Systemic therapy for EHE:
Customizing treatment for individual patients

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January 22, 2021

uchealth

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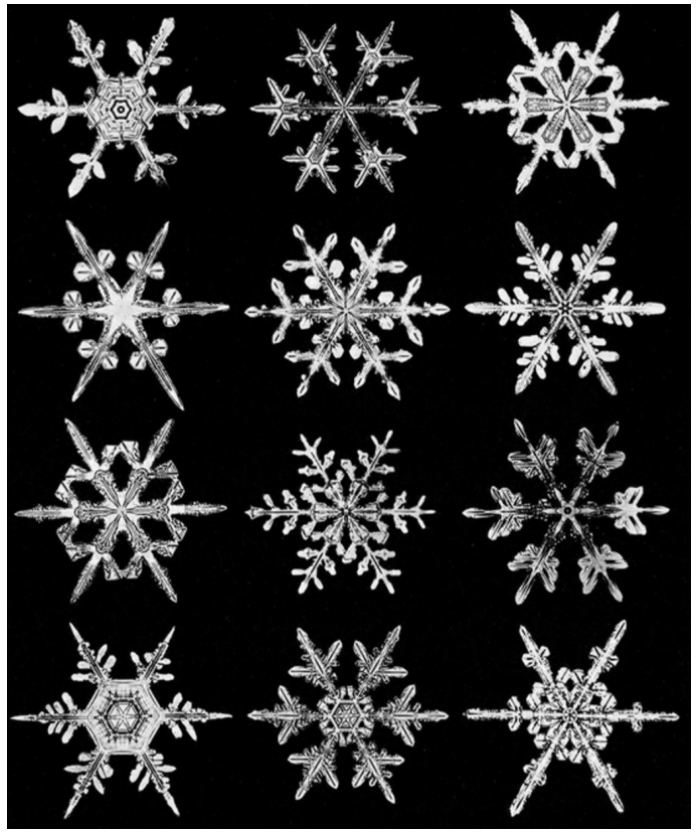
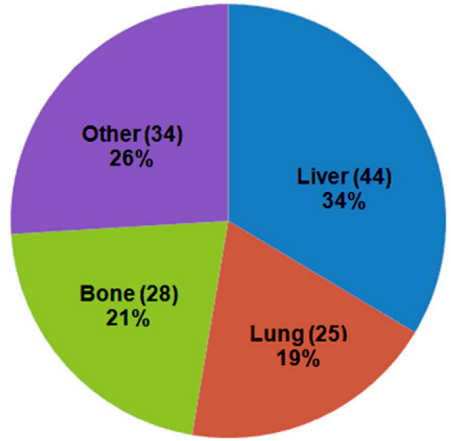
Patients with EHE are like snowflakes…

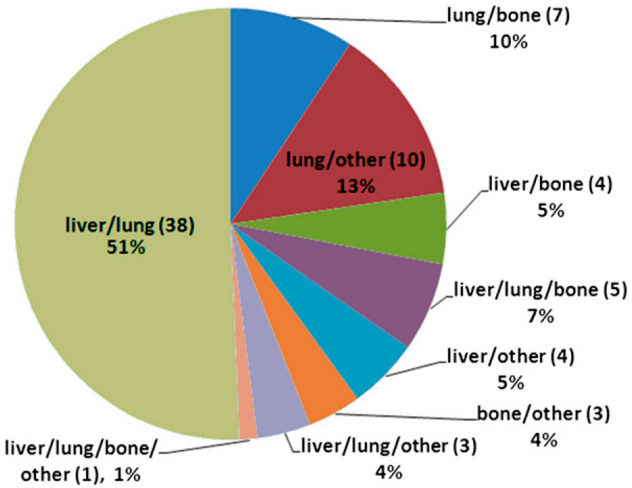
- **The tumors**
  - Location(s)
  - Fusion
  - Growth rate
- **The patients**
  - Genetic background
  - Immune system
  - Other medical conditions



Single-organ involvement (n=131)



Multi-organ involvement (n=75)

