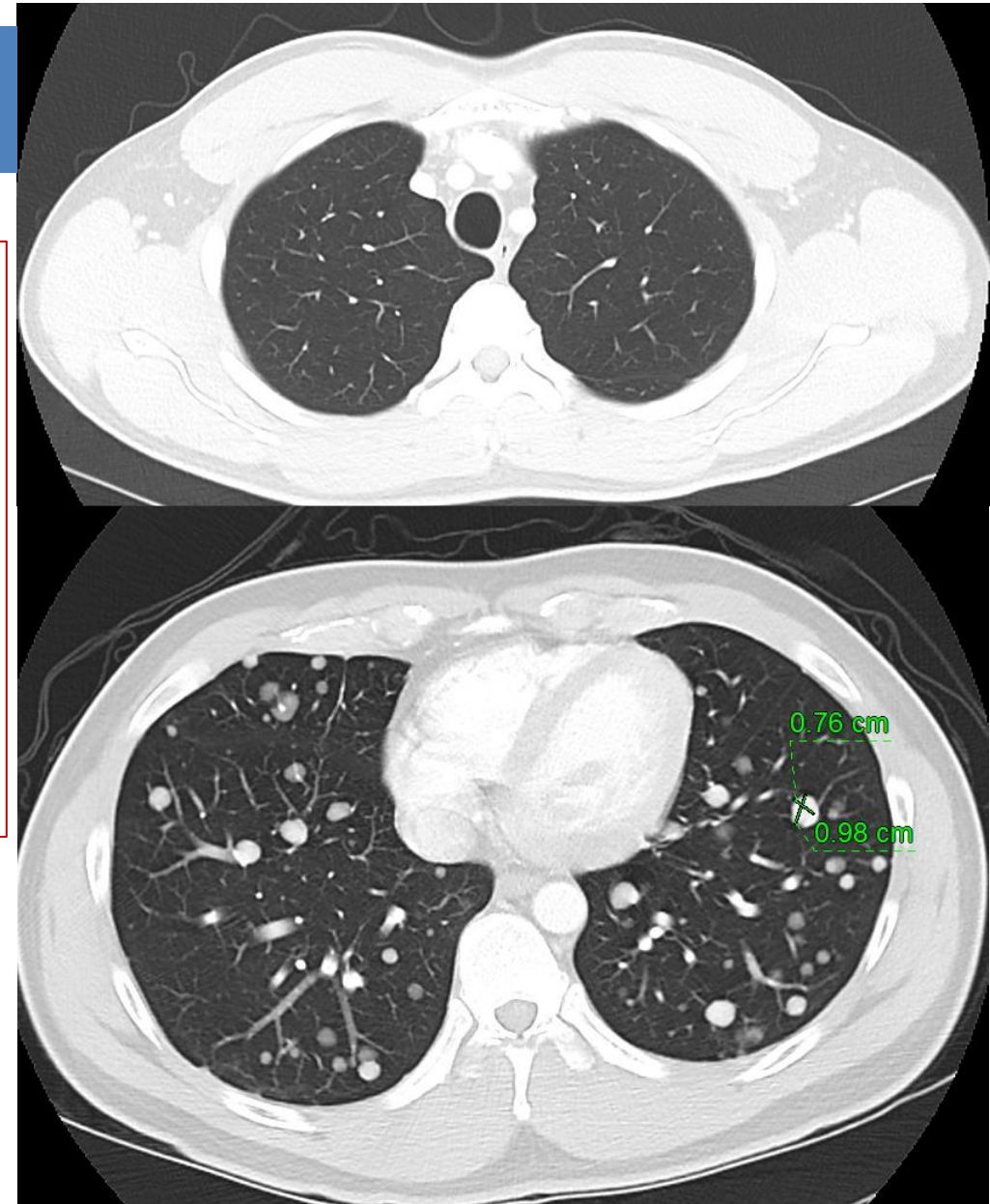
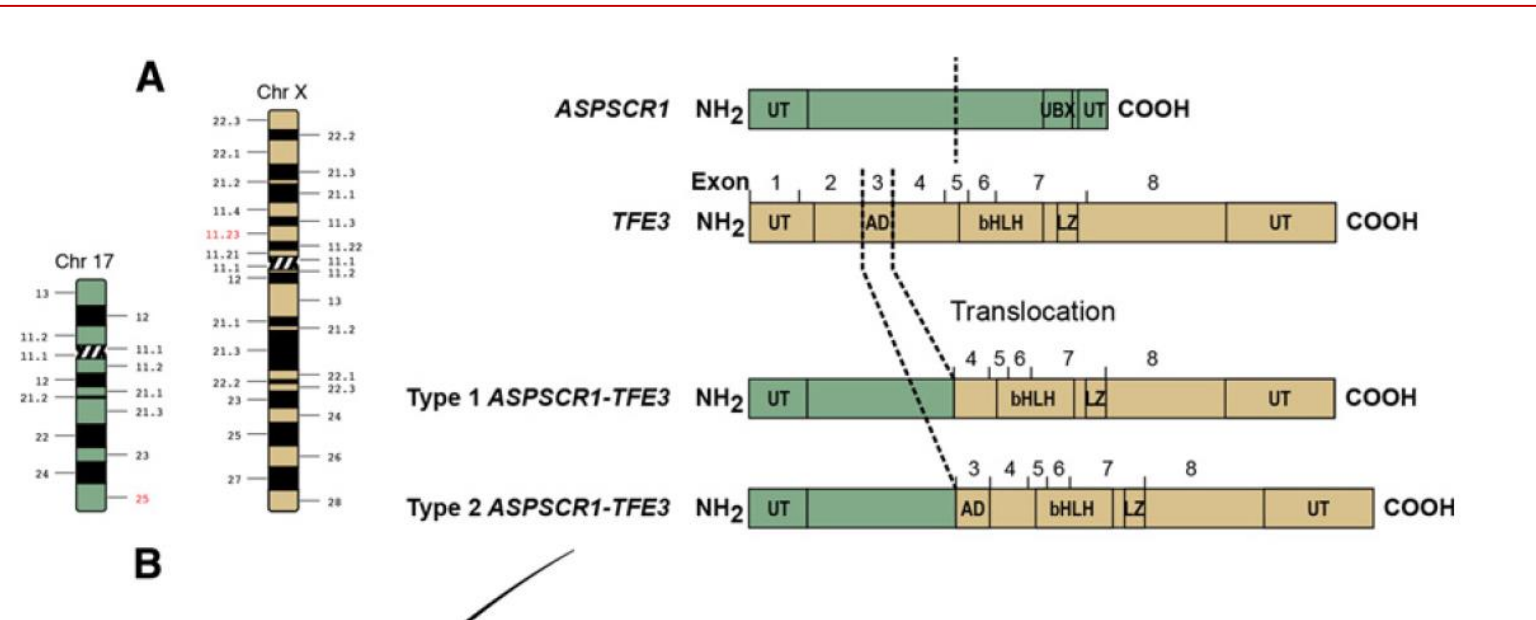
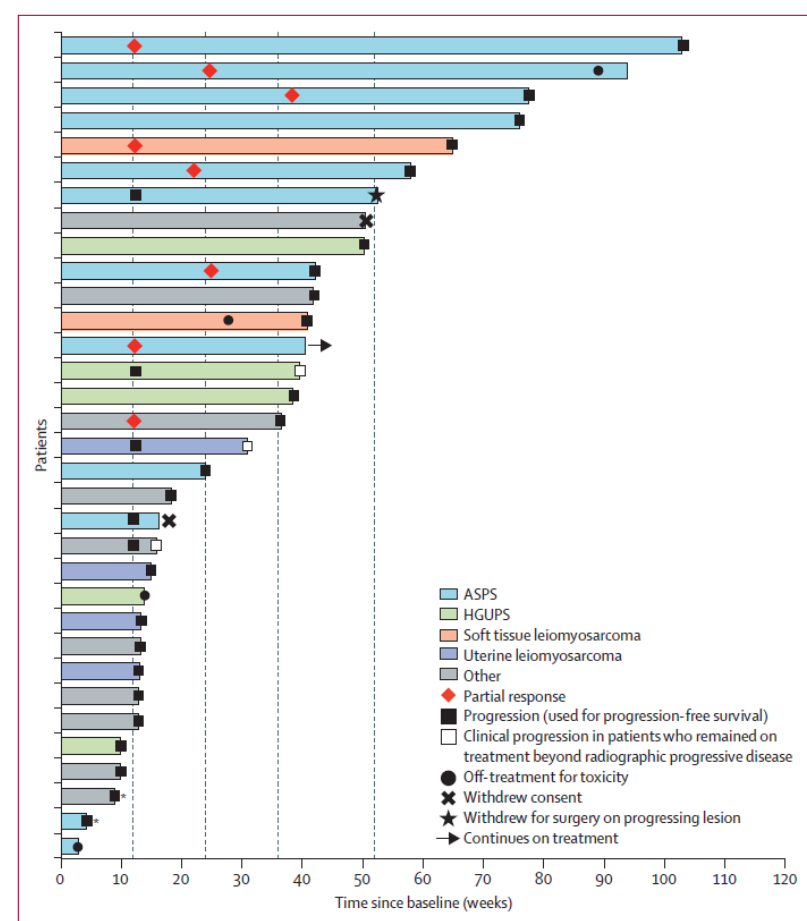
