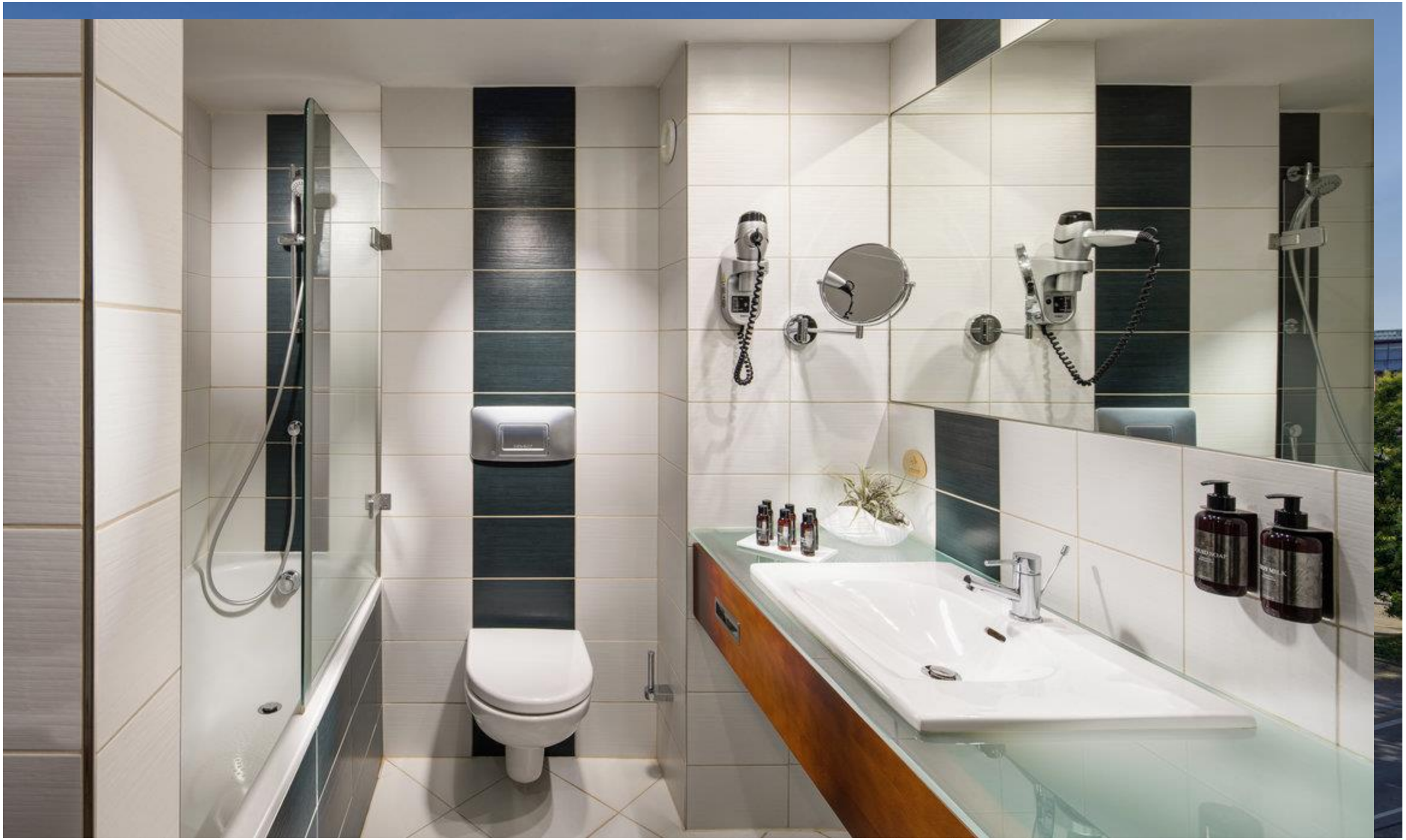
2. – 4. 10. 25 Bzenec...?


CHATEAU
BZENEC
2017
MODRÝ PORTUGAL



Quality Hotel Brno Exhibition Centre

- Křížkovského 496/20
  603 00 Brno - střed
  49.187871414810125, 16.582205397498846

- 2.- 4.10. 2025

- 4.10. 2025 odpoledne wine tasting Bzenec

Témata/ invited speakers/: ??

- Obecná onkologie
  - imunoterapie, CAR T exhausce? CAR-makrofágy? *Fraunhofer institute -Ulrike Kohl*?
- Podpůrná péče
  - Infekce
    - Diagnostika, terapie, prevence/profylaxe – úprava/modifikace pro nové způsoby léčby – blina, CARs??
  - CVK
  - Nové komplikace?
    - Malignancy-associated hemophagocytic lymphohistiocytosis *Jan Inge Henter?*
- Back to roots?
  - motto: „*all young adult cancer doctors are now immunologists. When I was a young, I was more a clinical pharmacologist/toxicologist. Middle generation are molecular biologists/geneticists…“ There are still some lessons and questions from the past to pass on to the younger generation of today.*
    - MTX + L-ASP??
- *Nová témata pro dětské hematology:*
  - VASCULAR ANOMALIES, VASCULAR MALFORMATIONS, AND THE ROLE OF THE HEMATOLOGIST DEC 6, 2024, ASH 2024. Targeted medical therapies for vascular anomalies VASCERN group?

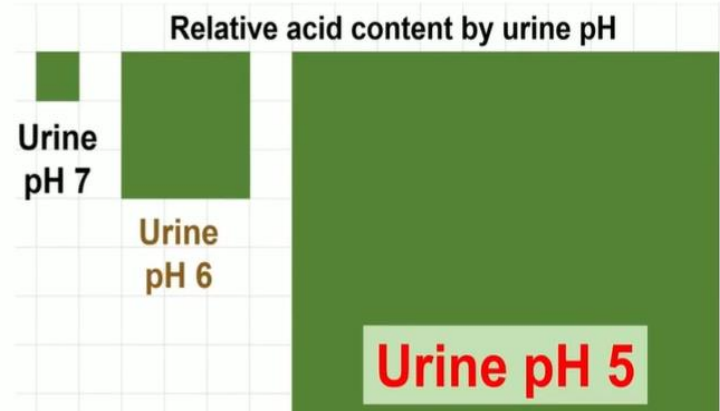
Never furosemide

(acidifies the urine, and slows MTX eliminat

Four practice-changing advances for HDMTX

Methotrexate diet

- No colas (no Coke, no Pepsi, etc.) – pH 2.5
- No carbonated drinks (no Sprite, no Fanta) – pH 3
- No juices (no orange, no apple, etc.) – pH 3
- Yes water ☺
- Yes milk ☺