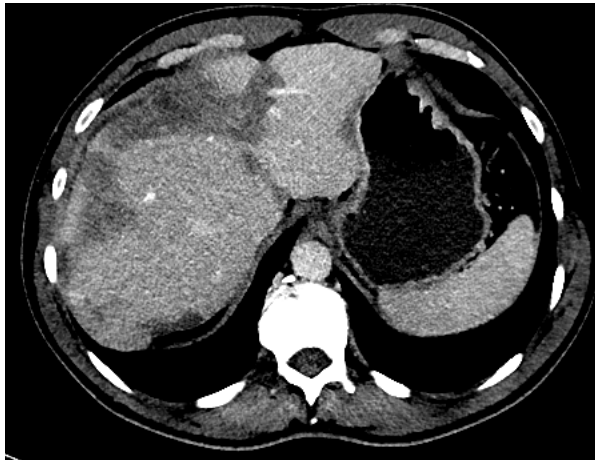


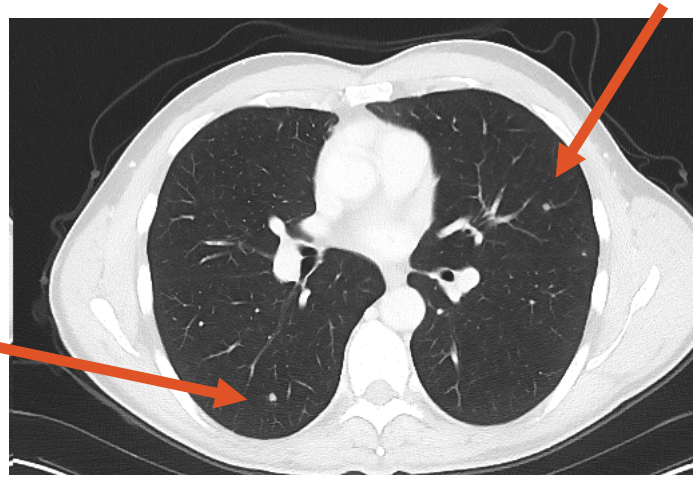
Assess the individual patient and tumor characteristics before treatment decisions

