DRUG-INDUCED LIVER INJURY

How the clinical signature impacts benefits & risks

June 6, 2017

Mark Avigan, MD CM
Associate Director for Critical Path Initiatives
Office of Pharmacovigilance & Epidemiology
CDER, FDA

The views being presented are my own and not an official position of the FDA

Overview of Presentation

- DILI risk assessment in benefits & risk analysis
  - Key elements
  - Temporal variables
- Acute DILI vs benefits: timeline graph profiles
- Examples of distinct agent-specific DILI forms
  - immunoallergic, ‘classic’ & autoimmune
- RUCAM criteria in the face of different DILI clinical & temporal signatures

Benefits vs Risks
A simplified framework

Treatment Indicated for Life-threatening / debilitating disease

Treatment Indicated for Minor symptomatic non-debilitating condition

High clinical response rates with improved long-term survival

Low clinical response rates with no improvement of long-term survival

Rapid & sustained clinical response

Delayed or transient clinical response

Unremarkable SAE risk profile

Substantial SAE risk profile; Difficult to mitigate risk

Lack of equivalent alternative treatments

Safe & effective alternative treatments

Assessment of DILI Risk

Key Components

- Risk Components
  - Population frequency
  - Drug-associated Causality
  - Clinical Severity
  - Clinical Signature Temporal Features

- Risk factors
  - Genomic
  - DDIs

Levels of DILI Severity

5	Death/Tx
4	Acute Liver Failure
3	Serious: Disabled, Hospitalized
2	Hy's Case: Detectable Slight Functional Loss
1	Serum Enzyme Elevations Only; Many People Adapt
0	Most People Tolerate Exposure - No Adverse Effects Seen

Categories of DILI Likelihood

5 definite, almost certain (estimated range >95%)

4 very likely (estimated range >75 to 95%)

3 probable (estimated range >50 to 75%)

2 possible (estimated range >25 to 50%)

1 unlikely (estimated range 5 to 25%)

0 very unlikely (estimated range <5%)

percentage ranges do not imply exactness, but may be helpful as adjectives to get more consistency between evaluators

FDA categories consistent with NIH DILIN scale, but inverted)

Assessment of DILI Risk

Temporal Features

Offset of Benefits vs DILI Risk

Temporal features of treatment to consider

Biopharmacological Lens

Duration of treatment / Cumulative Exposure

- Response times of biosystem therapeutic targets

Offset

- Profiles of liver cell cytoprotective & regenerative responses
- Profiles of drug & metabolite levels in liver cells
- Profiles of drug-induced adaptive & innate immune activities
- Profiles of drug-related autoimmunity

Offset of Benefits vs DILI Risk

Temporal features of treatment to consider

Clinical Lens

Duration of treatment / Cumulative Exposure

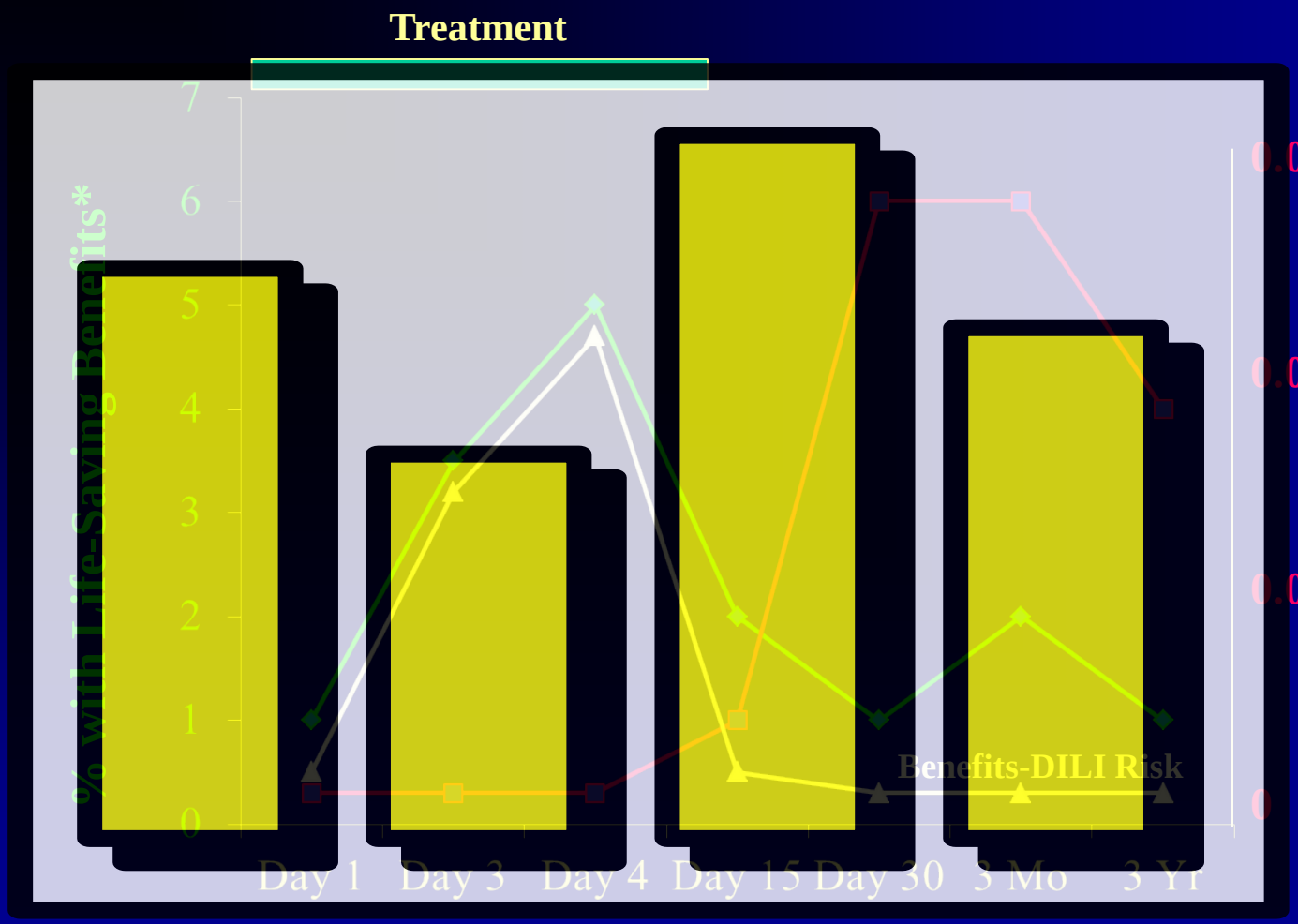
- Time to attain benefit
- Permanence vs transience of benefit

Offset

- Time to onset of increasing DILI risk
- Permanence vs transience of DILI risk
- Acute vs chronic forms of DILI risk