Asparaginase and Antimetabolites, including MTX

Mechanisms of **Antagonism & Synchronization**

Robert L. Capizzi, MD

November 20, 1938 –
October 22, 2015

ALL (MTX)
Capizzi 1

42 Children and 32 Adults with Refractory ALL
All previously treated with asparaginase and MTX or both

[CANCER RESEARCH 47, 1313–1318, March 1, 1987]

L-Asparaginase-induced Modulation of Methotrexate Polyglutamylation in Murine Leukemia L5178Y[1]

Pratima Sur, Daniel J. Fernandes,[2] Timothy E. Kute, and Robert L. Capizzi[3]

Oncology Research Center [P. S., D. J. F., T. E. K., R. L. C.] and the Department of Biochemistry [D. J. F.], Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103

ABSTRACT

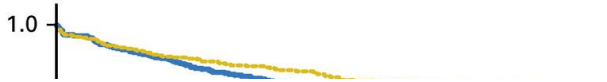
The modulation of methotrexate polyglutamylation by L-asparaginase has been examined in mice bearing sublines of leukemia L5178Y that have different sensitivities to asparaginase. A single i.p. injection of 200 IU/kg of asparaginase completely inhibited ascites tumor cell growth in the parental L5178Y/S+ tumor for 120 h compared to 72 and 30 h in the L5178Y/S and L5178Y/S± sublines, respectively. Similarly, DNA and protein synthesis were completely inhibited by asparaginase for 96 h in L5178Y/S+ cells, but only for 72 and 24 h in L5178Y/S and L5178Y/S± cells. In each tumor the temporal patterns of depletion and recovery of S-phase cells were similar to the patterns of suppression and recovery of DNA and protein synthesis observed in that tumor.

When methotrexate was administered at either 96 or 24 h after asparaginase during the asparaginase-induced S-phase nadirs of L5178Y/S+ and L5178Y/S± cells, respectively, subsequent methotrexate polyglutamylation was inhibited 83 and 92% compared to tumor cells exposed to methotrexate only. Recovery of methotrexate polyglutamylation in both tumors following L-asparaginase pretreatment coincided in time

further supported by studies which demonstrated that L-asparagine was an essential amino acid for L5178Y cells (7). Our earlier observations related the observed Asnase-induced antagonism of MTX to both inhibition of cellular uptake of MTX (8) and inhibition of DNA synthesis secondary to the inhibition of protein synthesis (4). However, the studies concerning MTX uptake and retention were performed prior to our current understanding of the relationship of MTX polyglutamylation to MTX uptake and cytotoxicity (9, 10).

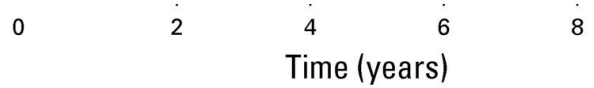
Further studies of the schedule dependency between Asnase and MTX revealed pharmacological synergy when Asnase was administered at longer time intervals (>48 h) before MTX, or when Asnase was administered at an appropriate time interval after MTX (2, 4). In addition, the delayed administration of Asnase did not alter the antileukemic effect of MTX but did attenuate the toxicity of MTX to normal organs of mice, an effect which allowed mice to tolerate a larger dose of MTX (2).

A



Dexamethasone and High-Dose Methotrexate Improve Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report From Children's Oncology Group Study AALL0232

JCO, 2016



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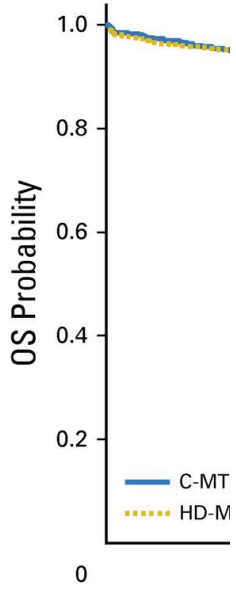

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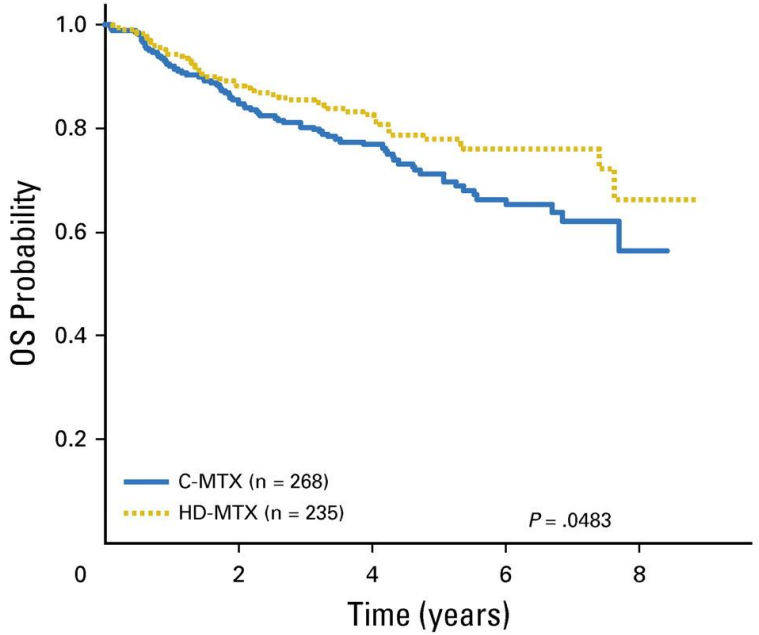

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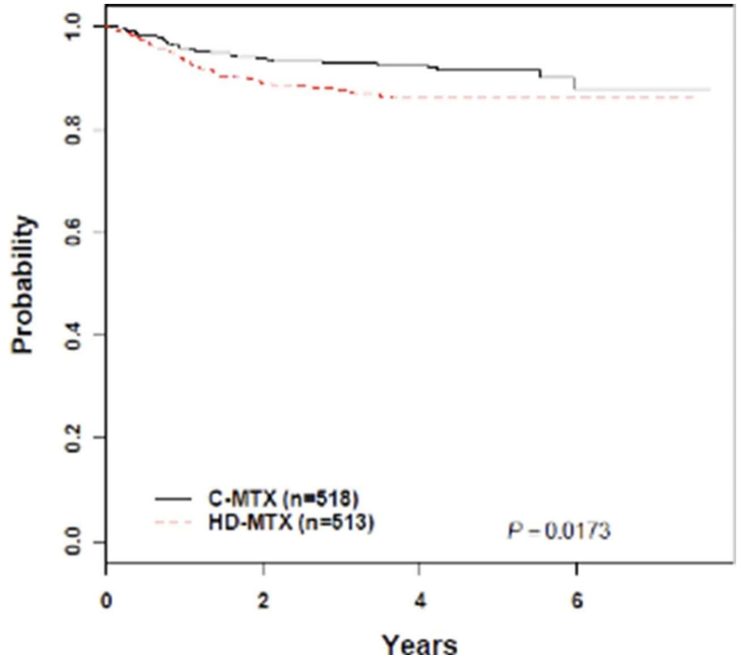
614. ACUTE LYMPHOBLASTIC LEUKEMIA: THERAPY, EXCLUDING TRANSPLANTATION: ADVANCES IN TREATMENT AND PRECLINICAL STUDIES | DECEMBER 03, 2015