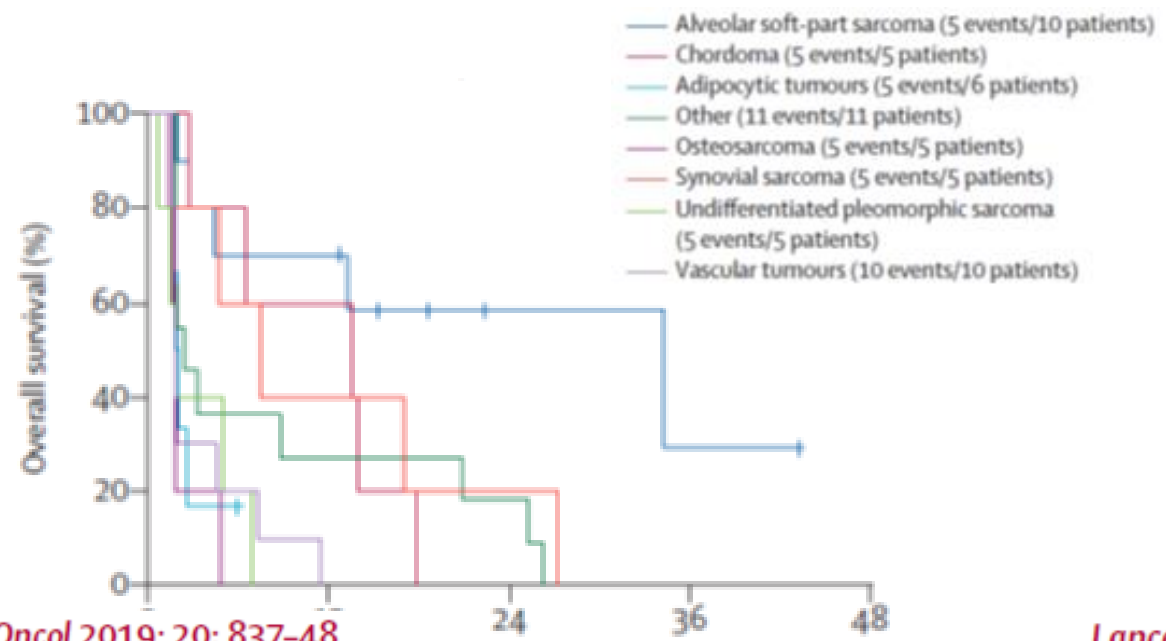
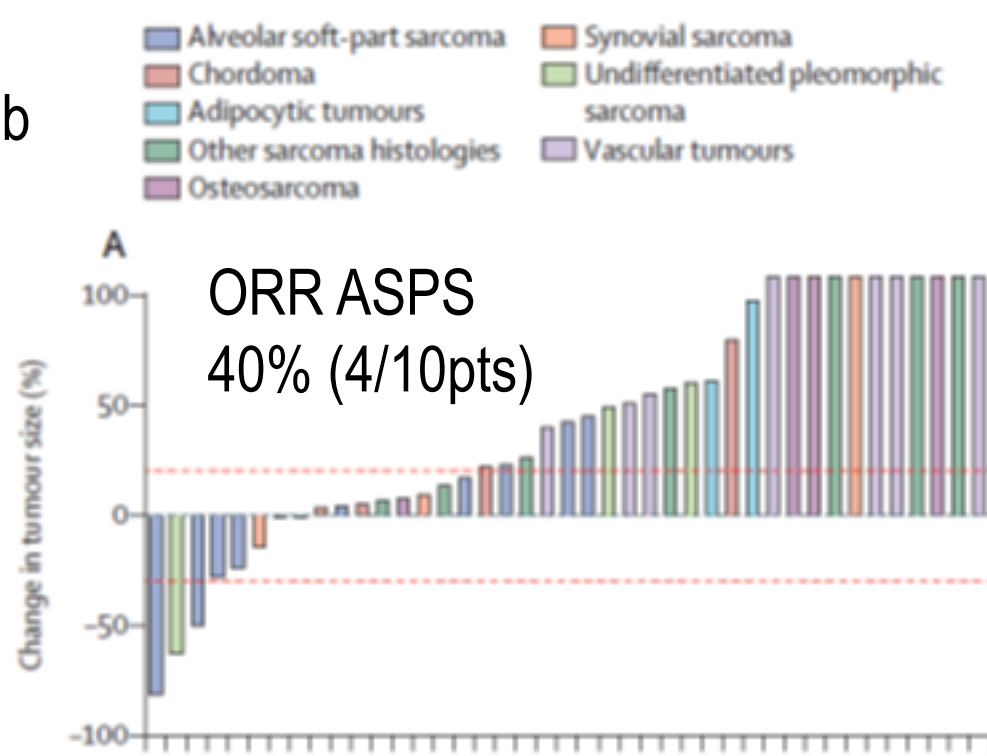