Drug A: Benefits vs DILI Risk

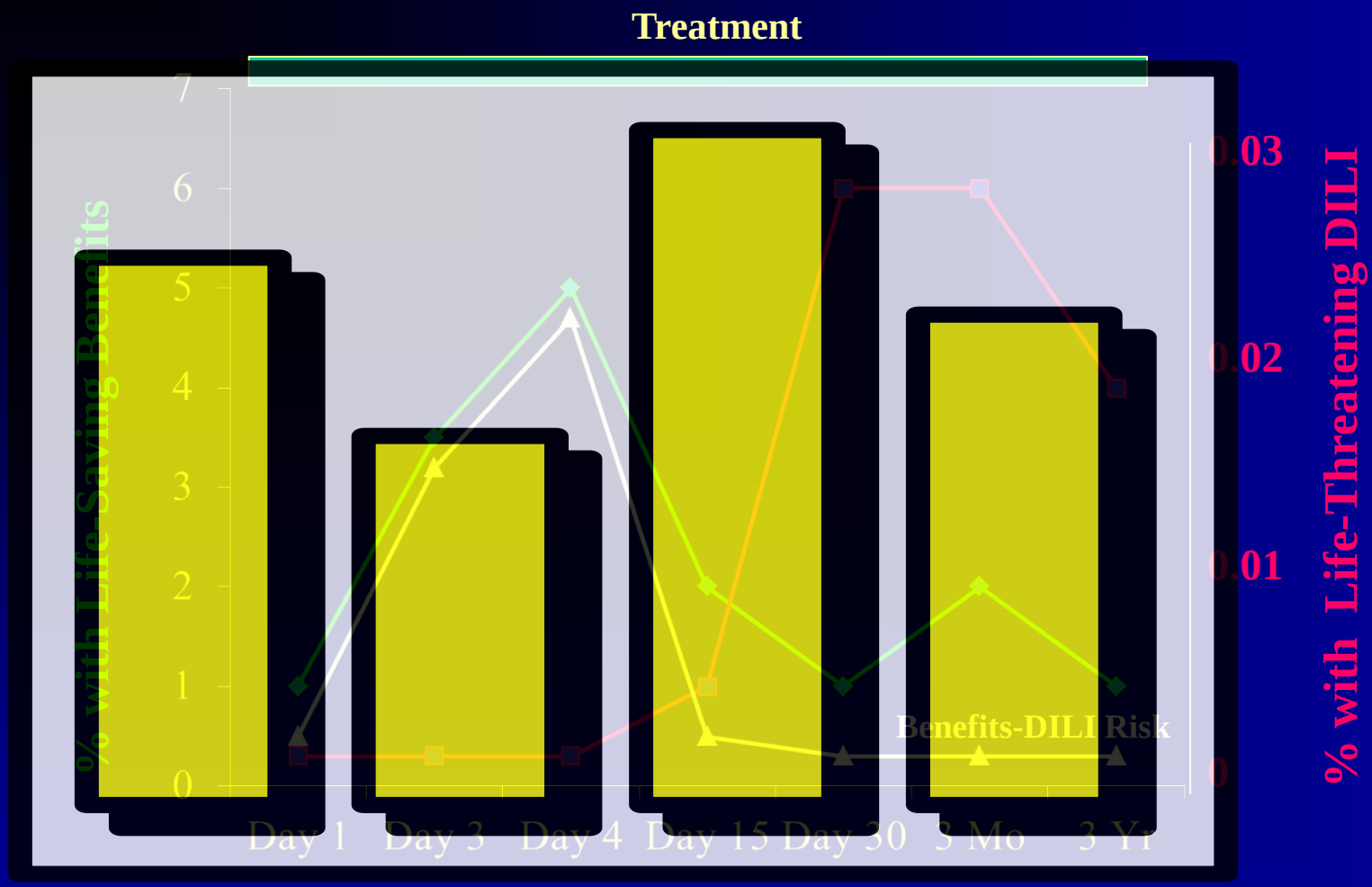
Time-line profile in treatment population



**Scales are for hypothetical discussion & have no regulatory inference

Drug A: Benefits vs DILI Risk

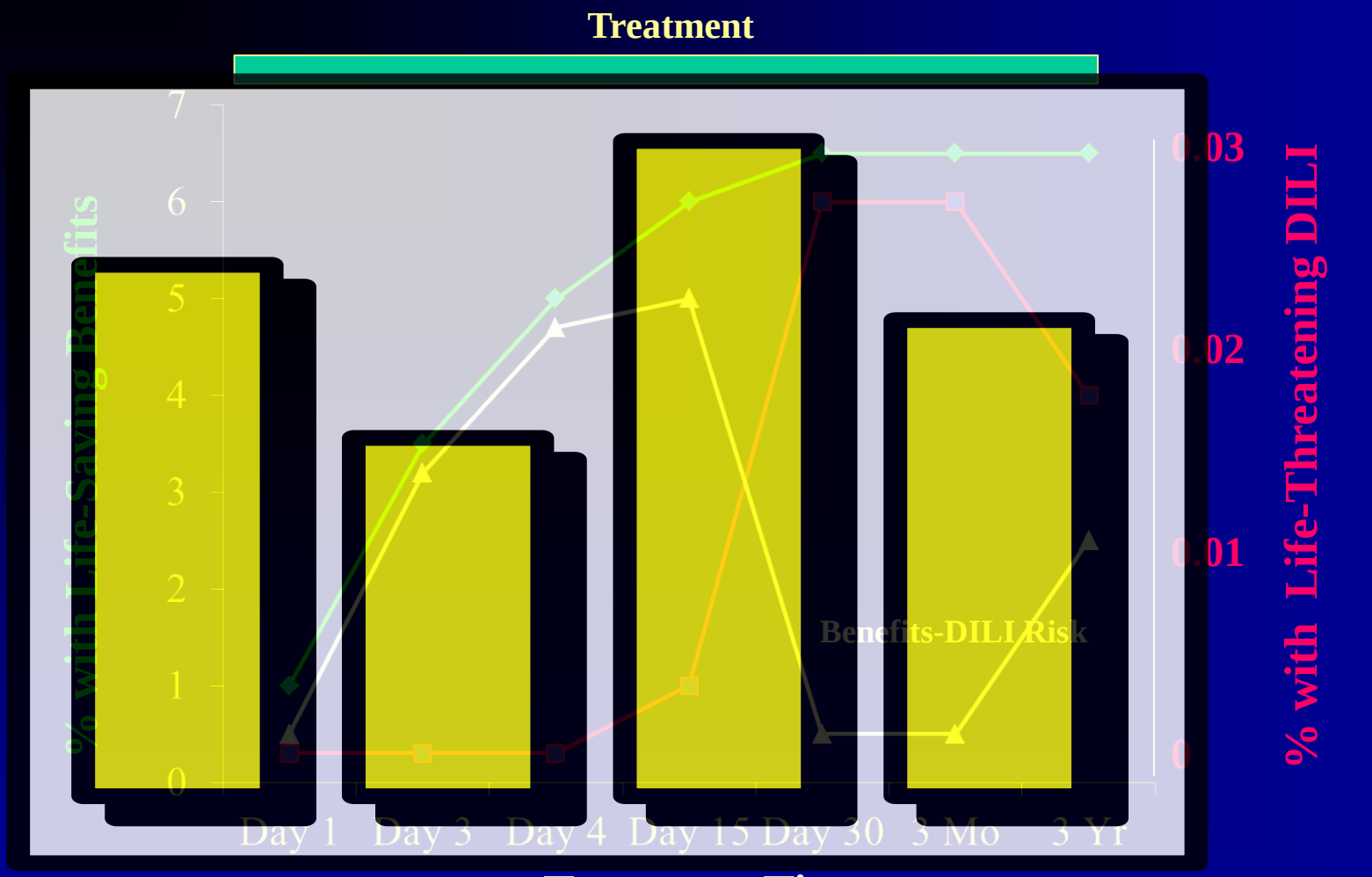
Time-line profile in treatment population