Capizzi-Style Methotrexate with Pegasparagase (C-MTX) Is Superior to High-Dose Methotrexate (HDMTX) in T-Lineage Acute Lymphoblastic Leukemia (T-ALL): Results from Children's Oncology Group (COG) AALL0434

Stuart S. Winter , MD,[1] Meenakshi Devidas , PhD,[2] Si Chen , MS,[*,2] Barbara Asselin , MD,[3] William L. Carroll , MD,[4] Brent L Wood , MD PhD,[5] Natia Esiashvili , MD,[*,6] Briegel J Nikki , PharmD,[*,7] Robert J. Hayashi , MD,[*,8] Mignon L. Loh , MD,[9] Andrew J. Carroll , PhD,[10] Nyla A. Heerema , PhD,[11] Elizabeth Raetz , MD,[12] Naomi J. Winick , MD,[13] Stephen P. Hunger , MD,[14,15] Kimberly P. Dunsmore , MD[16]



LEUKEMIA & LYMPHOMA
2019, VOL. 60, NO. 12, 2849–2850
https://doi.org/10.1080/10428194.2019.1668941

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Taylor & Francis Group

COMMENTARY

Methotrexate and asparaginase: not so simple

Paul S. Gaynon

Children's Hospital Los Angeles, University of Southern California, Los Angeles, CA, USA

Better use of conventional agents has brought the 5-year overall survival of childhood acute lymphoblastic leukemia to 90% [1]. Among these are methotrexate and asparaginase.

Almost 50 years ago, Robert Capizzi found that asparaginase and asparagine depletion inhibit protein, DNA, and RNA synthesis in susceptible lymphoblasts that lack asparagine synthetase (asparagine auxotrophs), and thereby render them safe from thymidine deprivation as induced by methotrexate. Incubation with asparaginase before or simultaneously with

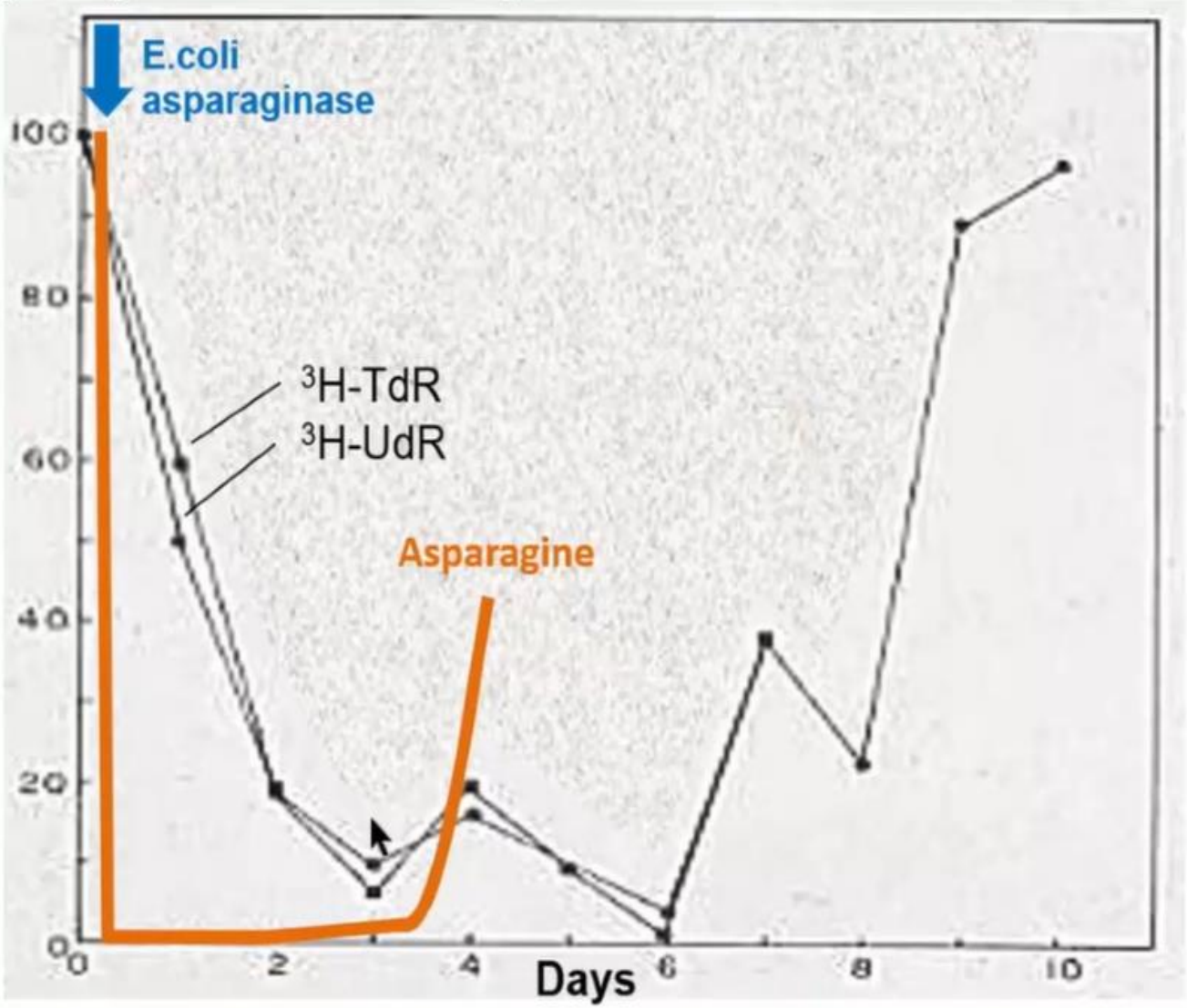
3 weeks following each methotrexate infusion, likely prior to the subsequent methotrexate infusion. Sample size precluded any examination of clinical efficacy [6].