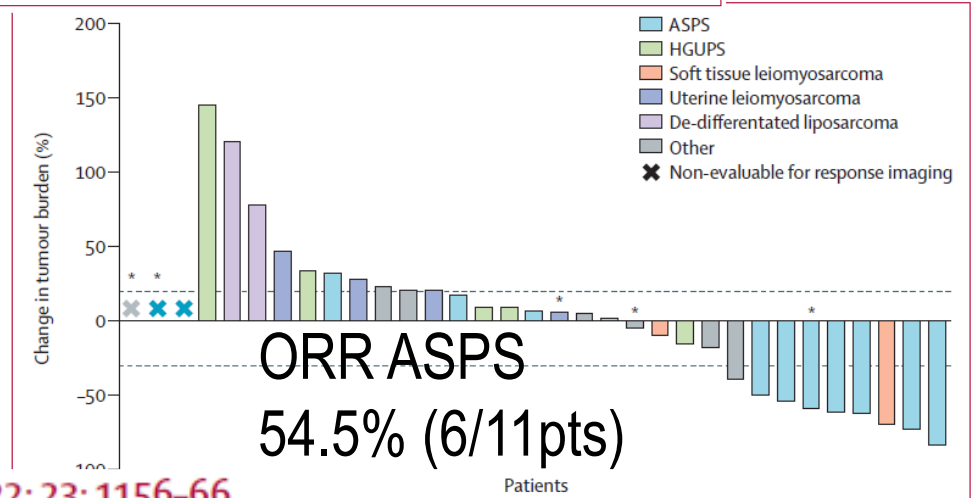
Table 1. Alveolar Soft-Part Sarcoma Sites and Origins of Metastasis^{a,b,c}