**Scales are for hypothetical discussion & have no regulatory inference

Drug B: Benefits vs DILI Risk

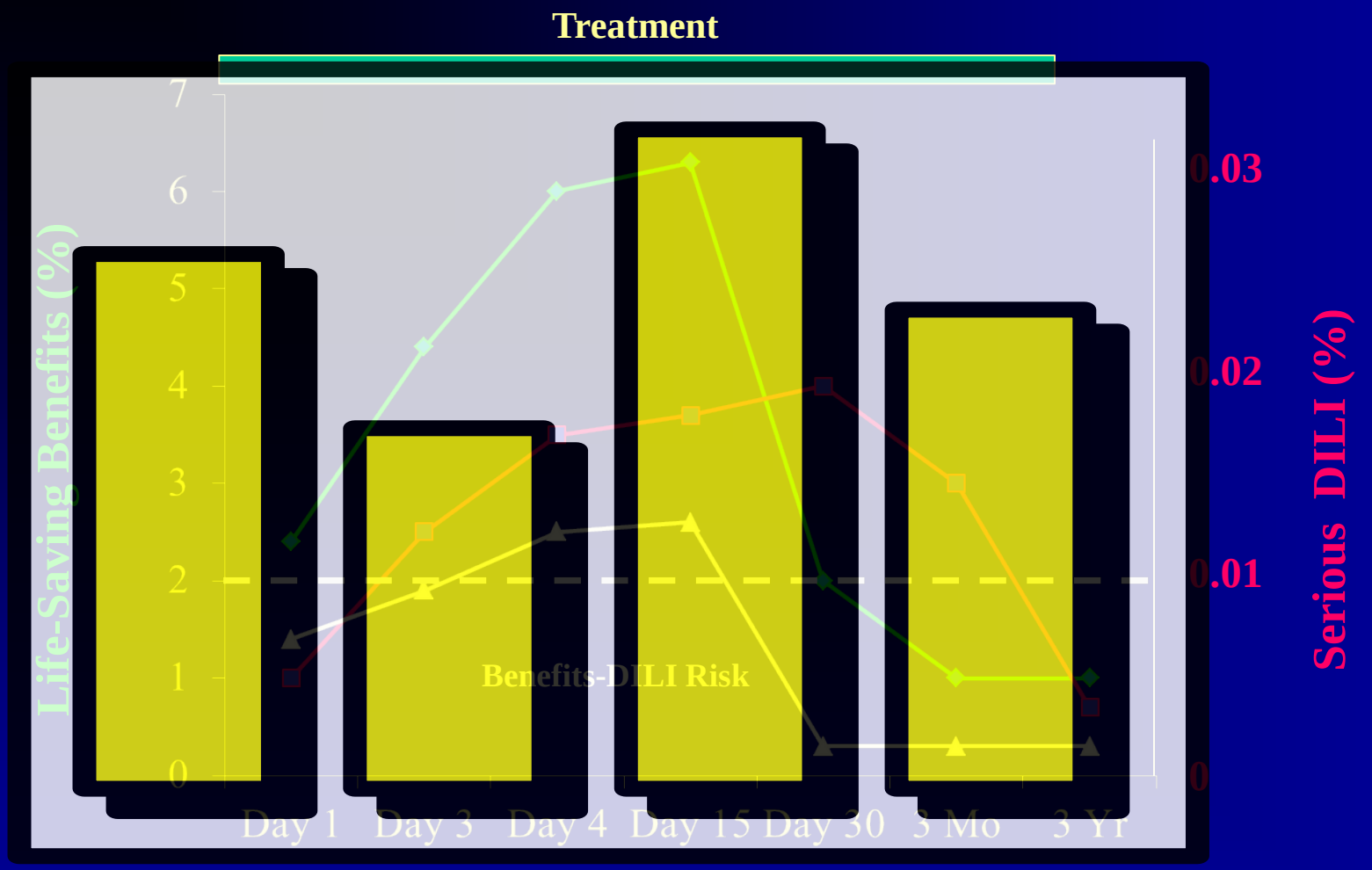
Time-line profile in treatment population



**Scales are for hypothetical discussion & have no regulatory inference

Drug C: Benefits vs DILI Risk

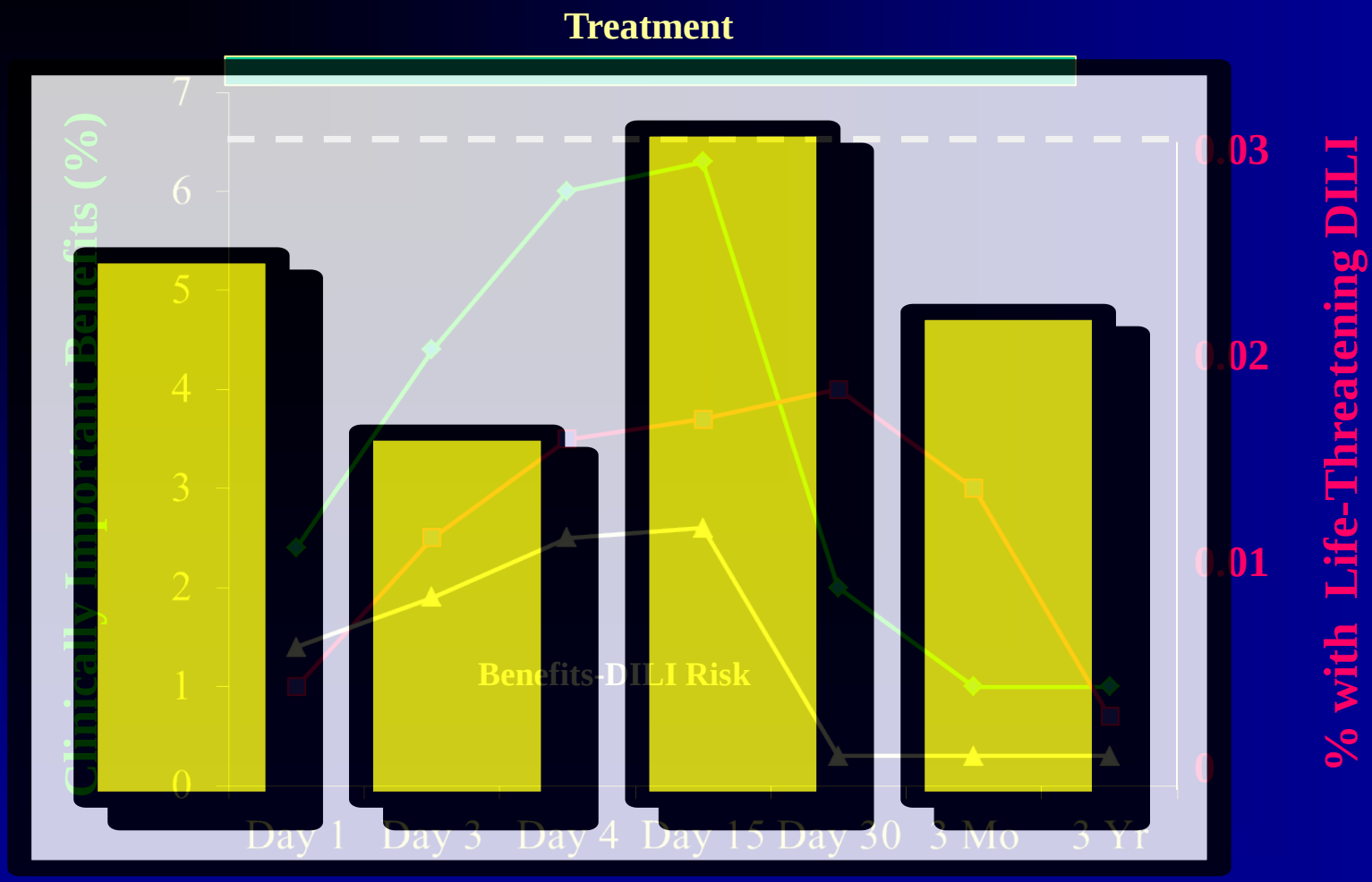
Time-line profile in treatment population



**Scales are for hypothetical discussion & have no regulatory inference

Drug D: Benefits vs DILI Risk

Timeline profile in treatment population



**Scales are for hypothetical discussion & have no regulatory inference

Diverse DILI Phenotypes/Clinical Patterns*

- Acute hepatic necrosis
- Acute viral-like hepatitis
- Immunoallergic hepatitis
- Drug-associated autoimmune hepatitis
- ALF
- Cholestatic hepatitis
- Bland cholestasis
- Persistent Hepatitis
- Acute fatty liver & lactic acidosis
- NASH
- Sinusoidal obstruction syndrome
- Chronic hepatitis
- Vanishing bile duct syndrome
- Nodular regeneration
- Cirrhosis