PEG had no effect on the 48 h MTX levels. Erythrocyte MTXPG's were modestly decreased compared to profound decreases earlier in vitro experiments (see Table 1). The authors point out that they studied erythrocytes with asparagine synthetase and not lymphoblasts lacking asparagine synthetase. PEG added 12 day to "Protocol M," 80 day vs. 68 day. PEG increased red blood cell and platelet transfusions,

Asparaginase: Protein Synthesis Inhibition & G1 Arrest

ALL DNA Synthesis in presence of MTX *in vitro*

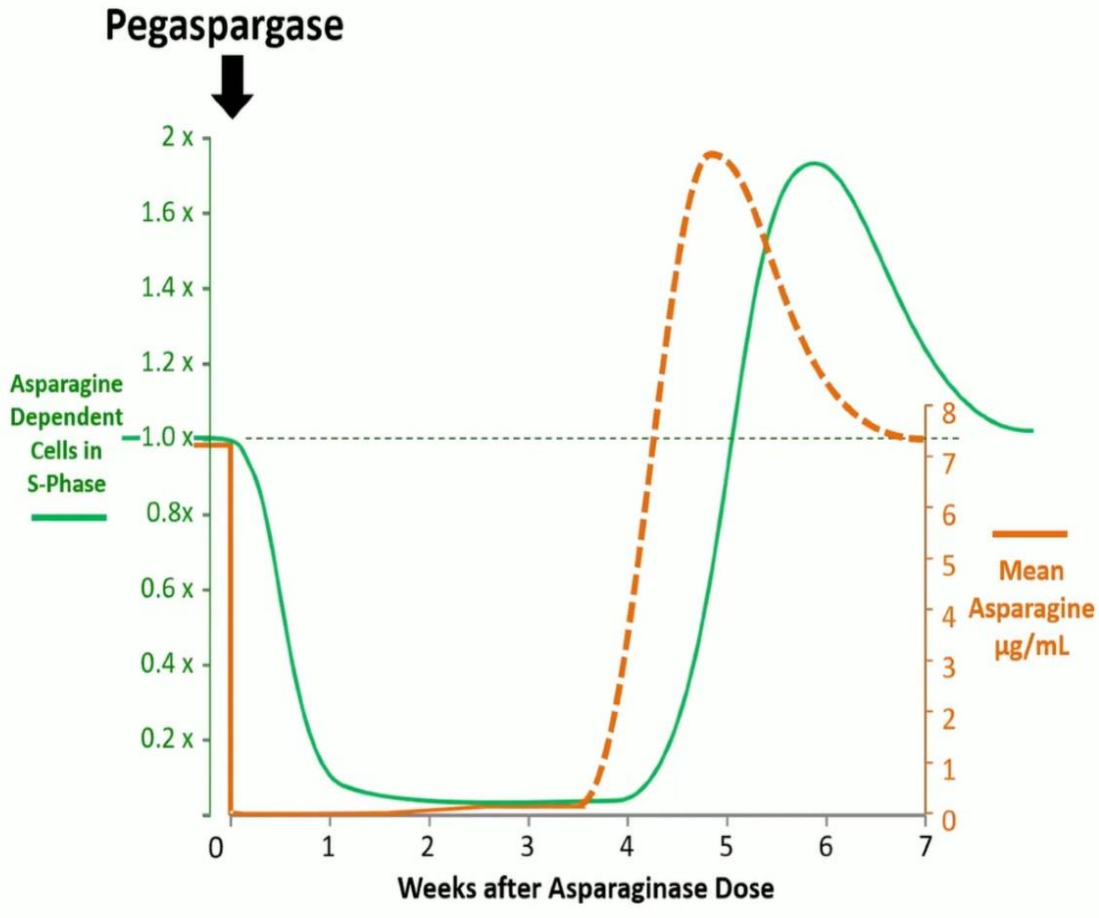
% of Pre-treatment Value

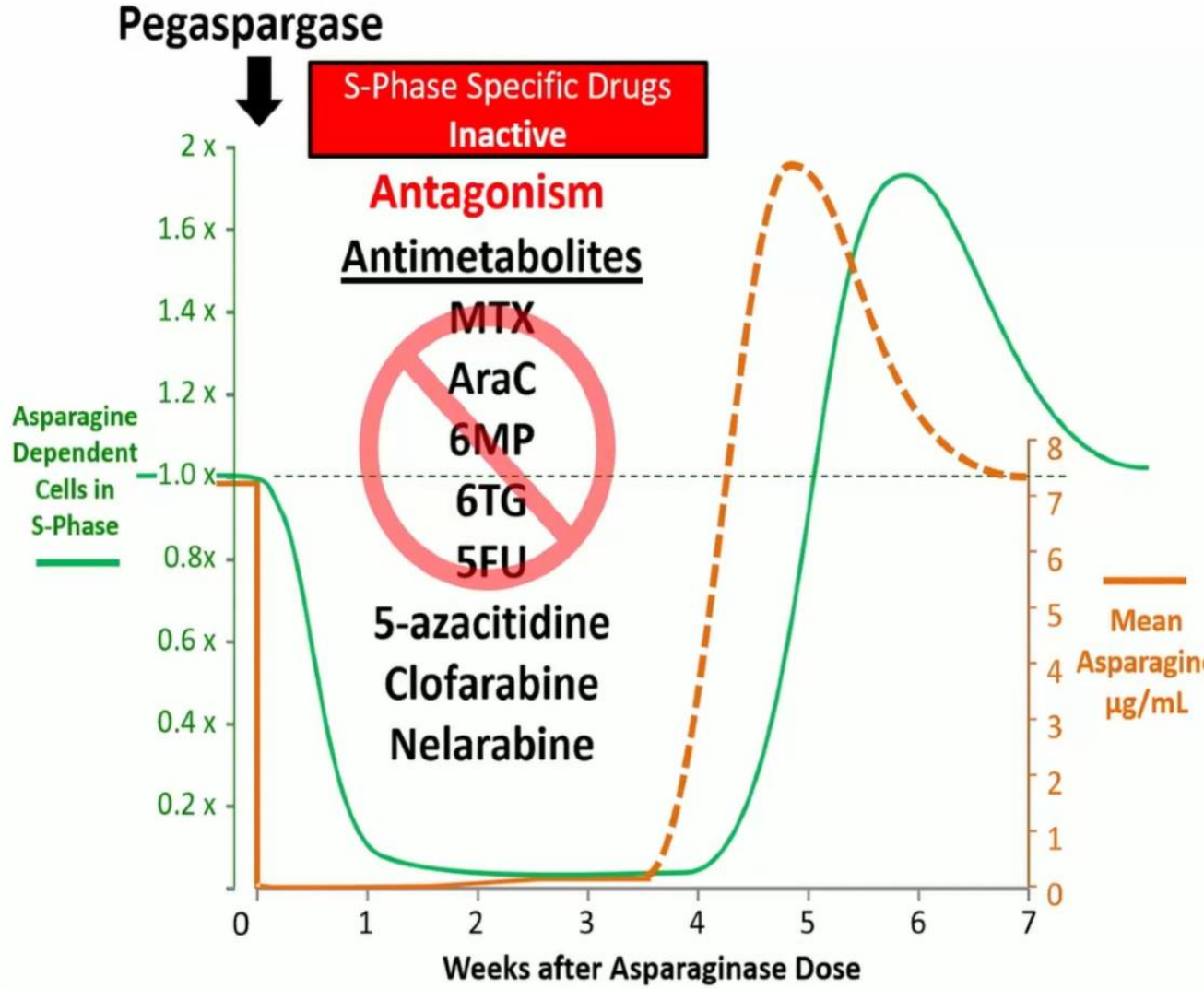


Asparaginase is the only protein synthesis inhibitor in today's chemotherapy armamentarium