Origin		Metastasis	
Site	Frequency (%)	Site	Frequency (%)
Extremity	58-60	Lung	90
Trunk, pelvis, retroperitoneum	16-28	Bone	26
Head and neck	12	Brain	11-19
Other or unknown ^a	14	Other ^b	24

Durvaluab tremelimumab

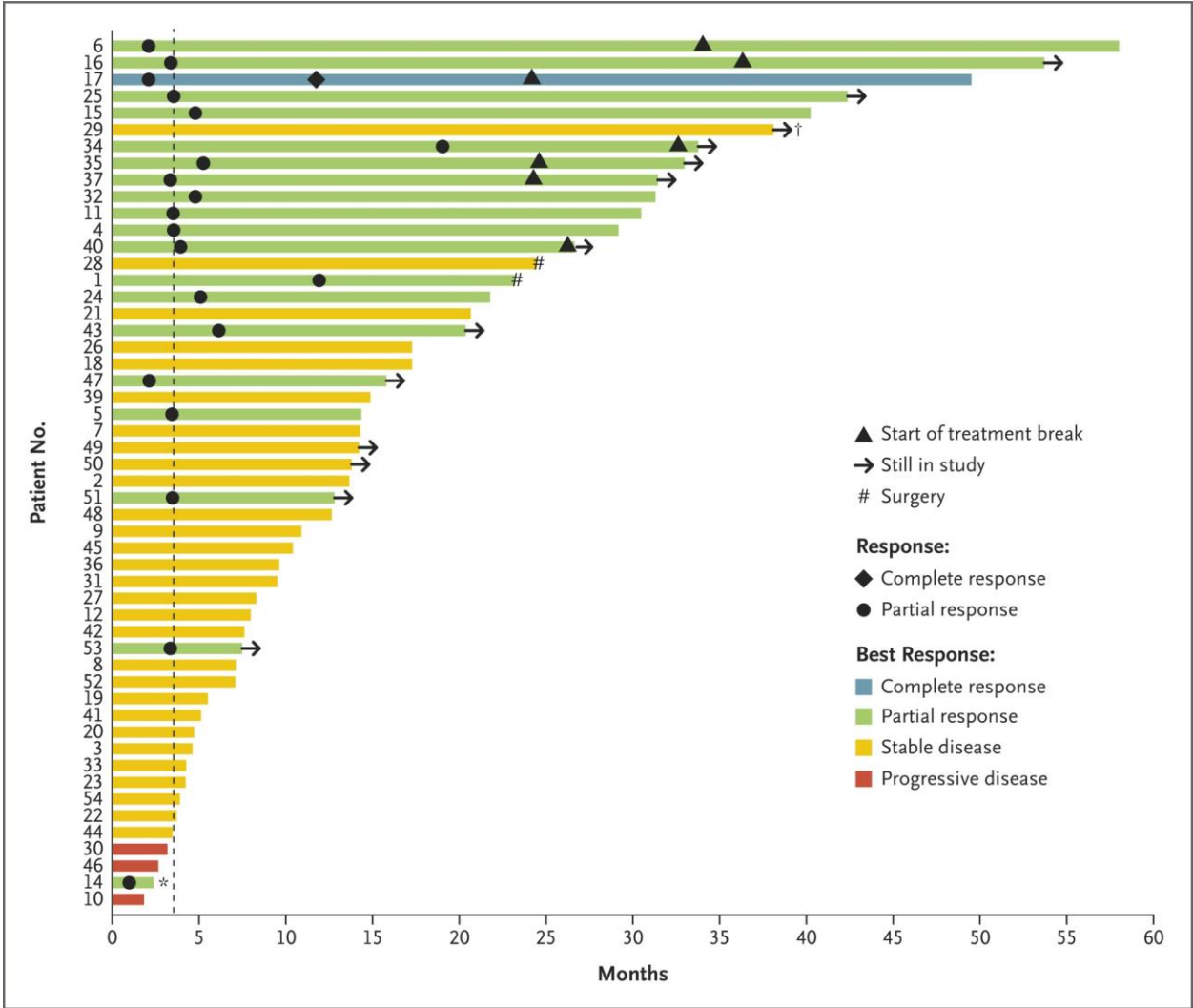
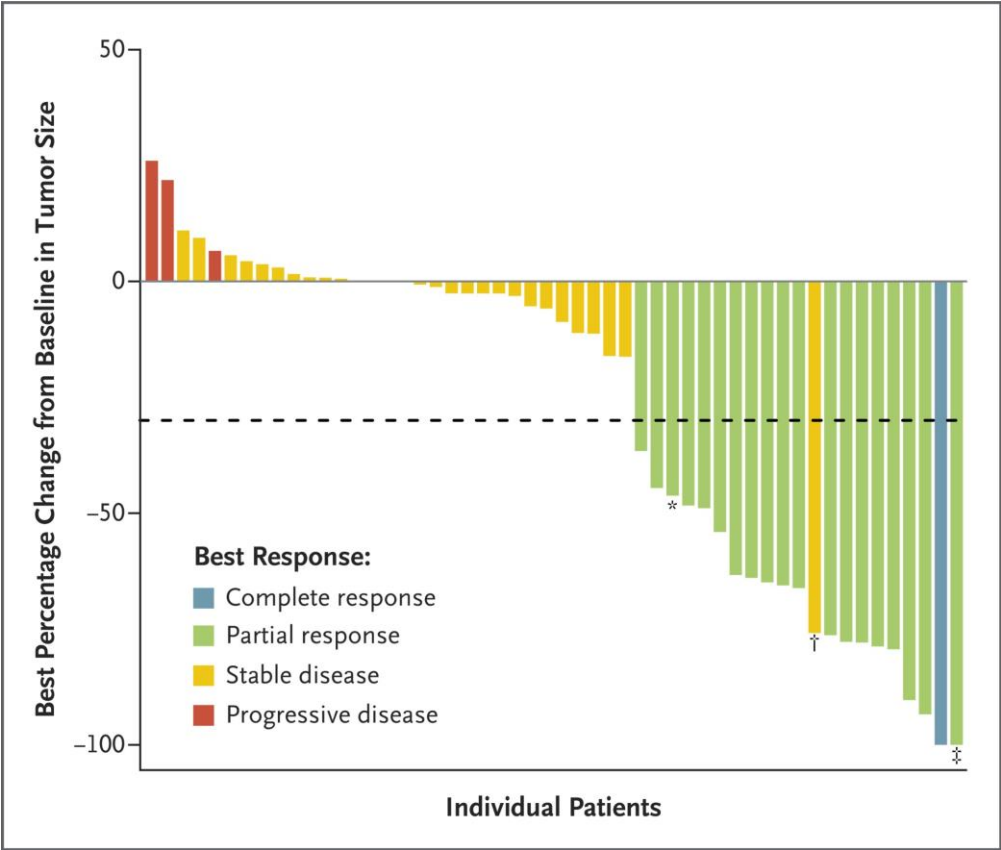


axitinib pembrolizumab



Single Agent Atezolizumab

32% ORR – FDA approval



Chen AP et al. N Engl J Med 2023;389:911-921

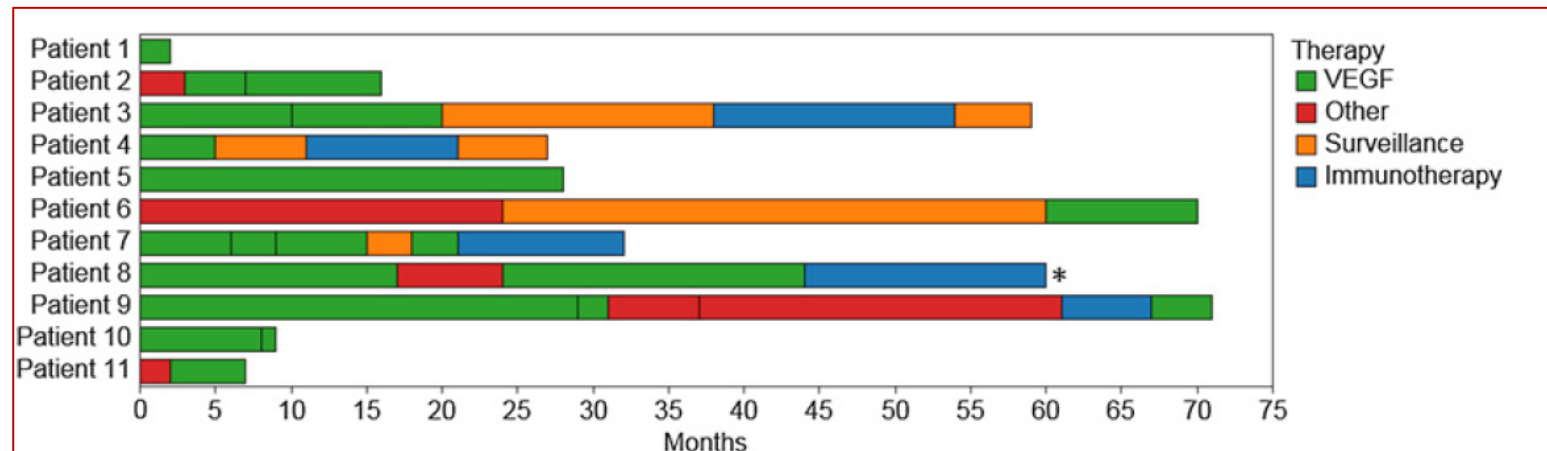
NCCN Guidelines Version 1.2023

Soft Tissue Sarcoma

Alveolar Soft Part Sarcoma (ASPS)

Preferred regimens

- Sunitinib^{70,71}
- Pazopanib⁷²
- Pembrolizumab⁷³
- Pembrolizumab in combination with axitinib⁷⁴
- Atezolizumab^{9,75}



VEGF-TKI (Cediranib) single agent

CPI single agent

CPI + CTLA4

CPI + VEGF-TKI

How Do We Sequence Agents?