***DILIN; [Fontana et al.; Hepatology, 52, 2010]**

Selected Idiosyncratic DILI Signatures

Temporal risk profiles

- Immunoallergic hepatitis
- Acute viral-like hepatitis (‘Classic’ type)
- Drug-associated autoimmune hepatitis phenotypes

Drugs Associated with Immunoallergic DILI

Examples

- Antibiotics
  - sulfa drugs
  - quinolones
  - ketolides
- Aromatic anticonvulsants
- Allopurinol
- Celecoxib
- Nevarapine
- Efavirenz

Immunoallergic Clinical Signature
Telithromycin-associated DILI

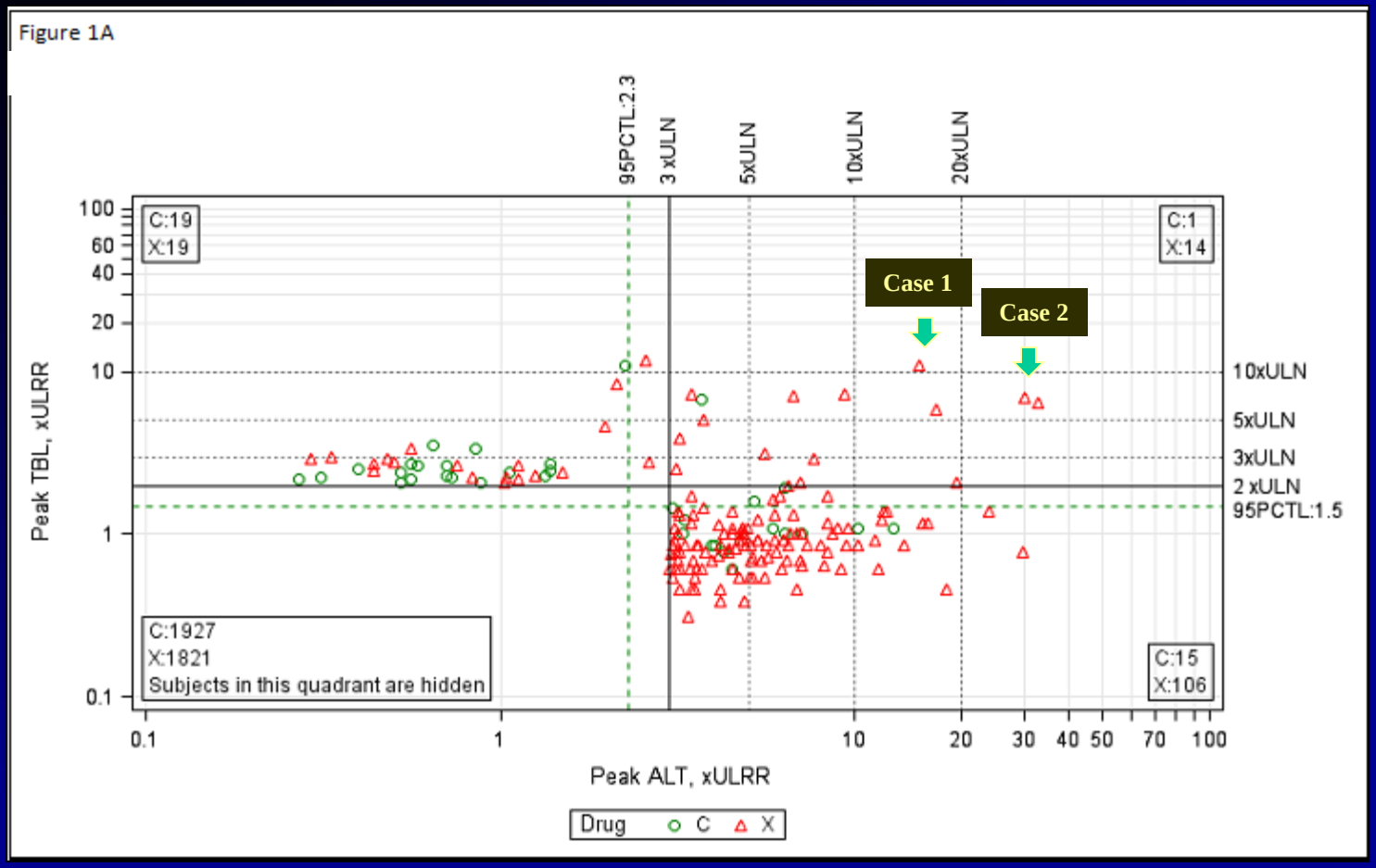
- First oral ketolide approved for treatment of CABP, AECB & bacterial sinusitis
- Hepatotoxic profile characterized in a comprehensive review of P-M published and spontaneously reported cases
  - 42 cases evaluated by FDA expert panel
    - Serious outcomes: 32/42 hospitalized; 4/42 died; 1/42 liver x-plant
    - 25/42 developed hepatocellular jaundice
    - 26/42 assessed as 'probable' or 'highly likely'
    - 4/42 had previous telithromycin exposure
    - Clinical signature marked by very short time to onset (**median 10 days, range 2-43 days**), rapid onset of fever (29%), abdominal pain (45%) and jaundice. Some cases reported eosinophilia (19%) and/or ascites (17%)
      - Immunoallergic features suggest new or previous hypersensitivity to telithromycin or a metabolite, or cross-sensitization with a structurally-related macrolide

‘Classic’ Idiosyncratic Clinical Signature
Ximelagatran-associated DILI

- Prodrug of melagatran (a direct thrombin inhibitor)
- Not approved in US & withdrawn elsewhere because of hepatotoxicity
- Long-term exposure (LTE) protocols for 2ndary prevention of VTE & thromboembolism associated with non-valvular Afib
- Cases of *advanced* liver injury marked by concurrent increases of serum ALT >3x ULN & total bilirubin >2x ULN
- 0.5% ximelagatran LTE groups (n=37/6.948) developed *advanced* liver injury with 1 related death vs 0.08% (n=5/6,230) in comparator groups
- ALT > 3x ULN: 7.6% ximelagatran LTE subjects (n=531/6,948) vs 1.1% warfarin LTE subjects
- High rates of adaptation with continued treatment
- ALT > 3x ULN: Time to onset typically ranged between 2 weeks and 6 months of treatment (93% of cases); **Highest incidence 2-3 months; 30% of cases occurred after 3 months; 7% after 6 months; 2% after 12 months**