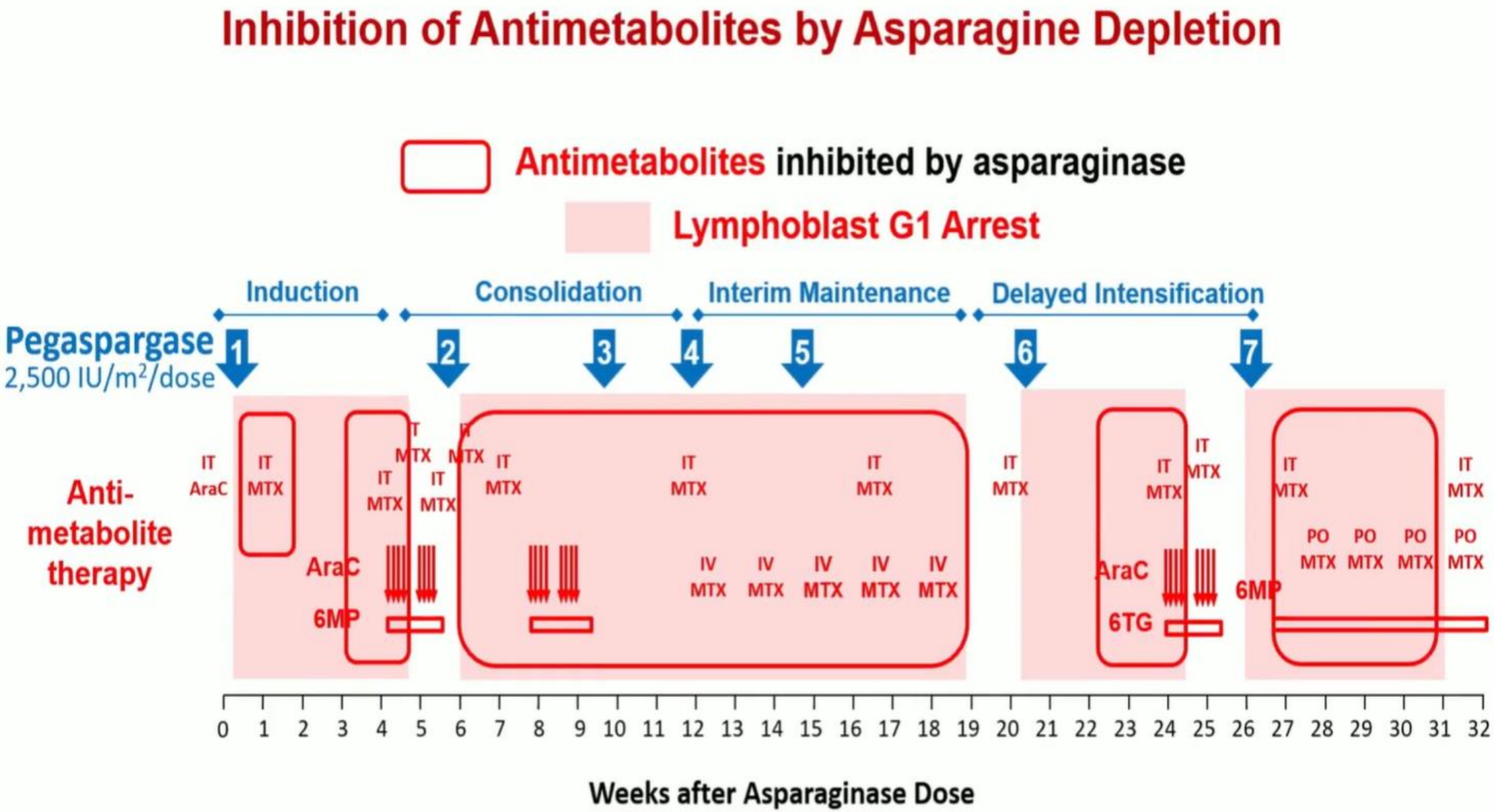
Asparaginase inhibits >90% of blast DNA synthesis within 3 days
Recovery begins 4 days after asparagine repletion