First line vs salvage?

Is it Different for the Various Clinical Presentations

How Do We Approach ASPS?

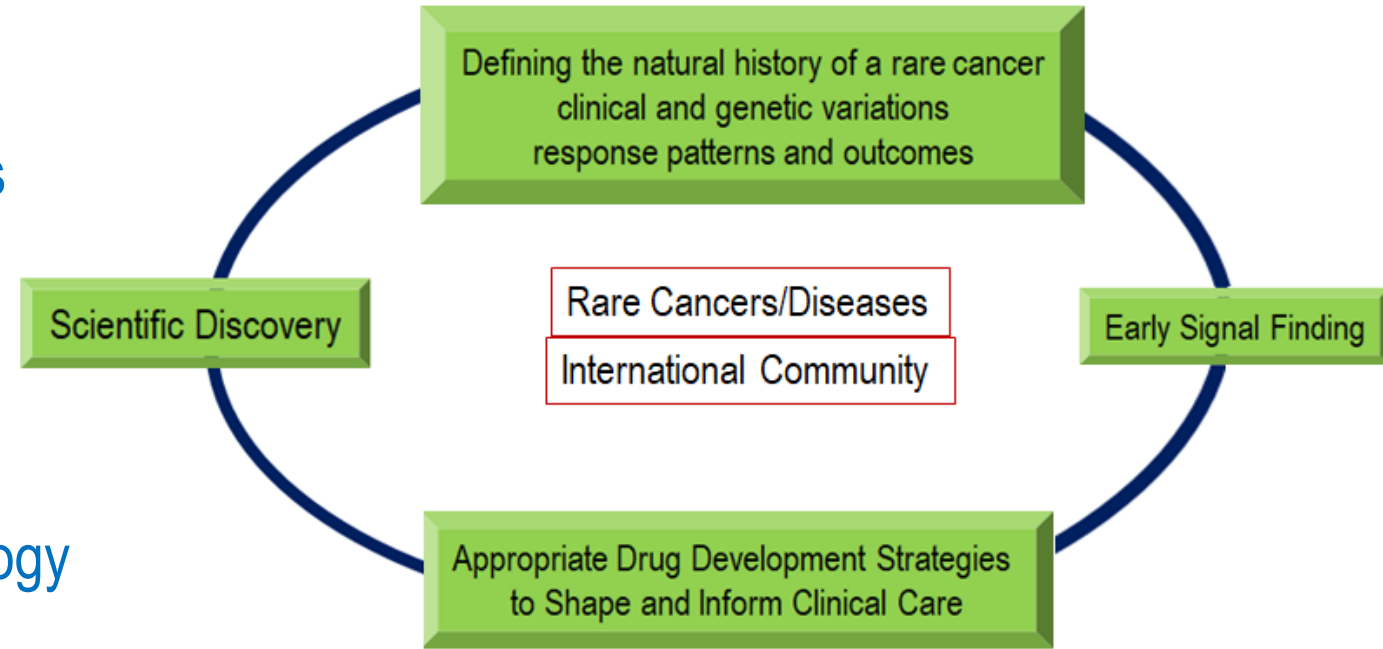
What can we learn from people being treated with these agents?

Discovery and Innovation in Drug Development and Patient Care in Rare Cancers

Comprehensive Development Strategies

1. Ensure Successful Development Programs (P1→P3)
2. Inform Clear Clinical Application
3. Define Natural History of a Rare Disease
 - Best Treatment Outcomes Data
4. Further our Understanding of Disease Biology And Outcomes
5. Build Inclusive Collaborative Networks
6. Set the Paradigm for Drug Development Strategies