SPORTIF V eDISH Plot: Peak Liver Tests*

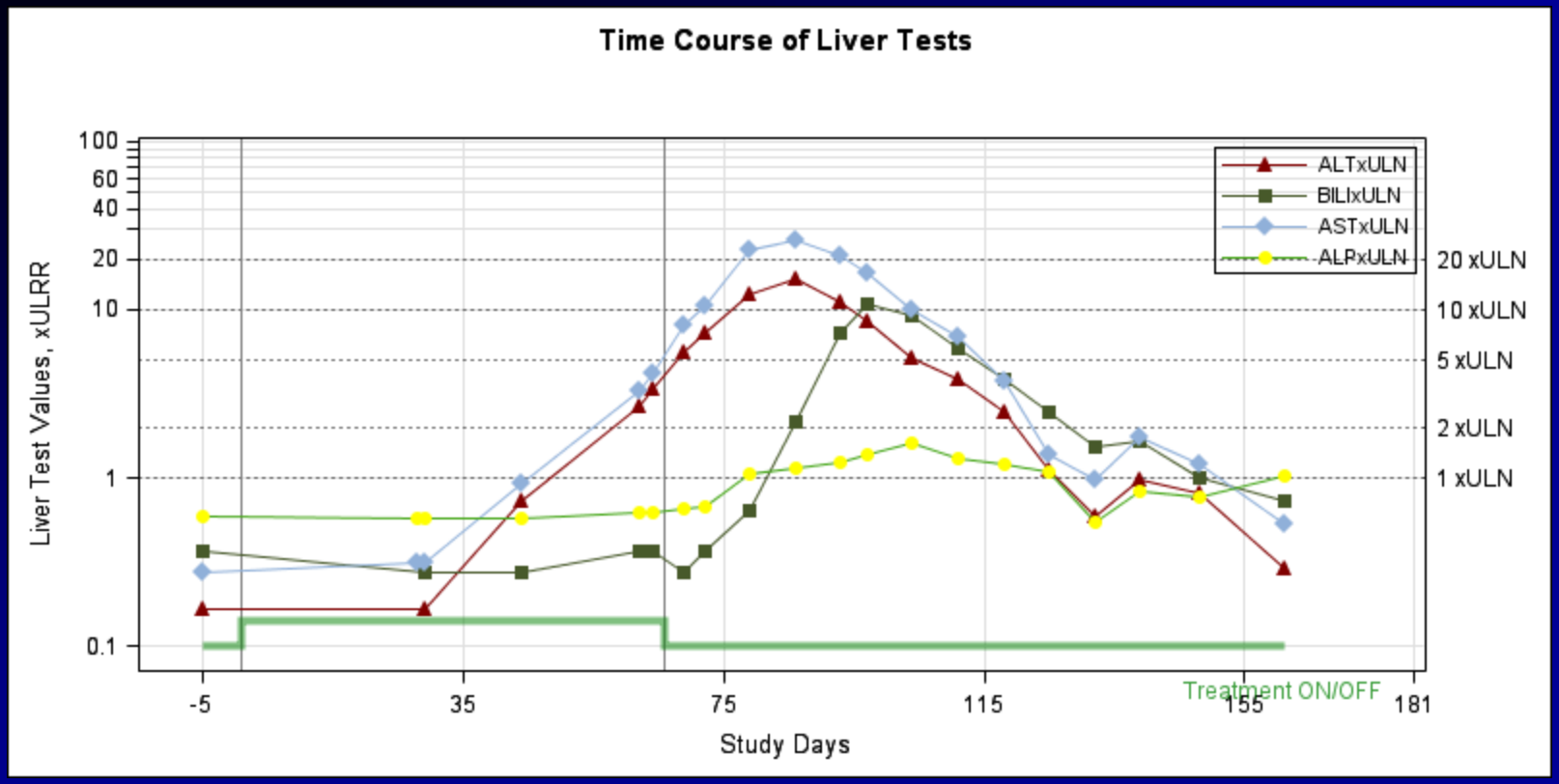
Ximelagatran (X) vs Warfarin (C)



Adapted from M Desai (2004) Review:** ***https://www.fda.gov/ohrms/.../2004-4069B1_06_FDA-Backgrounder-C-R-MOR.pdf

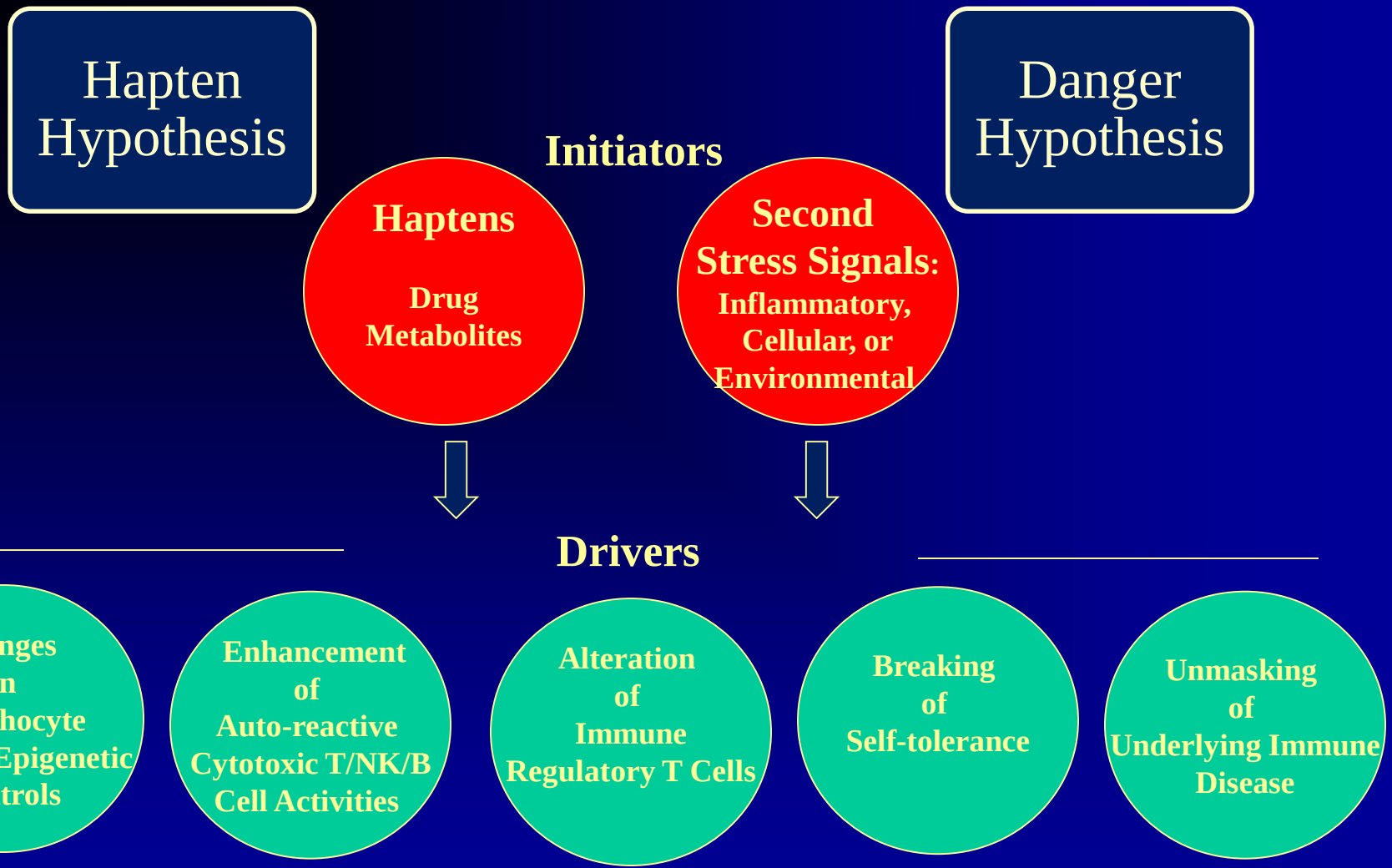
‘Classic’ Idiosyncratic DILI

Ximelagatran-associated DILI (SPORTIF V); Case 1



Adapted from M Desai (2004) Review:** ***https://www.fda.gov/ohrms/.../2004-4069B1_06_FDA-Backgrounder-C-R-MOR.pdf

Drug-induced Autoimmune Injury



Drug-induced AIH & IMH Signatures

- Acute & Chronic DIAIH with serum autoantibodies (+ ANA, + SMA, etc.)
  - e.g. nitrofurantoin, minocycline, methyldopa, hydralazine
- Cytokine agonists / inhibitors
  - e.g. infliximab, β-interferon
- Checkpoint inhibitors
  - e.g. Ipilimumab, nivolumab, pembrolizumab, atezolizumab
- Anti-T cell therapies
  - e.g. Daclizumab HYP

