Tenecteplase: A Better tPA for Acute Ischemic Stroke?

Jack C. Rose, MD
Co-Medical Director, WHHS Stroke Program
Bell Neuroscience Institute of Silicon Valley
Board Certified: Neuro Critical Care, Vascular Neurology, & Neurology

Disclosures

Financial/Commercial:

- None

Unapproved (FDA) use of drugs:

- Intravenous alteplase for AIS beyond 3 hrs
- Intravenous tenecteplase for AIS
- Intraarterial tenecteplase for AIS

What do you call a walking, talking neurosurgical patient?

NEUROSURGERY RESIDENCY.COM

What do you call a walking, talking neurosurgical patient?

Pre-op.

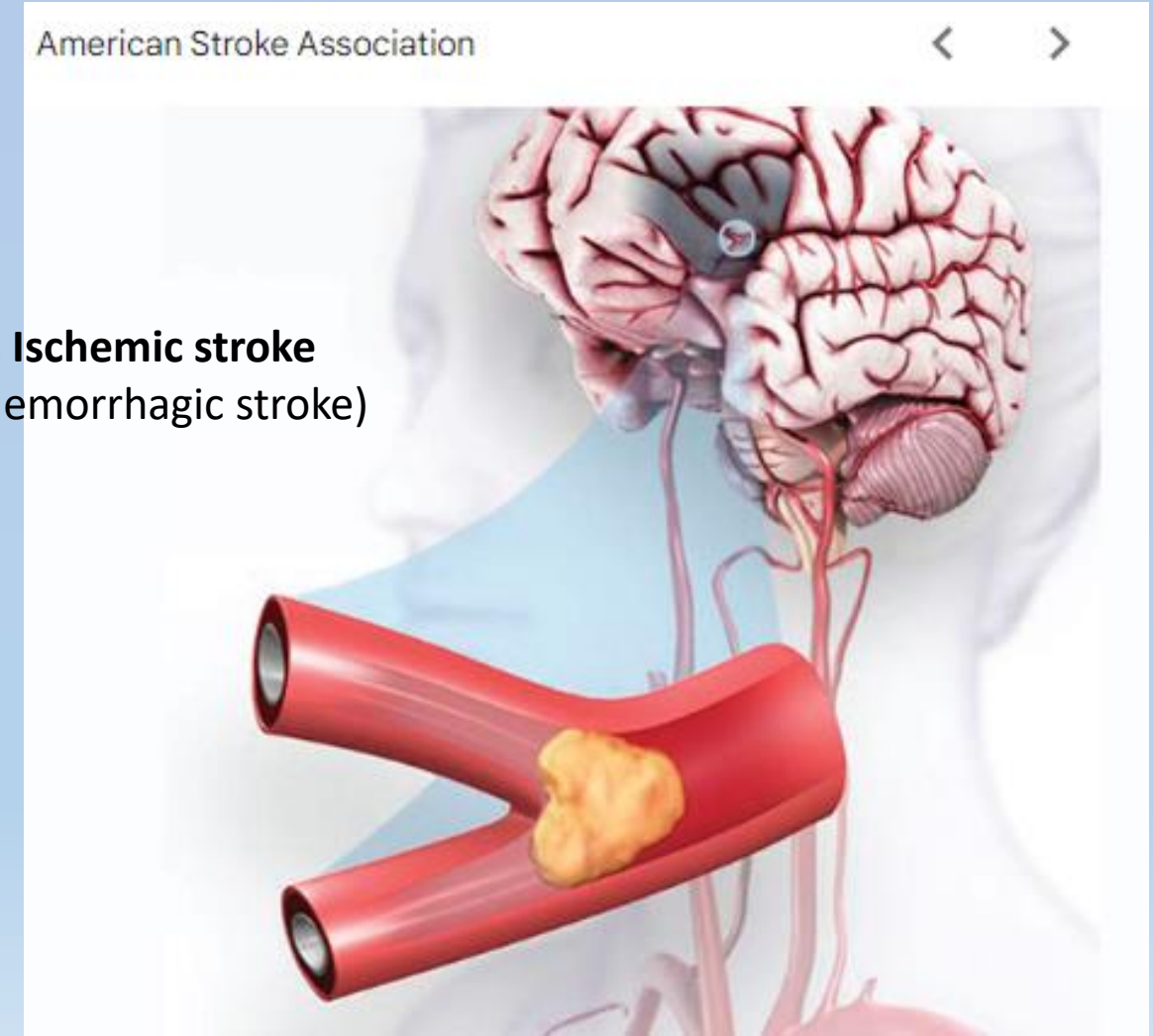
NEUROSURGERY RESIDENCY.COM

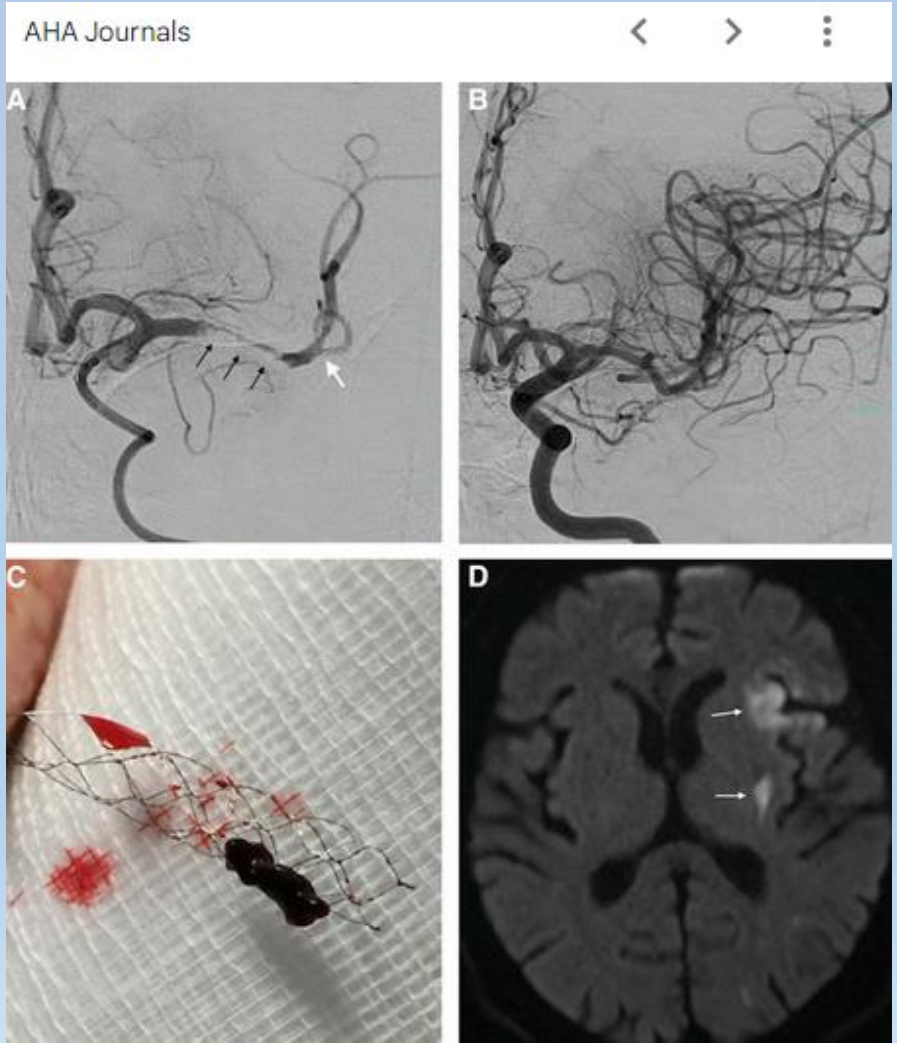
Stroke

~800,000 per year in USA **5th leading cause death** **1st leading cause of adult disability** **Health care costs in billions**