****Inclusive to what is important to the patient!**





Community
Treatment
Community

Community

Patient
Registry

Academic
Consultation

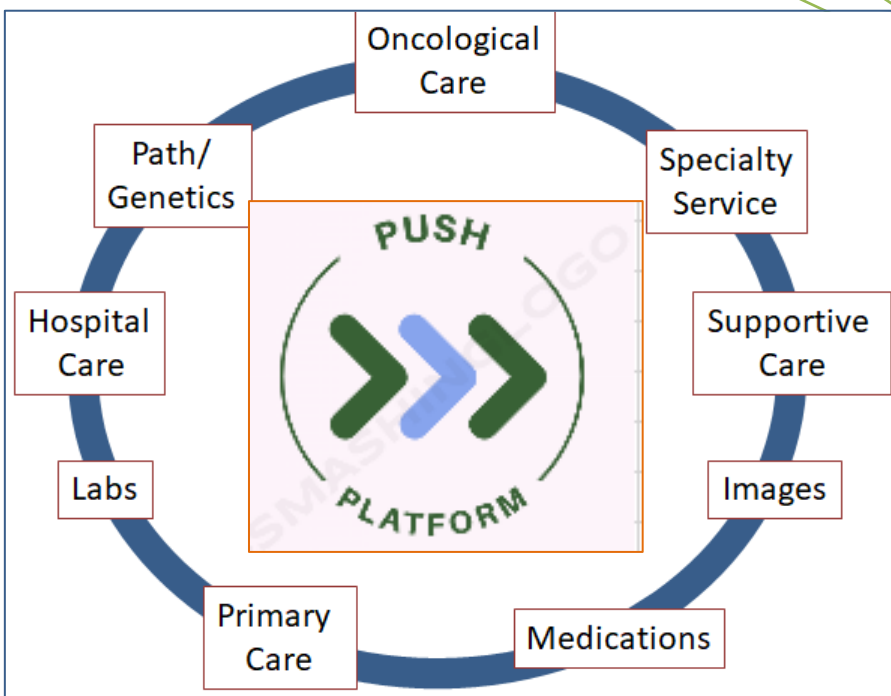
Path
Review

Surgery

Path
Review

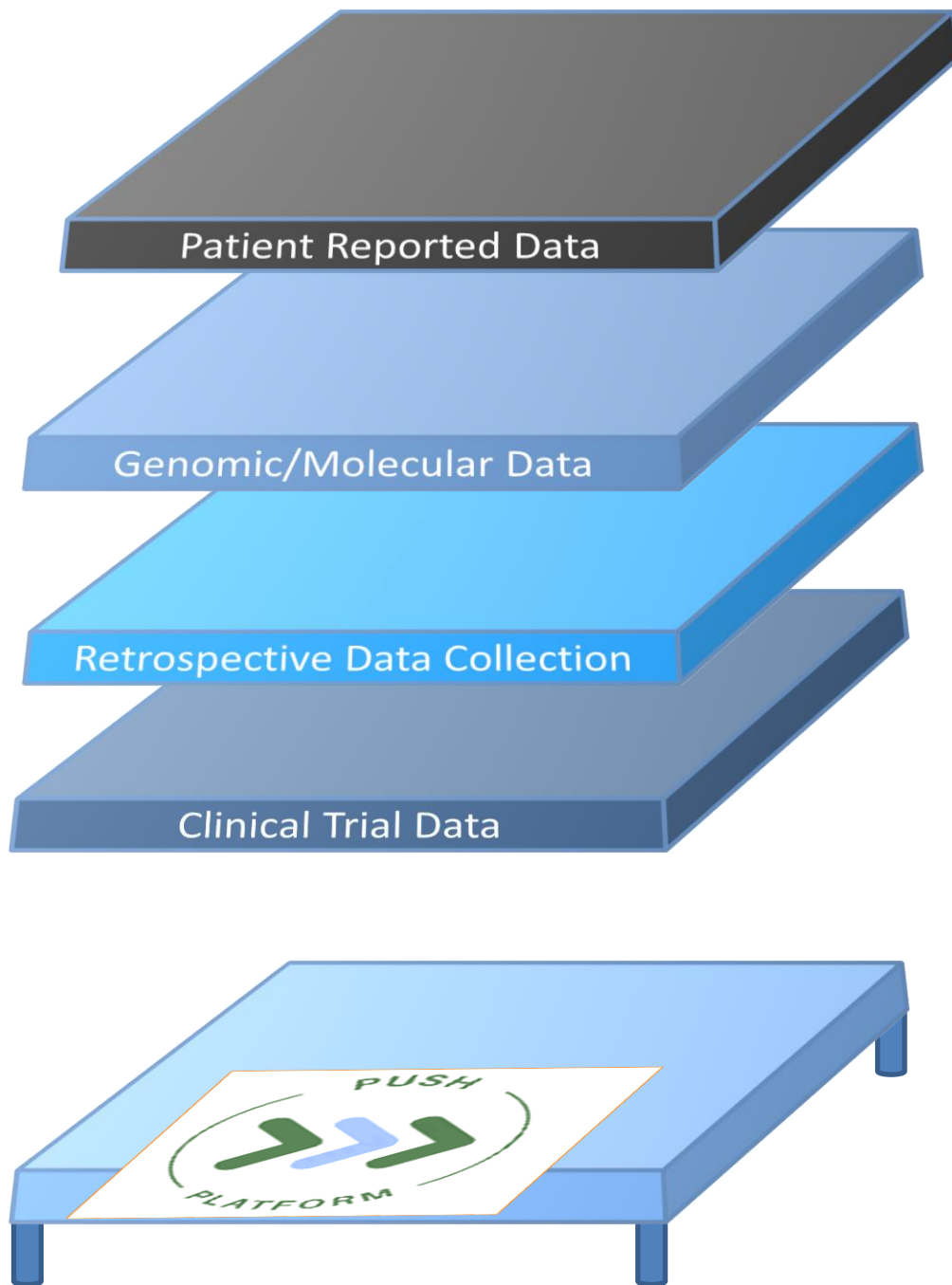
Accurate and Complete History

IIT Trial Database



RWD; Nat Hx clinical and genetic variants; RWE response

ettering



Patient Reported Outcome Measures
APP-Based CRFs
Registries from Pt Advocacy groups

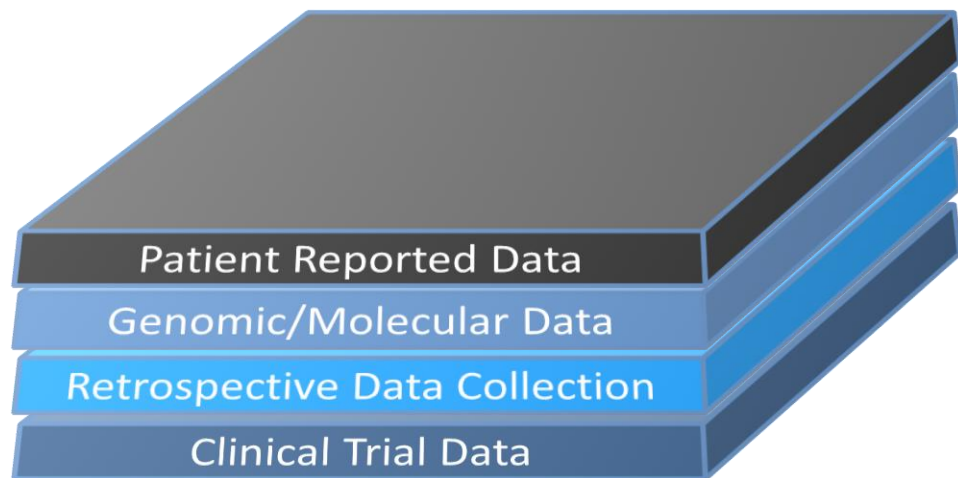
Genomics from Individual Pt Tumor Samples (NGS, WGS)
Pre/Post Treatment Analyses
Circulating Tumor DNA/Cells
Large Tumor Centric Data Sets

Academic Chart Reviews
Comprehensive Data Extraction Efforts

Previously Run Trials (IIT; Cooperative Group)