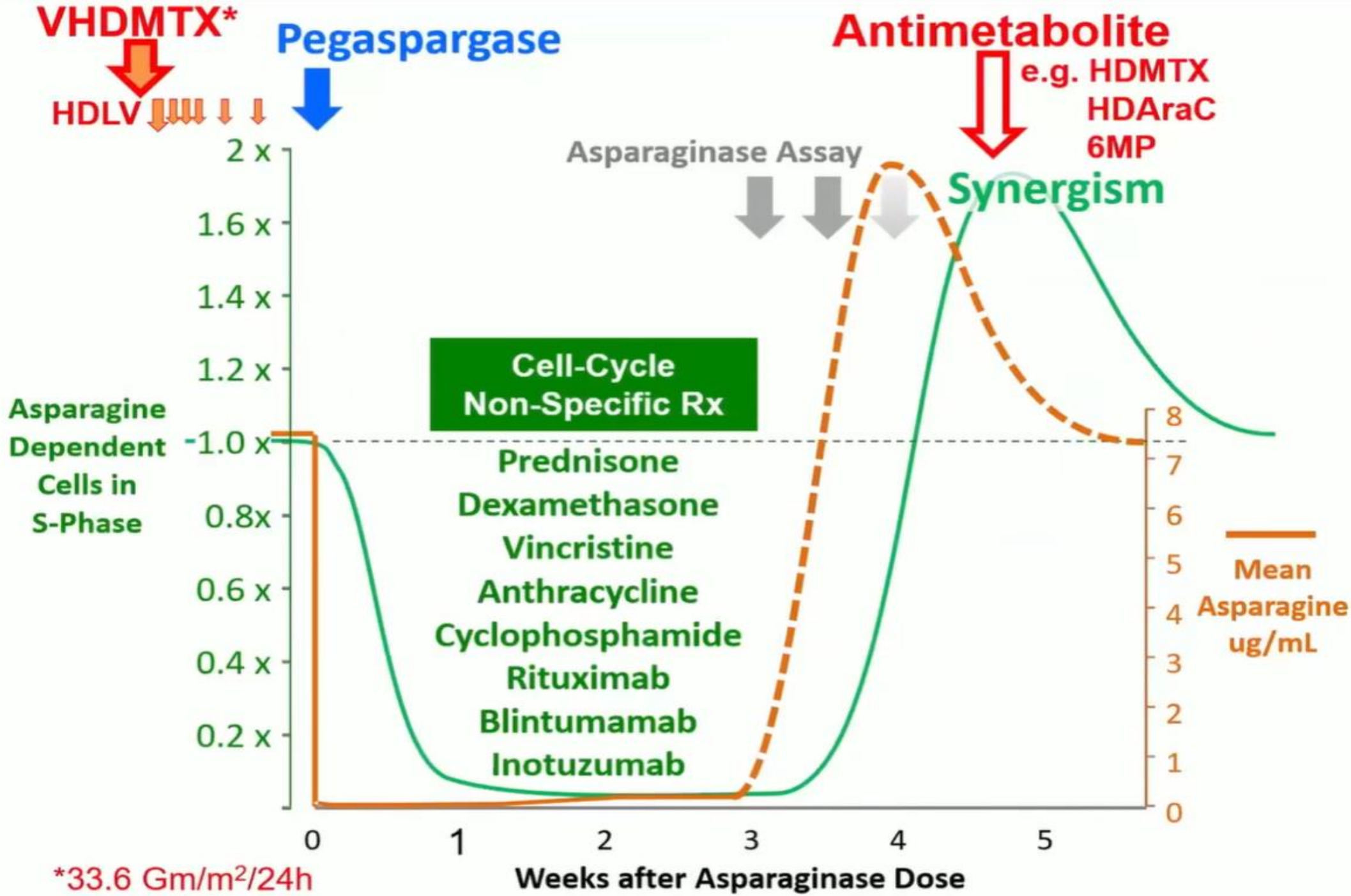
Bob Capizzi, Joe Bertino, Bob Handschumacher Yale University **1971**


Pegaspargase
2 x
1.6 x
1.4 x
1.2 x
1.0 x
0.8x
0.6 x
0.4 x
0.2 x
Asparagine Dependent Cells in S-Phase
8
7
6
5
4
3
2
1
0
Mean Asparagine µg/mL
0
1
2
3
4
5
6
7
Weeks after Asparaginase Dose


Pegaspargase
S-Phase Specific Drugs Inactive
Antagonism
Antimetabolites
MTX
AraC
6MP
6TG
5FU
5-azacitidine
Clofarabine
Nelarabine
2 x
1.6 x
1.4 x
1.2 x
1.0 x
0.8x
0.6 x
0.4 x
0.2 x
Asparagine Dependent Cells in S-Phase
8
7
6
5
4
3
2
1
0
Mean Asparagin µg/mL
0
1
2
3
4
5
6
7
Weeks after Asparaginase Dose

Současné ALL protokoly...




VHDMTX*
HDLV
Pegaspargase
Antimetabolite
e.g. HDMTX
HDAraC
6MP
Asparaginase Assay
Synergism
2 x
1.6 x
1.4 x
1.2 x
1.0 x
0.8x
0.6 x
0.4 x
0.2 x
Asparagine Dependent Cells in S-Phase
Cell-Cycle Non-Specific Rx
Prednisone
Dexamethasone
Vincristine
Anthracycline
Cyclophosphamide
Rituximab
Blintumamab
Inotuzumab
8
7
6
5
4
3
2
1
0
Mean Asparagine ug/mL
0
1
2
3
4
5
*33.6 Gm/m²/24h
Weeks after Asparaginase Dose

Nové dg pro dětské hematology??

Rare or complex disease(s) or condition(s) or highly specialized interventions	Code/ICD/ Orphacode / Group of codes	Incidence (number of case / year (in the EU)	Prevalence (in the EU)
Arteriovenous malformation			
Blue Rubber Bleb Nevus syndrome	ORPHA1059	6	500
Capillary malformation-arteriovenous malformation	ORPHA137667	120	10000
Cerebral arteriovenous malformation	ORPHA46724		
CLAPO syndrome	ORPHA168984		
CLOVES syndrome	ORPHA140944	60	5000
Cutis Marmorata Telangiectatica Congenita	ORPHA1556	12	1000
Diffuse lymphatic anomaly, Diffuse neonatal hemangiomatosis	ORPHA141209, ORPHA2123		
Facial arteriovenous malformation	ORPHA156230		
Familial cerebral cavernous malformation	ORPHA221061	600	50000
Glomuvenous malformation	ORPHA83454	30	2500
Gorham-Stout syndrome	ORPHA73	6	500
Kaposiform hemangioendothelioma	ORPHA2122		

Rare or complex disease(s) or condition(s) or highly specialized interventions	Code/ICD/ Orphacode / Group of codes	Incidence (number of case / year (in the EU)	Prevalence (in the EU)
Primary intralymphatic angioendothelioma	ORPHA458768		
Proteus syndrome	ORPHA744	6	500
PTEN hamartoma tumor syndrome	ORPHA306498	30	2500
Pulmonary arteriovenous malformation	ORPHA2038		
Rapidly involuting congenital hemangioma	ORPHA141184	60	5000
Rare arteriovenous malformation	ORPHA211266	120	10000
Rare capillary malformation	ORPHA211247	60	5000
Rare lymphatic malformation	ORPHA2415	600	50000
Rare venous malformation	ORPHA211252	1200	100000
Spindle cell hemangioma	ORPHA210584		
Sturge-Weber syndrome	ORPHA3205	120	10000

Rare or complex disease(s) or condition(s) or highly specialized interventions	Code/ICD/ Orphacode / Group of codes	Incidence (number of case / year (in the EU)	Prevalence (in the EU)
Klippel-Trénaunay-Weber syndrome	ORPHA2346	60	5000
LUMBAR association	ORPHA83628		
Macrocystic lymphatic malformation	ORPHA79489		
Maffucci syndrome	ORPHA163634	6	500
Megalencephaly-capillary malformation-polymicrogyria syndrome	ORPHA60040	12	1000
Microcystic lymphatic malformation	ORPHA79490		
Mixed cystic lymphatic malformation	ORPHA458792		
Mucocutaneous venous malformation	ORPHA2451		
Non-involuting congenital hemangioma	ORPHA141179	20	500
Parkes-Weber syndrome	ORPHA90307	30	2500
Partially-involuting congenital hemangioma	ORPHA458785		
PHACE syndrome	ORPHA42775		
Primary intralymphatic angioendothelioma	ORPHA458768		