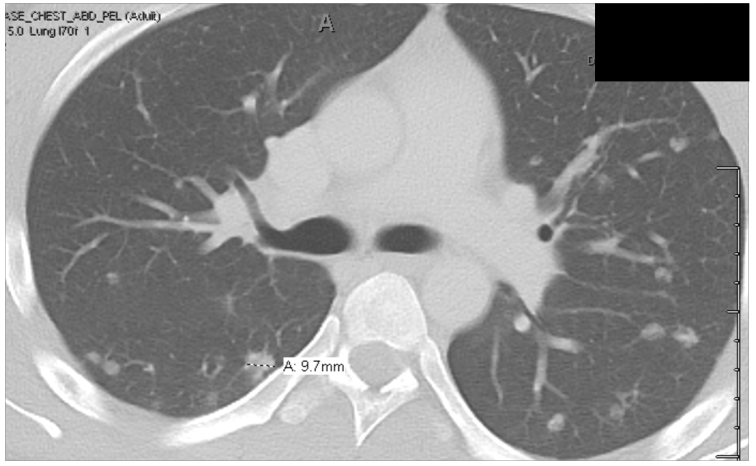
Lau et al, Chest, 2011

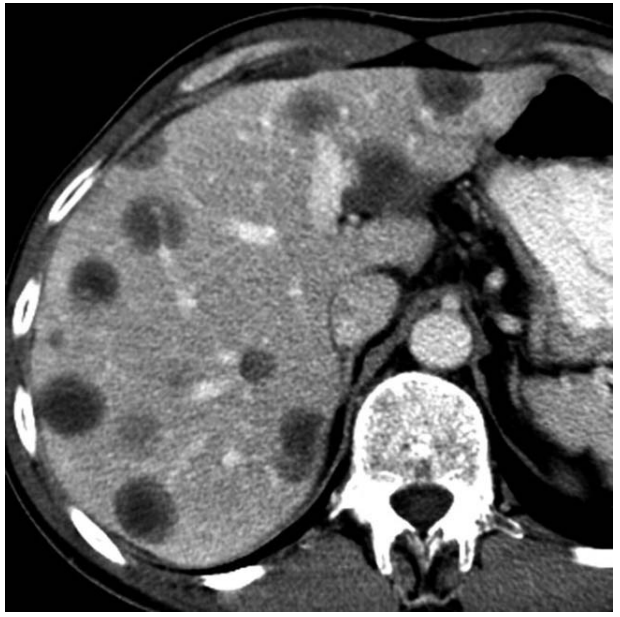
A disease of extremes…

- 45 yo F undergoes CT imaging for abdominal pain
- Found to have innumerable pulmonary nodules, largest less than 2 cm in size, and discrete cystic appearing lesions in the liver
- Liver biopsy confirms EHE.
- Interval imaging over next 5 years shows stable disease.



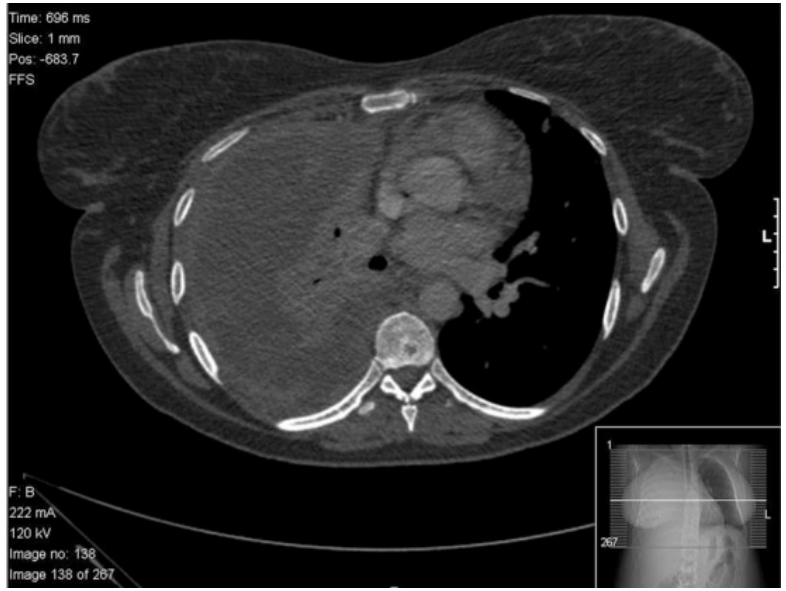






A disease of extremes…

- 55 yo M presents with severe back pain
- Imaging reveals multiple lytic lesions in the spine and in numerous other bones.
- Also found to have diffuse “ground glass” changes in the lungs concerning for right lung pleural involvement.
- Pathology shows fusion, but appears more aggressive like an angiosarcoma
- Chemotherapy initiated but patient developed respiratory failure within several weeks and hospice/comfort care was initiated.



My EHE rules…

- Everyone gets a path review and a fusion test to confirm EHE
- Most patients get at least two scans before deciding if treatment is necessary – **unless** high degree of symptoms
  - Patients can have stable disease without progression for years (up to 30!), and 5 year overall survival >81%
- Current treatments are stabilizing at best… so don't use toxic treatments for stable disease
- Liver transplantation…consider early on but…
  - Lifelong immunosuppression may limit eligibility for future clinical trials or treatment with immunotherapy (does this impact immune system/inflammation driving EHE growth/stability?)
  - Risk of morbidity with procedure and infections afterward

Lau et al, Chest, 2011
Makhlouf et al, Cancer 1999

My treatment algorithm: EHE

Disease status	Treatment Options	Surveillance
Solitary site of disease (ie liver only)	**Resection (SOC)** Local ablative procedures Consider liver transplantation eval	After resection image site of disease every 4-6 months for first couple years then less often
Widely metastatic, unresectable (liver/lung, lung only)	Surveillance Diet, exercise, anti-inflammatory meds (Celebrex)	Serial scans of disease locations: CT chest, MRI liver, bone scan every 4-6 months Once indolence established can decrease intervals of scans
Limited progression of metastatic/unresectable disease	**Local ablative therapies** particularly if only one or two lesions are changing in size	Scans of disease locations every 3-4 months
Widespread progression, new lesions, or high risk locations (ie pleural, bone)	Systemic treatment recommended (clinical trials preferred if available) Targeted radiation or ablative therapies to symptomatic bone lesions	Scans every 2-3 months on therapy