Inducing Autoimmunity – *Challenge*

Use of checkpoint inhibitors for oncotherapy

- Monoclonal inhibitors of CTLA-4, PD-1 or PD-1 receptors: Currently approved products include ipilimumab, nivolumab, pembrolizumab & atezolizumab
- Linked to high risk for autoimmune organ injuries mediated by 'souped-up' auto-reactive T & NK cells
- Characteristic auto-Abs not typically detected
- Autoimmune injuries: colitis > SCAR, hepatitis/ALF, endocrine organs, nephritis & other organs with comparatively short latencies after treatment initiation
- Risk levels for life-threatening AEs including severe immune-mediated hepatitis (IMH) is sufficiently high for valuable assessment in clinical efficacy trials

Immune-mediated Hepatitis (IMH)
Checkpoint inhibitor-associated DILI

- IMH identified in clinical trials as serious complication
- Can progress to acute liver failure and death
- Clinical onset after initiation of treatment often within a few cycles (**1-3 months**) but ranges widely; Can recur with renewed treatment
- Liver Bx shows panlobular lymphocytic infiltrates & necrosis
- Product labels of checkpoint inhibitors contain warnings of IMH with liver monitoring instructions & risk management actions, including immediate treatment discontinuation procedures & treatment with corticosteroids or other immunosuppressive agents
- IMH susceptibility factors remain undefined
  - Pro-inflammatory localized interactions between metastatic tumor cell antigens & activated T-cells?
  - Unmasking of subclinical idiopathic autoimmune diathesis?

Checkpoint Inhibitors

Post-market: Life-threatening autoimmune AEs

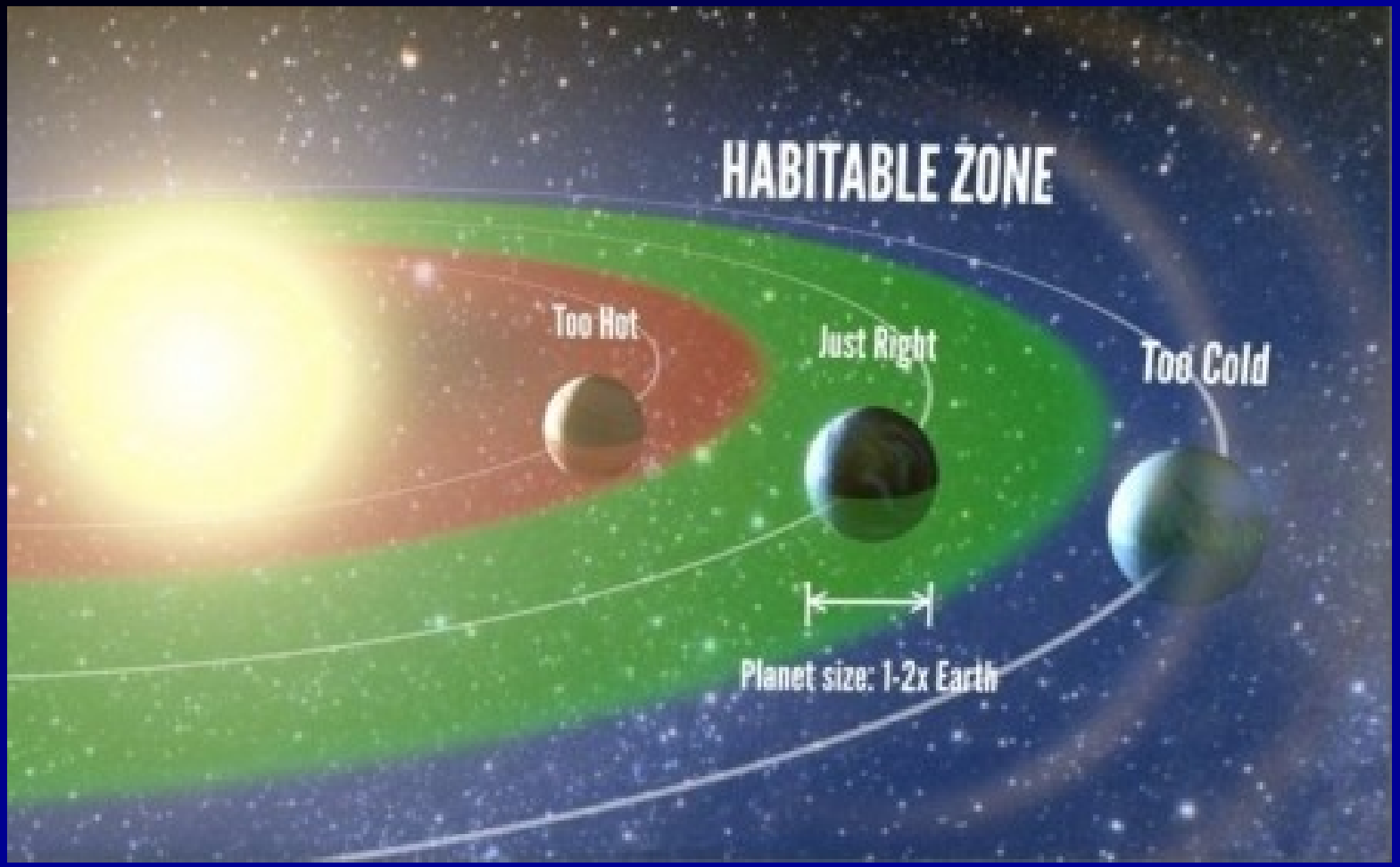
- In first 3 yrs of ipilimumab marketing – Serious AE reports submitted to FAERS (crude nos):
  - Colitis ~ 380 reports
    - Some reports of intestinal perforation
  - Autoimmune hepatitis &/or Hepatic Failure ~ 50 reports
    - Liver metastases (melanoma) often present
    - Onset after a small no of q3wk infusions
    - Some reports of fatal outcomes with rapidly deteriorating liver function

Checkpoint Inhibitors
Post-market IMH Cases of Interest: Example
60 yr old Male

- Melanoma metastases, brain & liver (2 lesions < 3cm, abd CT scan)
- Given 2 doses of *ipilimumab* (3mg/kg), 3 wks apart
- 3 wks after 2nd dose: Pt admitted with new onset weakness, diarrhea, tea colored urine & hepatic encephalopathy
  - ALT: 1704, AST: 3371, ALP: 886 (baseline: 84), T. Bili: 5.1, LDH, >2500, US: heterogeneous liver, IgG: 699, IgM: 72, ANA: 27 U (not elevated), Viral serology: unremarkable
  - Began po 80 mg Prednisone & Lactulose
- 2 d later: IV methylprednisolone 100 mg bid, N-AC & Rifaxamin; Serum liver tests worsened
- Pt died in liver failure 5 days after admission

Personalizing Use of Checkpoint Inhibitors

Aiming for an Autoimmune 'Goldilocks Zone'



Daclizumab HYP (DAC HYP)
MS Clinical Trial AIH Cases

- IgG1 monoclonal Il-2 receptor inhibitor of CD-25+ effector T-cells including those targeting the myelin sheath
- Also inhibitor of Fox-3+ CD-25+ regulatory T-cells (T regs) with unintended paradoxical auto-immune side-effects
  - After cessation of DAC HYP, the recovery of T-regs is gradual (5-6 mo) & can extend beyond the recovery time of autoreactive T-cells. This may explain the long time to onset of certain autoimmune AEs

- FDA Approved for Relapsing MS in pts with inadequate responses to 2 other agents
- Label contains boxed warning for liver failure, AIH & other autoimmune disorders

Drugs@FDA: Zinbryta; Other Reviews p. 164-186

Autoimmune Clinical Signature
DAC HYP-associated DILI

- Among 2,003 DAC-treated study subjects in safety population
  - one case of FHF (causally-related*)
  - 11 cases of liver injury causally-related* to DAC HYP marked by peak ALT increases ≥ 10X ULN and/or > 3X ULN with T Bili ≥ 2X ULN
    - Median time to onset after start of DAC HYP – **13 mo**
    - 6/11 cases identified as DAC HYP-related AIH
      - Long time to onset of AIH ~ **15 mo** (range 4 – 49 mo)
      - Negative ANA in 5/7 AIH cases)
      - Gradual recovery times, steroid responsive
  - In SELECT, a randomized phase IIB study, 4% Daclizumab HYP randomized subjects had peak ALT elevations > 5X ULN, compared with < 1% in the placebo arm