Rare or complex disease(s) or condition(s) or highly specialized interventions	Code/ICD/ Orphacode / Group of codes	Incidence (number of case / year (in the EU)	Prevalence (in the EU)
PTEN hamartoma tumor syndrome	ORPHA306498	30	2500
Pulmonary arteriovenous malformation	ORPHA2038		
Rapidly involuting congenital hemangioma	ORPHA141184	60	5000
Rare arteriovenous malformation	ORPHA211266	120	10000
Rare capillary malformation	ORPHA211247	60	5000
Rare lymphatic malformation	ORPHA2415	600	50000
Rare venous malformation	ORPHA211252	1200	100000
SACRAL association	ORPHA2125		
Spindle cell hemangioma	ORPHA210584		
Sturge-Weber syndrome	ORPHA3205	120	10000
Tufted angioma	ORPHA1063	3	250
Venous malformation	ORPHA211252		
Verrucous hemangioma	ORPHA464318		

VASCULAR ANOMALIES, VASCULAR MALFORMATIONS, AND THE ROLE OF THE HEMATOLOGIST | DECEMBER 6, 2024

Targeted medical therapies for vascular anomalies

Alexandra Borst

Hematology Am Soc Hematol Educ Program (2024) 2024 (1): 709–717.

https://doi.org/10.1182/hematology.2024000599

Abstract

The last 2 decades of genetic discovery in the field of vascular anomalies have brought targeted medical therapies to the forefront of care patients with vascular anomalies and have broadened the role of hematologists/oncologists in this field. Many vascular anomalies have now been identified to be driven by somatic gain-of-function variants in the PI3K/AKT/ mTOR and Ras/MAPK intracellular signaling pathways. This has led to the introduction of various antiangiogenic agents that inhibit these pathways. Knowledge of the indications for and the safe administration of these agents in patients with vascular anomalies is now a crucial part of training for hematologists/oncologists.

References

1. Adams DM, Ricci KW. Vascular anomalies: diagnosis of complicated anomalies and new medical treatment options. *Hematol Oncol Clin North Am*. 2019;33(3):455-470.

Google Scholar Crossref PubMed

2. Queisser A, Seront E, Boon LM, Vikkula M. Genetic basis and therapies for vascular anomalies. *Circ Res*. 2021;129(1):155-173.

Google Scholar Crossref PubMed

27. Sterba M, Pokorna P, Faberova R, et al. Targeted treatment of severe vascular malformations harboring PIK3CA and TEK mutations with alpelisib is highly effective with limited toxicity. *Sci Rep*. 2023;13(1):10499.

Google Scholar Crossref PubMed

Volume 2024, Issue 1

December 6 2024

Previous Article Next Article

Potential Articles of Interest

Molecularly targeted therapies for acute myeloid leukemia
Eytan M. Stein, Hematology ASH Education Program, 2015

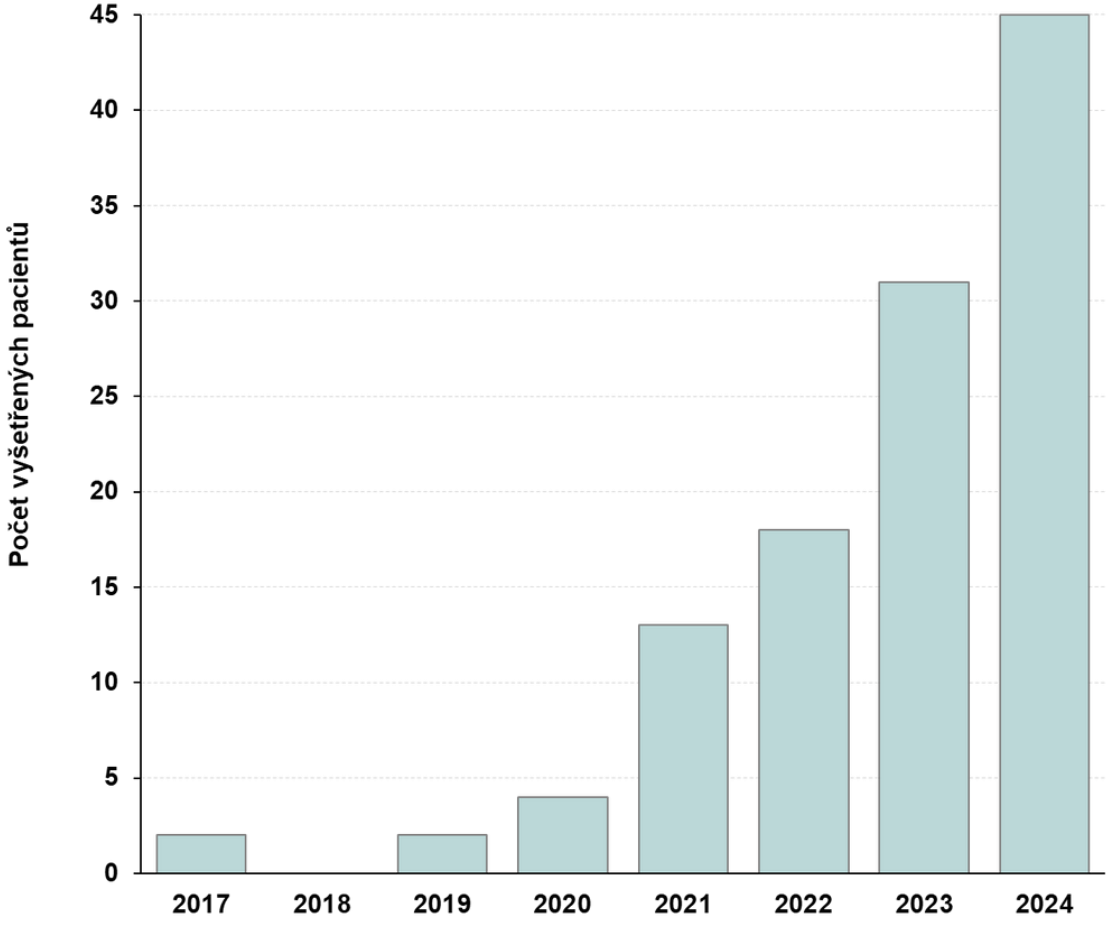
AL amyloidosis: from molecular mechanisms to targeted therapies
Giampaolo Merlini, Hematology ASH Education Program, 2017

Novel cellular therapies for leukemia: CAR-modified T cells targeted to the CD19 antigen
Renier J. Brentjens, Hematology ASH Education Program, 2012