Systemic treatment options: EHE

- **CLINICAL TRIALS!!!! (whenever possible!!!)**
  - "standard" therapies are stabilizing at best, rare long term responses
- **Second opinions from high volume sarcoma centers are critical**
  - EHE ≠ metastatic sarcoma on the google search
  - You can get treatment locally, BUT so worth it to have a full review at a sarcoma center
  - For ablations/IRE, high volume MD also very important
- **There aren't really "standard" therapies**
  - Most data is from case reports and series (<<<100 pts), anecdotes
  - Ongoing international collaboration to pool retrospective data and treatment experiences, registry efforts
  - Interest and awareness through patient advocacy groups are critical to advance EHE treatments

Systemic treatment options: cytotoxic chemotherapy

- Cytotoxic chemotherapies target rapidly growing cells
- May help to boost an immune response from cell death/inflammation
- May lead to clinical benefit without tumor shrinkage (symptoms)
- Rare responses (tumor shrinkage > 30%)
- Side effects: decreased immune cells, anemia, low platelets, hair loss, nausea/vomiting, fatigue, neuropathy, etc.
- I use for tumors resembling angiosarcomas either by pathology or by rapid growth

- Liposomal doxorubicin
- Doxorubicin alone or combinations
- Gemcitabine/docetaxel
- Single agent paclitaxel
- Carboplatin/paclitaxel

Rosenberg & Agulnik, Curr Treat Options Oncol 2018
Yousaf et al, Anticancer Research 2015

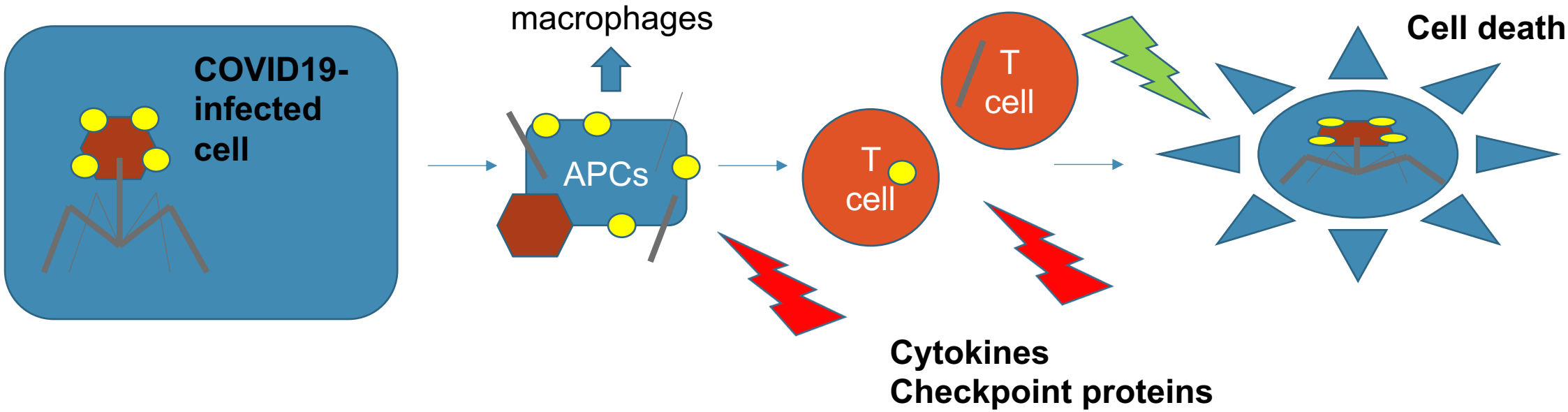
Systemic treatment options: targeted therapies

- Chemotherapy pills (most) that block key signaling pathways that cancer cells use to grow, communicate, spread, alter metabolism, and suppress the immune system
- Not all targets are known, a bit of a wild card
- Tend to work on slower growing sarcomas
- Many target VEGF, which drives abnormal cancer blood vessel growth
- Can stay on for years if effective
- Side effects: generally better than chemo, BUT… hypertension, bleeding/blood clots, nausea/vomiting, fatigue, diarrhea, etc.