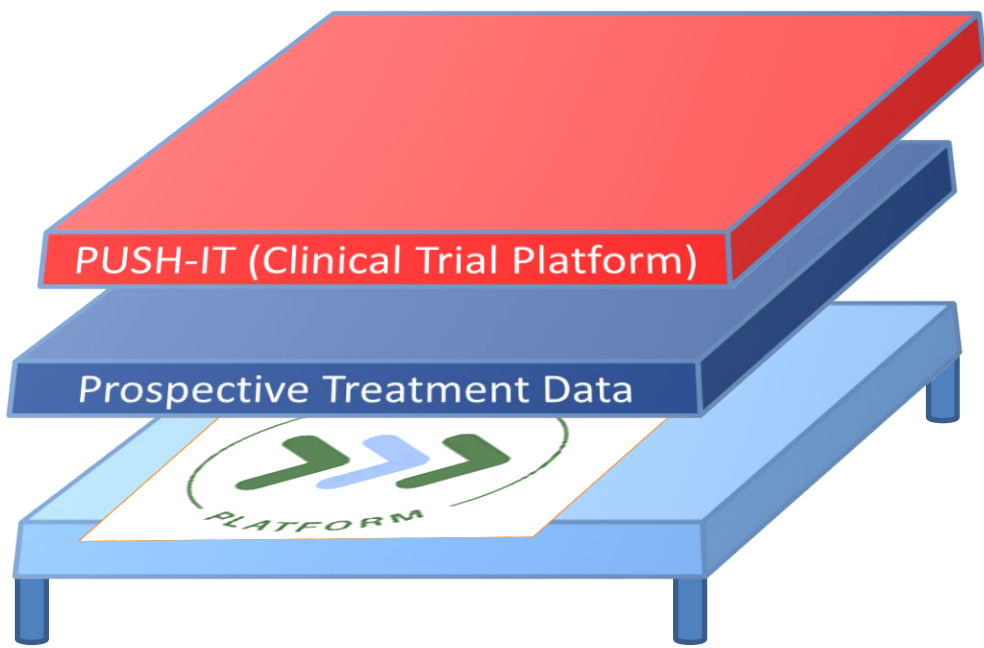
Industry Sponsored when Available
Non-Interventional (Simulated) Clinical Trials

Harmonized/Well Define Treatment Paradigms – SOC
Prospective Off-Label Use of Drugs
Drug Repurposing

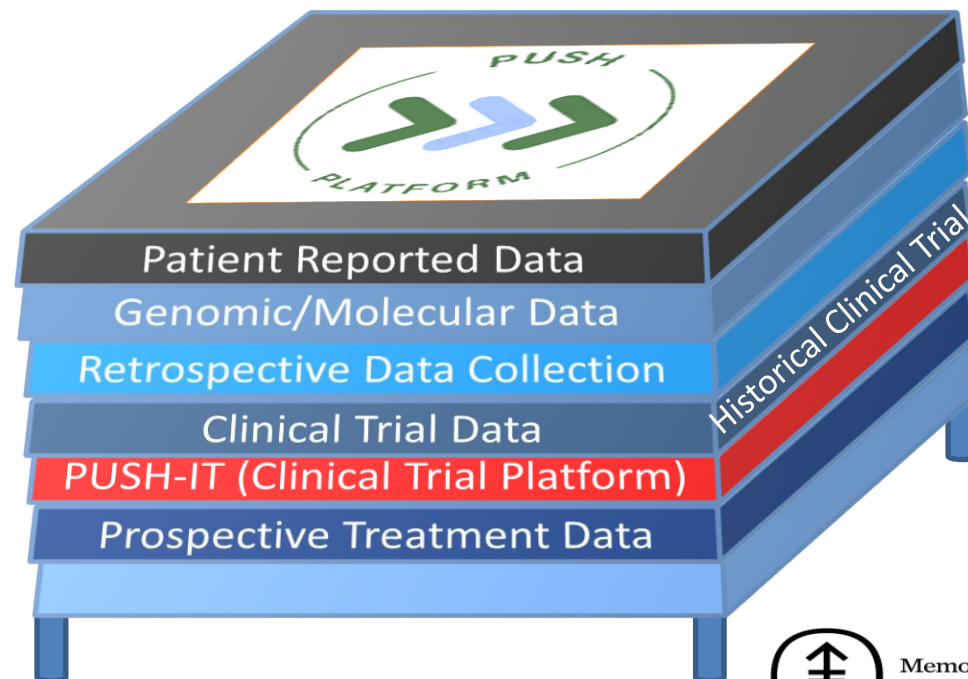


PUSH-IT

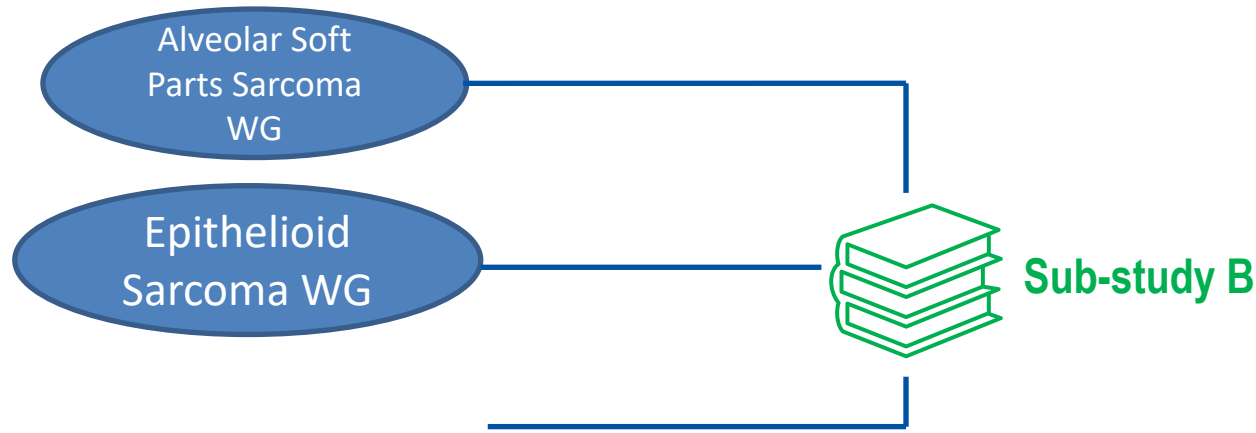
(International Trial)



Harmonized Prospective Treatment Data



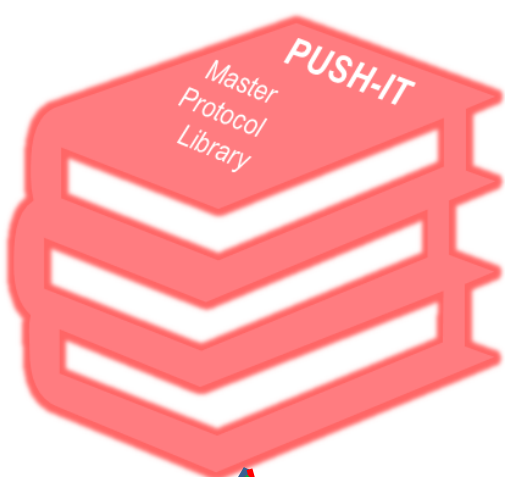
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Investigational group