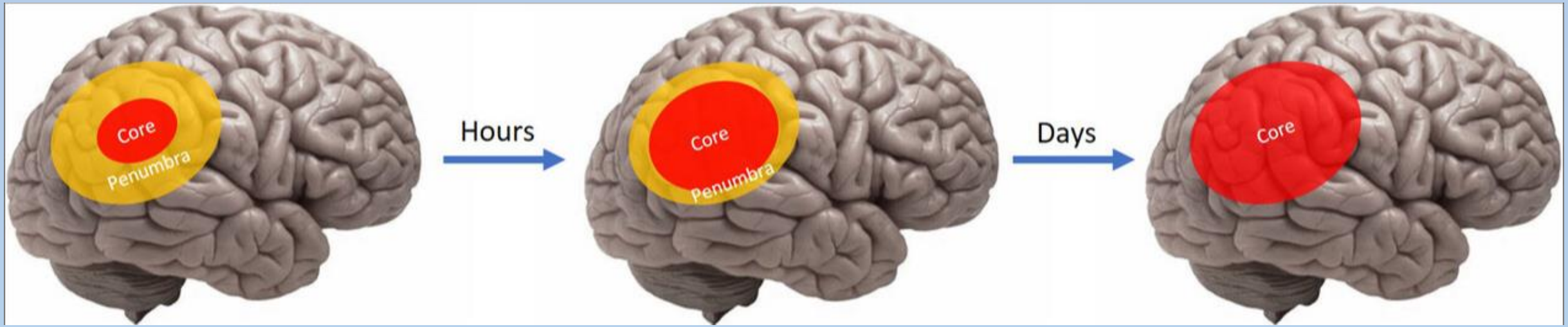
but **PREVENTABLE** **and** **TREATABLE!**

80% Ischemic stroke
(20% Hemorrhagic stroke)