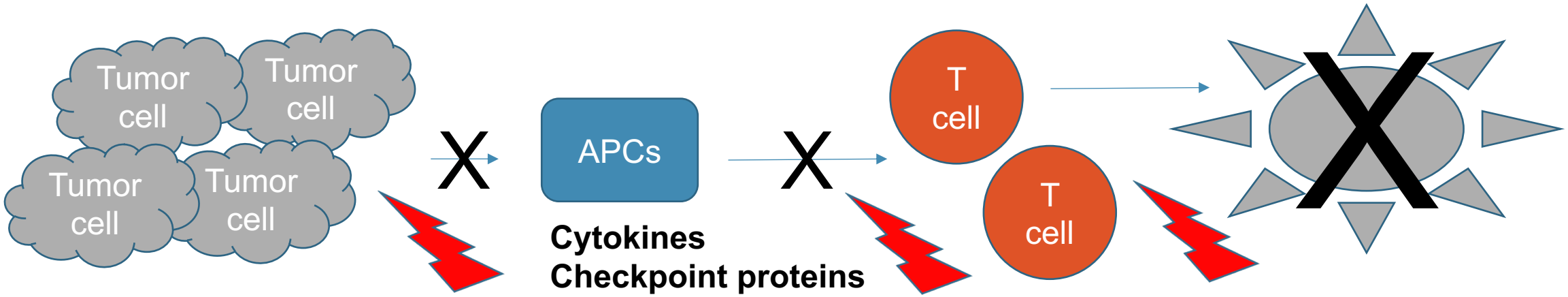
- **Pazopanib**
- Sorafenib
- Apatinib
- Bevacizumab
- mTOR inhibitors (sirolimus, rapamycin)
- **Trametinib**

Rosenberg & Agulnik, Curr Treat Options Oncol 2018

Immune therapy



Bad antigens – not recognized



Role of the immune system in EHE

- Sooooo much to understand about the immune system in EHE but…
- Prolonged stability with sudden breakthroughs fits paradigm of immune suppression -> escape
- Other sarcomas with similar clinical behavior have responded to immune therapies (alveolar soft part sarcoma)
- Occasional sporadic regressions without treatment
- Ablation/IRE or chemo -> increase antigen presentation -> abscopal benefit?
- Very little known on immune infiltrates in EHE tumors – but high stroma…
- Low mutational burden (translocation driven)
- Anecdotes of responders to checkpoint inhibitor therapy

De Baere et al, Eur J Cancer, 2018

Systemic treatment options: Immunotherapy

- Can target various steps in the immune response
  - Cytokine stimulation
  - Promoting more active T cell activity
  - Blocking tumor don't-eat-me signals
  - Blocking suppressive macrophages
- What are we targeting in EHE? Need better understanding of the immune environment in these tumors
- Side effects: Increase inflammation and autoimmune response against essentially every normal cell – can be fatal or long-term requiring steroids