Unproven Therapies
American Diabetes Association, Diabetes Care, 1998

Unproven Therapies
American Diabetes Association, Diabetes Care, 2003

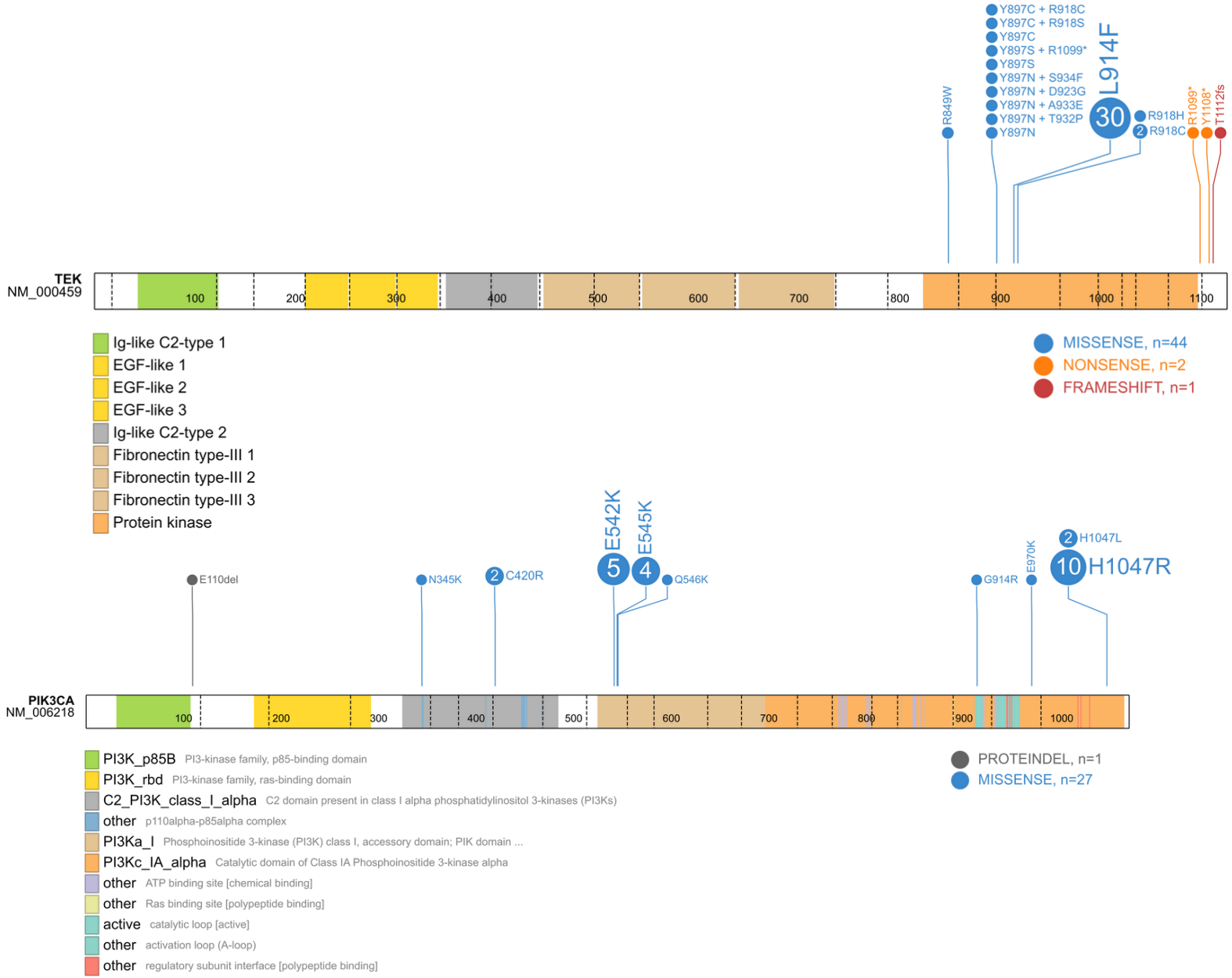
Unproven Therapies
American Diabetes Association, Diabetes Care, 1996



Vascular anomalies in UH Brno

- initially diagnosed through a comprehensive genomic profiling program for high-risk solid tumors
- customized targeted DNA sequencing panel with causal genes implemented since 2022
- tissue diagnostics performed for 123 patients with a 73% rate of positive causative findings
- 57 % of patients fall within the venous malformation category

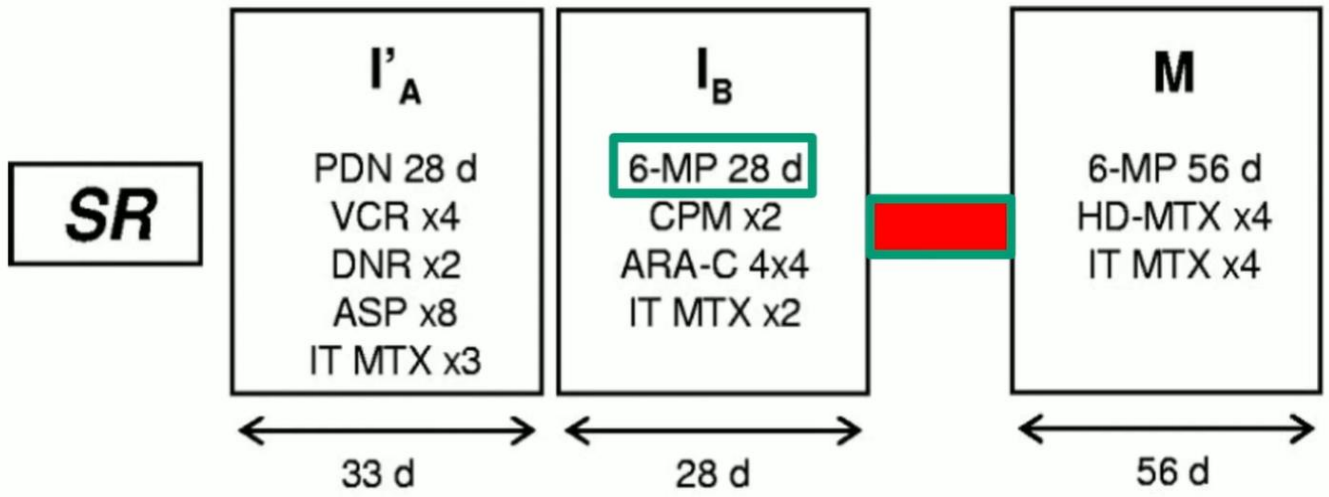
RTK	
TEK	47
PI3K/Akt/mTOR	
PIK3CA	28
PTEN	3
Ras/MAPK	
MAP3K3	3
KRAS	1
MAP2K1	1
RASA1	1
Others	
GNA11	1
GNAQ	1
IDH2	1



- Jiná témata?

HDMTX efficacy

Synergism – ALL BFM95



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