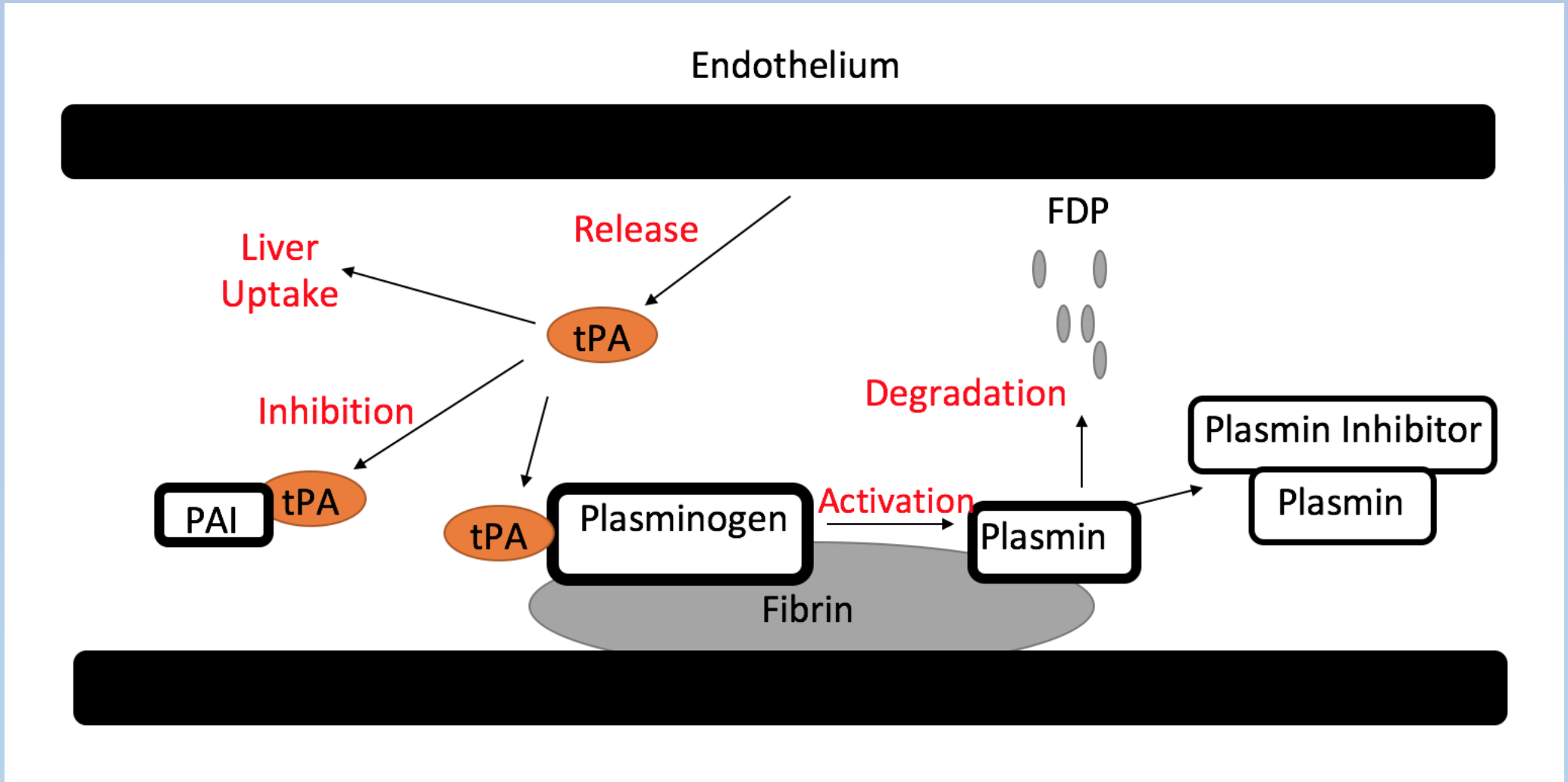
Acute Ischemic Stroke



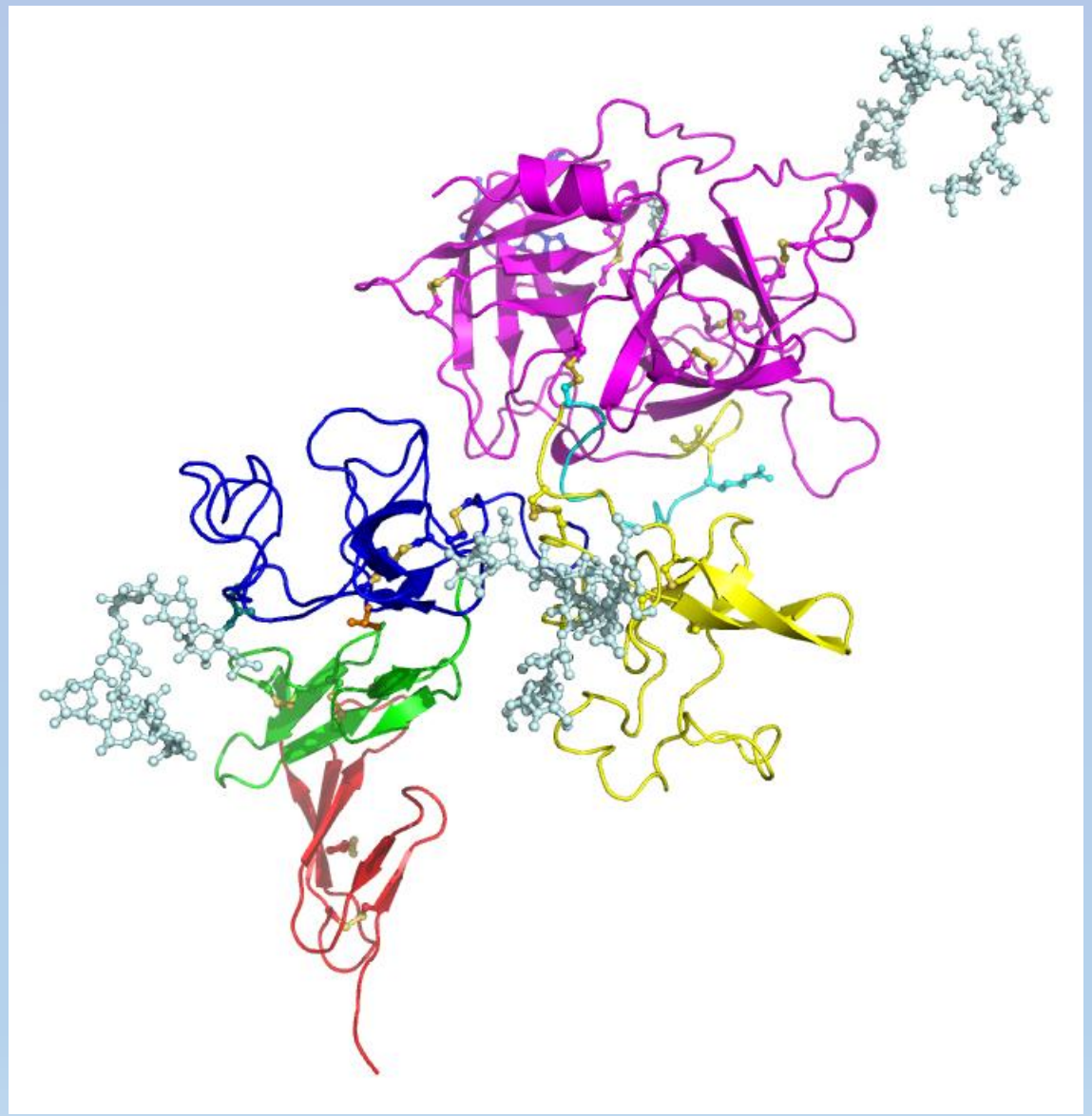
Acute treatment *(to prevent/minimize this)* → *drug (**thrombolytic**) or device (**endovascular thrombectomy**, aka EVT) or **BOTH**!*