*Causality with DAC-HYP assessed by FDA review as ‘probable’

Assessment of DILI Risk

RUCAM: Key Algorithmic Components

- Risk Components
  - DILI association previously identified
  - Drug-associated causality (differential dx)
  - Clinical severity
  - Temporal features

- Risk factors
  - Only a few (e.g. age, alcohol, pregnancy)

CIOMS Diagnostic Scale *(RUCAM)**

Individual Criteria	*Range of Scores*
Time from start of Rx until event	+1 to +2
Time from stop of Rx until event	0 to +1
Course after stop of Rx	-2 to +3
Age	0 to +1
Alcohol/Pregnancy	0 to +1
Concomitant Rx	-3 to 0
Non drug-related causes	-3 to +2
Previous drug information	0 to +2
Dechallenge/Rechallenge	-2 to +3

Causality Assessment: Total Scores

Highly Probable: 8-10; Probable: 6-8; Possible: 3-5; Unlikely: 1-2

*Danan & Benichou, J. Clin. Epidemiol.; 1993

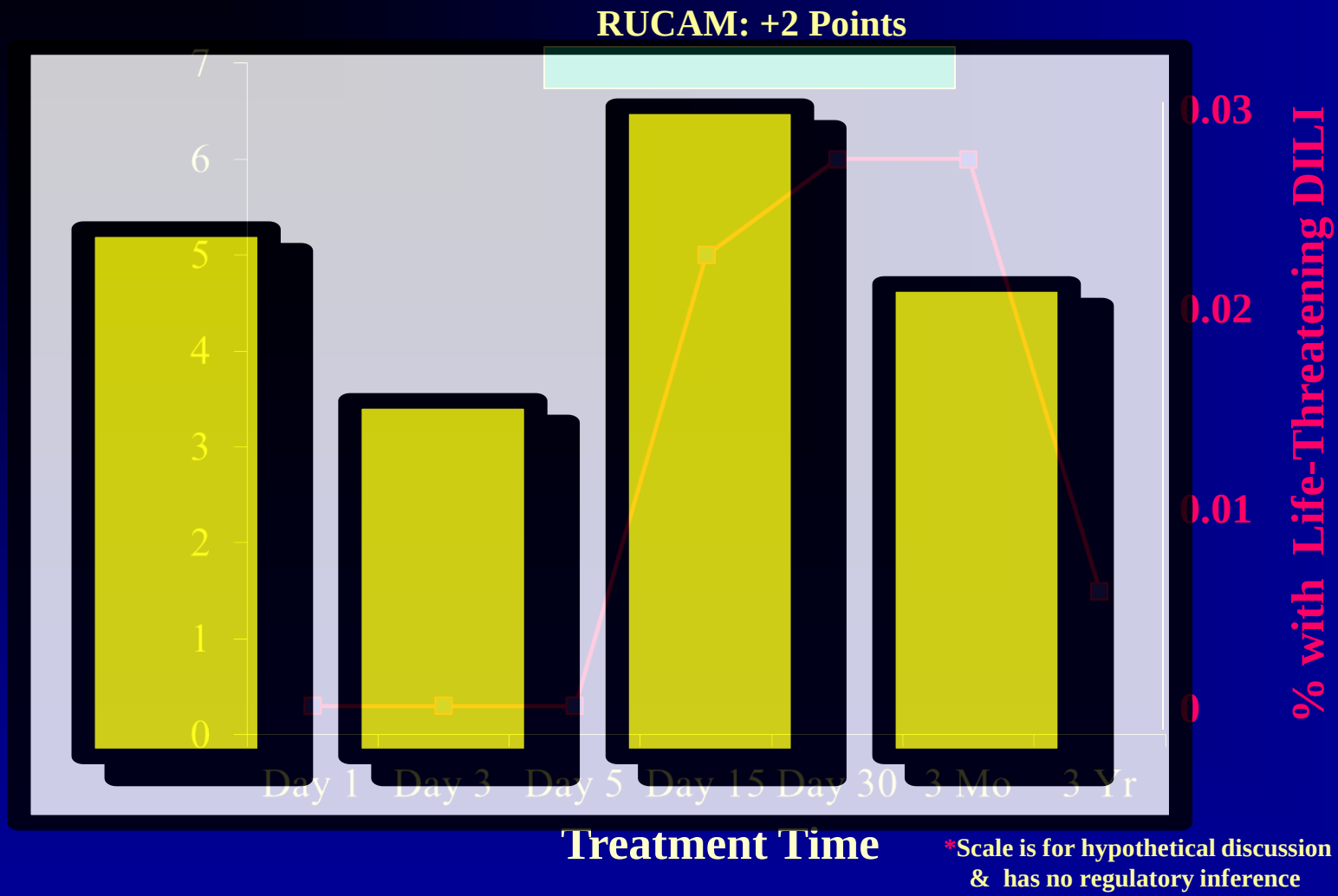
CIOMS Diagnostic Scale *(RUCAM)*

Time Course Elements

TYPE OF LIVER INJURY	*HEPATOCELLULAR*		*CHOLESTATIC/MIXED*		POINTS
TIME OF ONSET OF THE EVENT	FIRST EXPOSURE	SECOND EXPOSURE	FIRST EXPOSURE	SECOND EXPOSURE	—
TIME FROM DRUG INTAKE UNTIL REACTION ONSET	5 TO 90 DAYS	1 TO 15 DAYS	5 TO 90 DAYS	1 TO 90 DAYS	+2
	<5 OR >90 DAYS	>15 DAYS	<5 OR >90 DAYS	>90 DAYS	+1
TIME FROM DRUG WITHDRAWAL UNTIL REACTION ONSET	≤15 DAYS	≤15 DAYS	≤30 DAYS	≤30 DAYS	+1
RISK FACTORS	ALCOHOL		ALCOHOL OR PREGNANCY		+1
	AGE ≥ 55 YEARS		AGE ≥ 55 YEARS		+1
	>50% IMPROVEMENT 8 DAYS		—		+3
	>50% IMPROVEMENT 30 DAYS		>50% IMPROVEMENT 180 DAYS		+2
COURSE OF THE REACTION	—		<50% IMPROVEMENT 180 DAYS		+1
	LACK OF INFORMATION OR NO IMPROVEMENT		LACK OF INFORMATION OR NO IMPROVEMENT		+0
	WORSENING OR <50% IMPROVEMENT 30 DAYS		—		-1