Standard of care

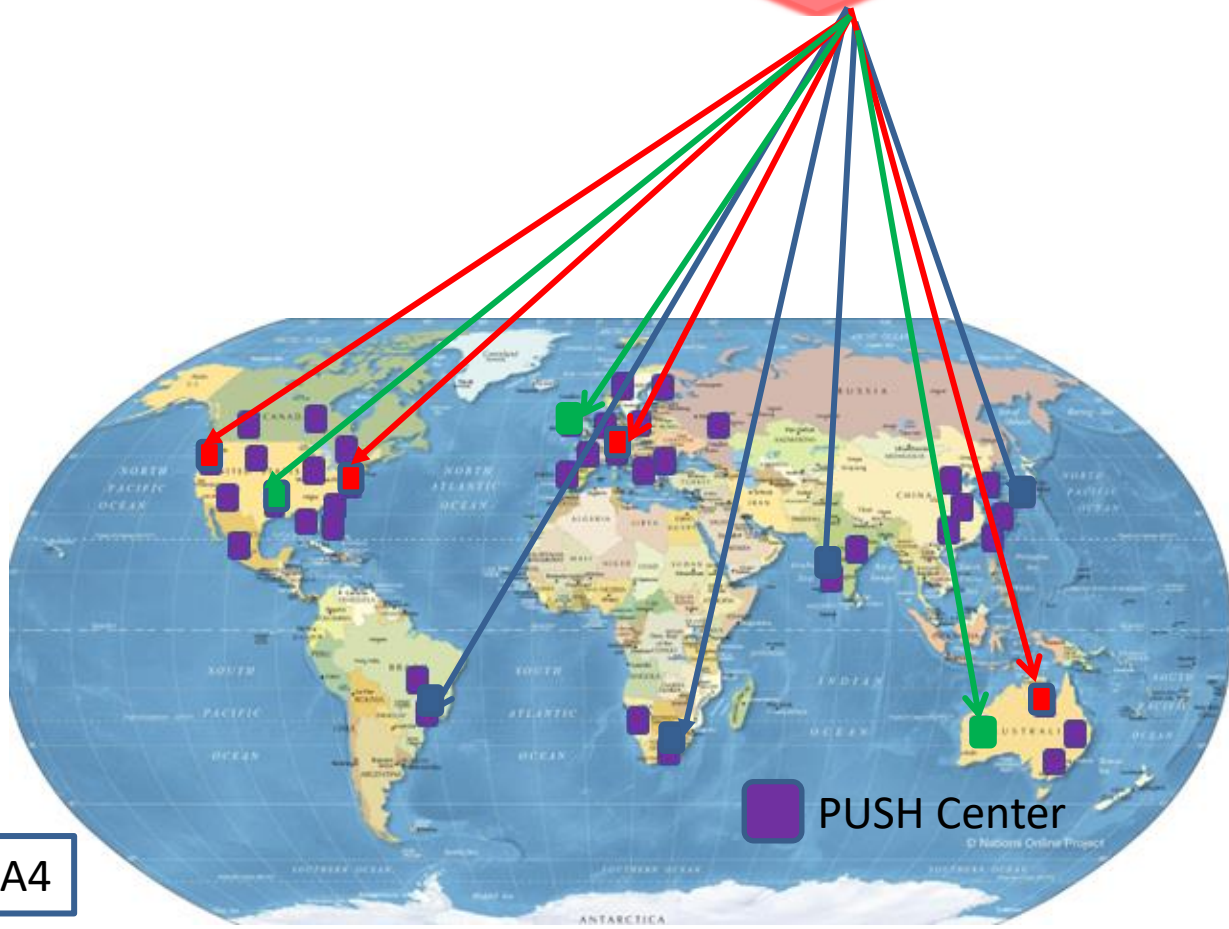
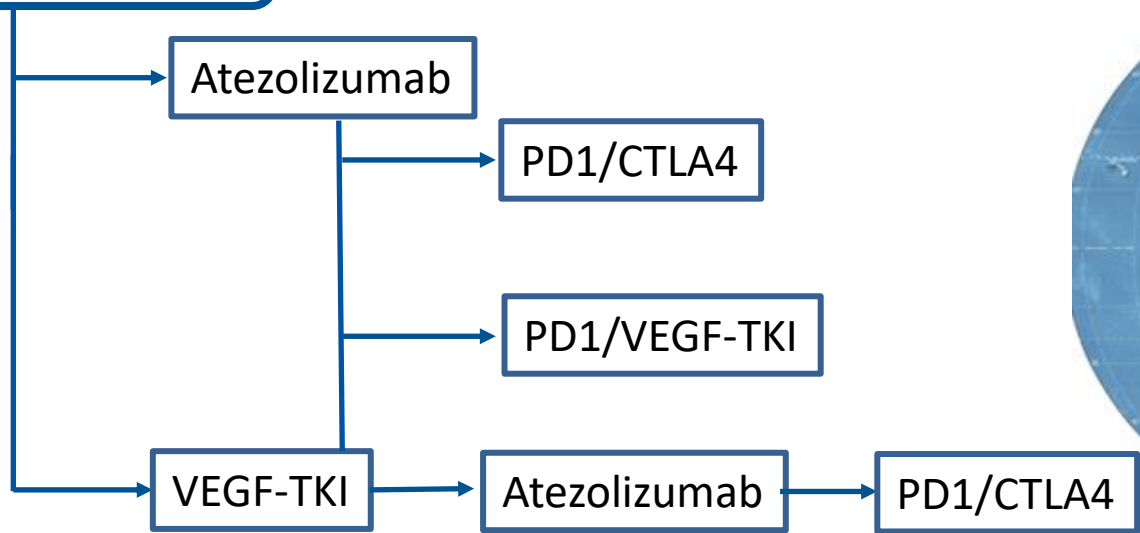
Observation



Treatment Roadmap

= inclusion/exclusion criteria
= radiologic assessments
= CRFs for clinical data collection

ASPS Investigational



Need to Ensure the Data We Collect is of Regulatory Grade
and Can be Useful for Repurposing Drugs

THANK YOU!!



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