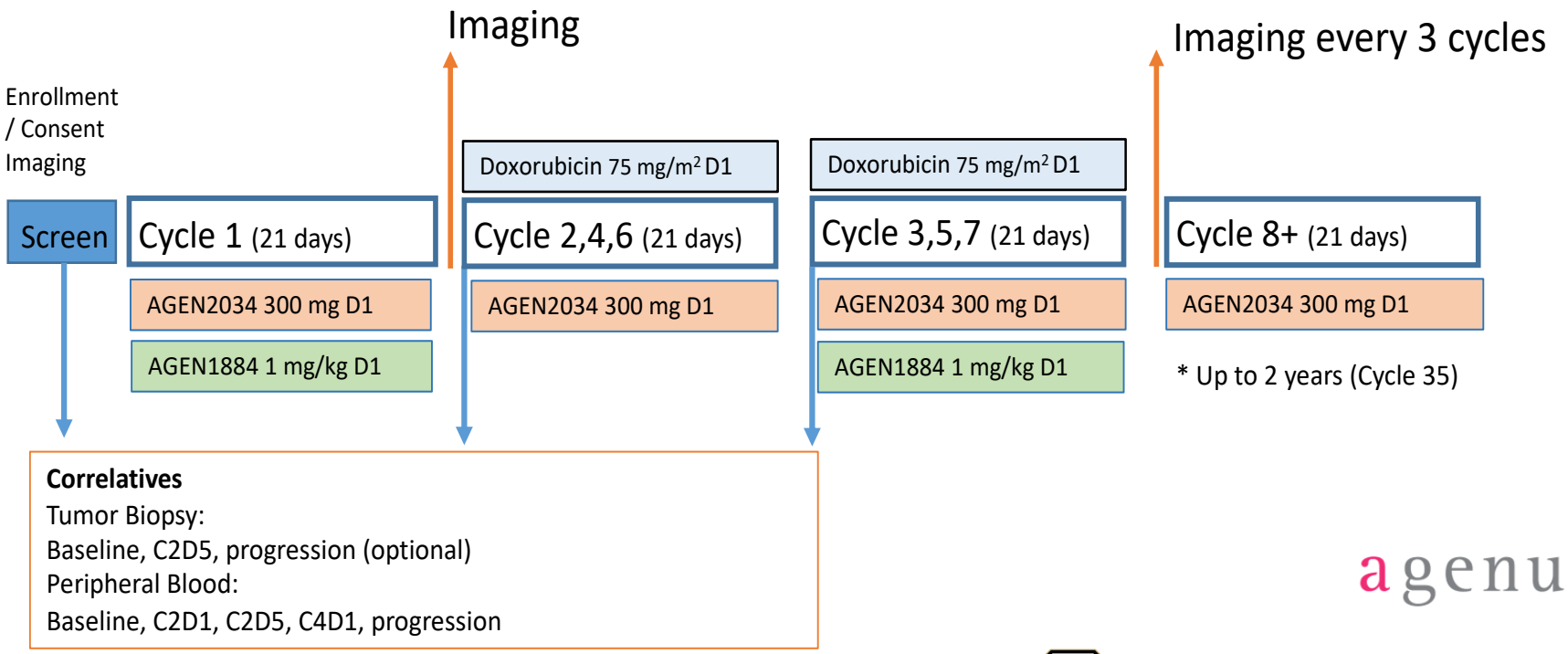
- Interferon +/- chemo
- Thalidomide/Lenalidomide
- Checkpoint inhibitors
- NSAIDs (Celebrex)
- cyclophosphamide

Yousaf et al, Anticancer Research 2015
Rosenberg & Agulnik, Curr Treat Options Oncol 2018

Doxorubicin plus dual checkpoint blockade

Hypothesis: Doxorubicin will increase antigen presentation/T cell expansion in combination with checkpoint blockade

Open Label, single arm, single center, investigator-initiated Phase II for up to 28 evaluable patients with advanced/metastatic sarcomas, anthracycline naïve, max of 1 prior therapy – **progressing EHE eligible**



Opened 1/2020 –
CU Cancer Center
NCT04028063, PI: Wilky

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Summary

- EHE is a disease of snowflakes – so much variability, but we can recognize some patterns clinically. Need scientific biomarkers to explain this.
- Seek out experts with experience with EHE
- Don’t over-treat stable EHE
- The immune system/inflammation is likely involved in EHE biology – but details are unknown, and role of immunotherapy just beginning to be explored
- Treatment decisions are driven by experience… which is not ideal. We need better and bigger analysis of that experience, and use it to design clinical trials.
- Partnership between research, physicians, patients, advocates critical to move the needle in these rare diseases

Thank you and questions!!!

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