Drug X: Benefits vs DILI Risk

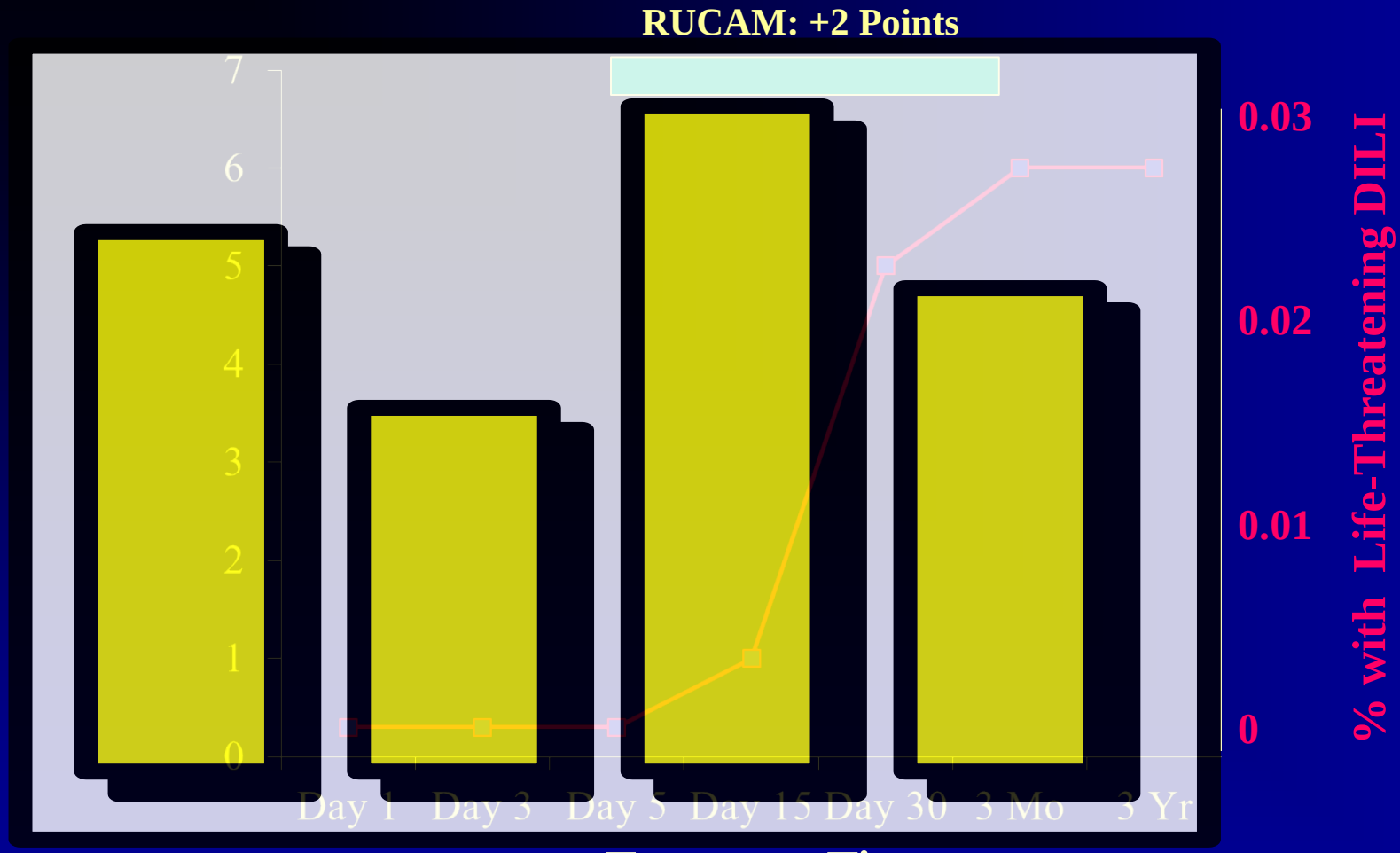
RUCAM vs time to DILI onset



*Scale is for hypothetical discussion & has no regulatory inference

Drug Y: Benefits vs DILI Risk

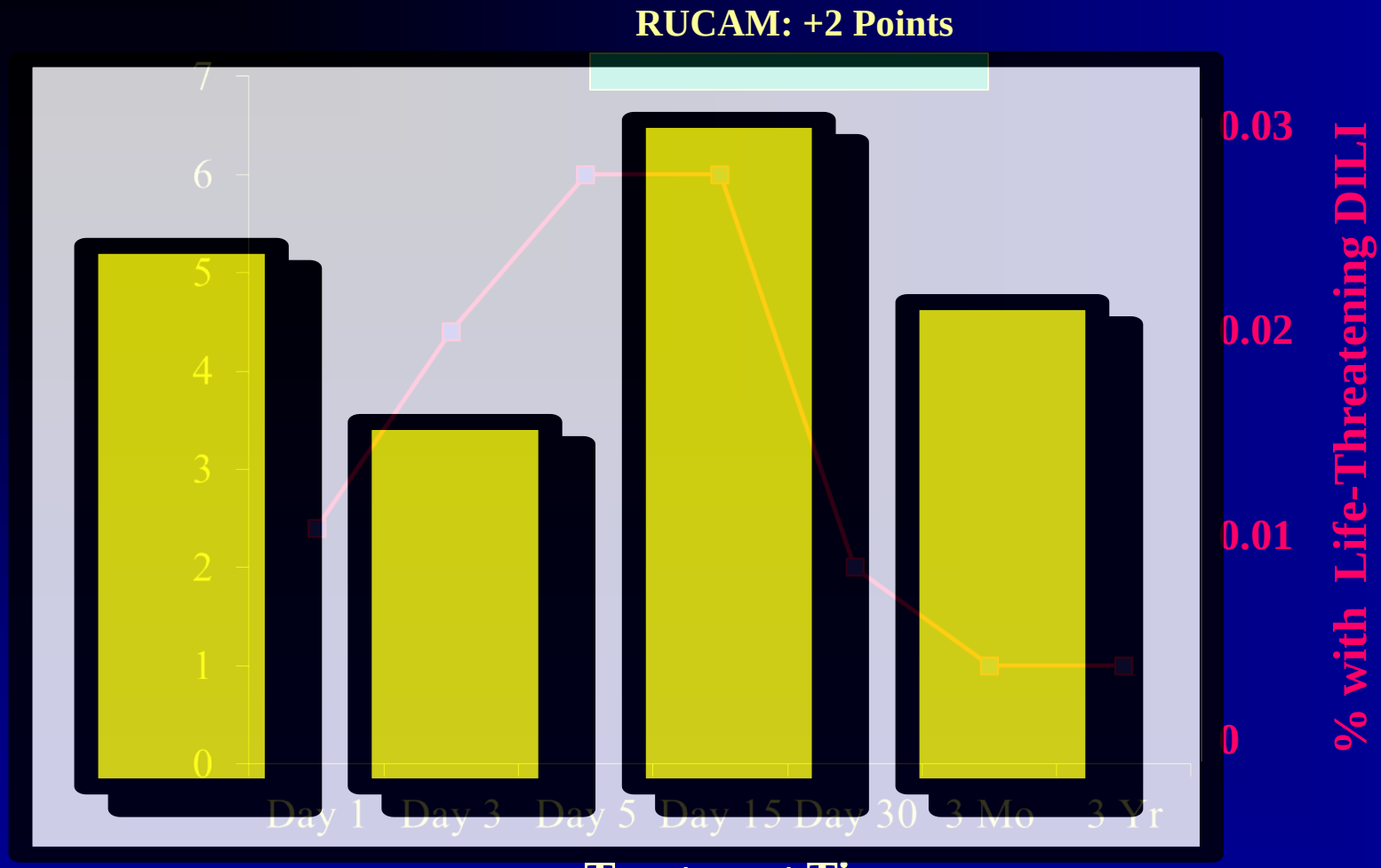
RUCAM vs time to DILI onset



*Scale is for hypothetical discussion & has no regulatory inference

Drug Z: Benefits vs DILI Risk

RUCAM vs time to DILI onset



*Scale is for hypothetical discussion & has no regulatory inference

Summary

- Acute hepatocellular DILI is associated with different clinical signatures determined by distinct underlying mechanisms of toxicity.
- To assess benefits & risks, agent-related DILI risk profiles must include evaluation of incidence, range of clinical severity, causality & temporal characteristics of the liver injury. An assessment of benefits must also take into account basic temporal characteristics associated with a treatment agent.
- The current version of RUCAM is a ‘one-size shoe fits all’ which does not take into account important differences in mechanisms & clinical signatures of acute liver cell injury caused by different agents. An ongoing challenge is aligning algorithmic scoring rules with an appropriate set of agent-related DILI risk criteria.

FDA DILI website: www.fda.gov/Drugs/ScienceResearch/ResearchAreas