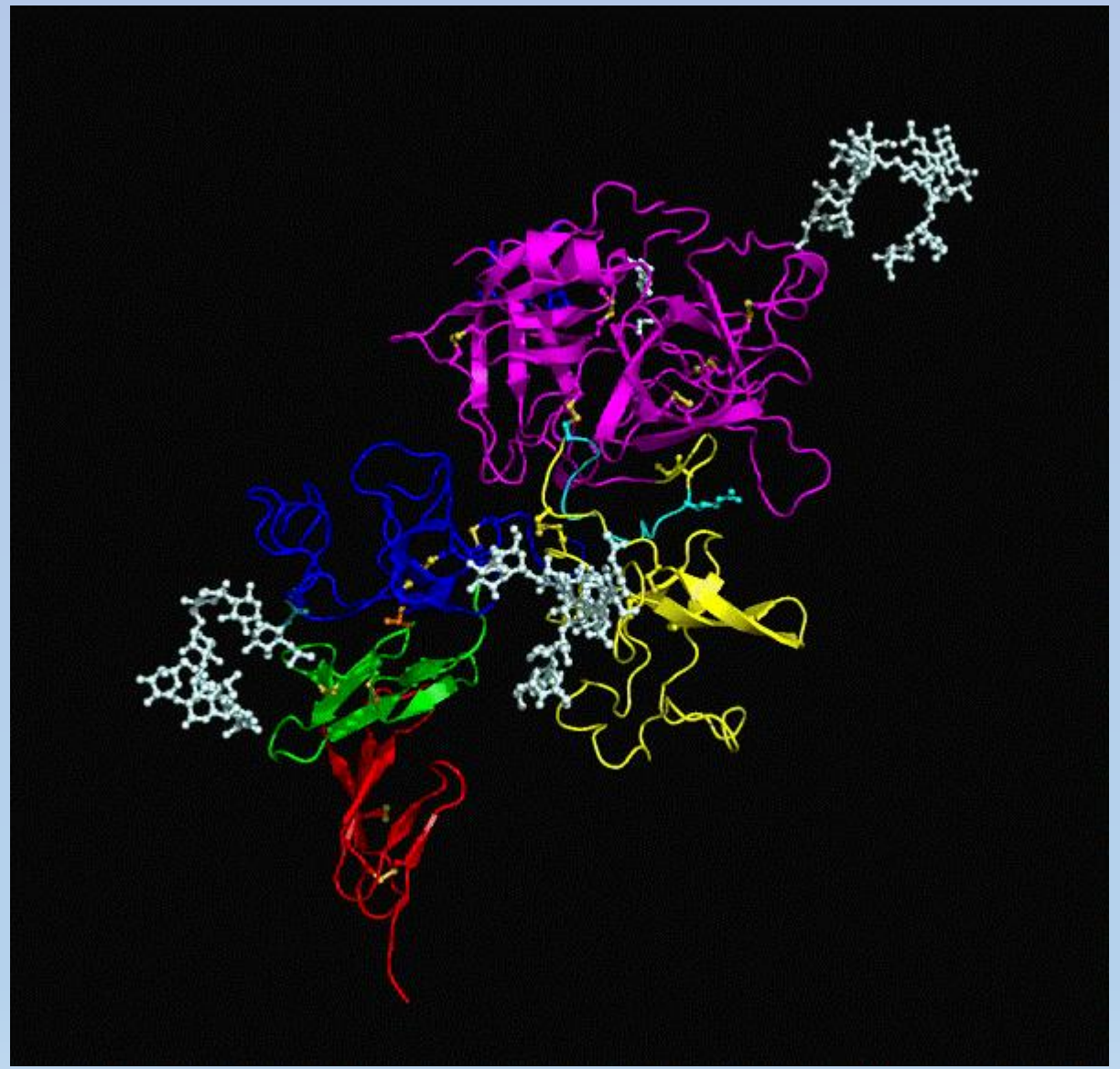
Robbins et al. *JACEP*, 2023

Tissue-type Plasminogen Activator (tPA)



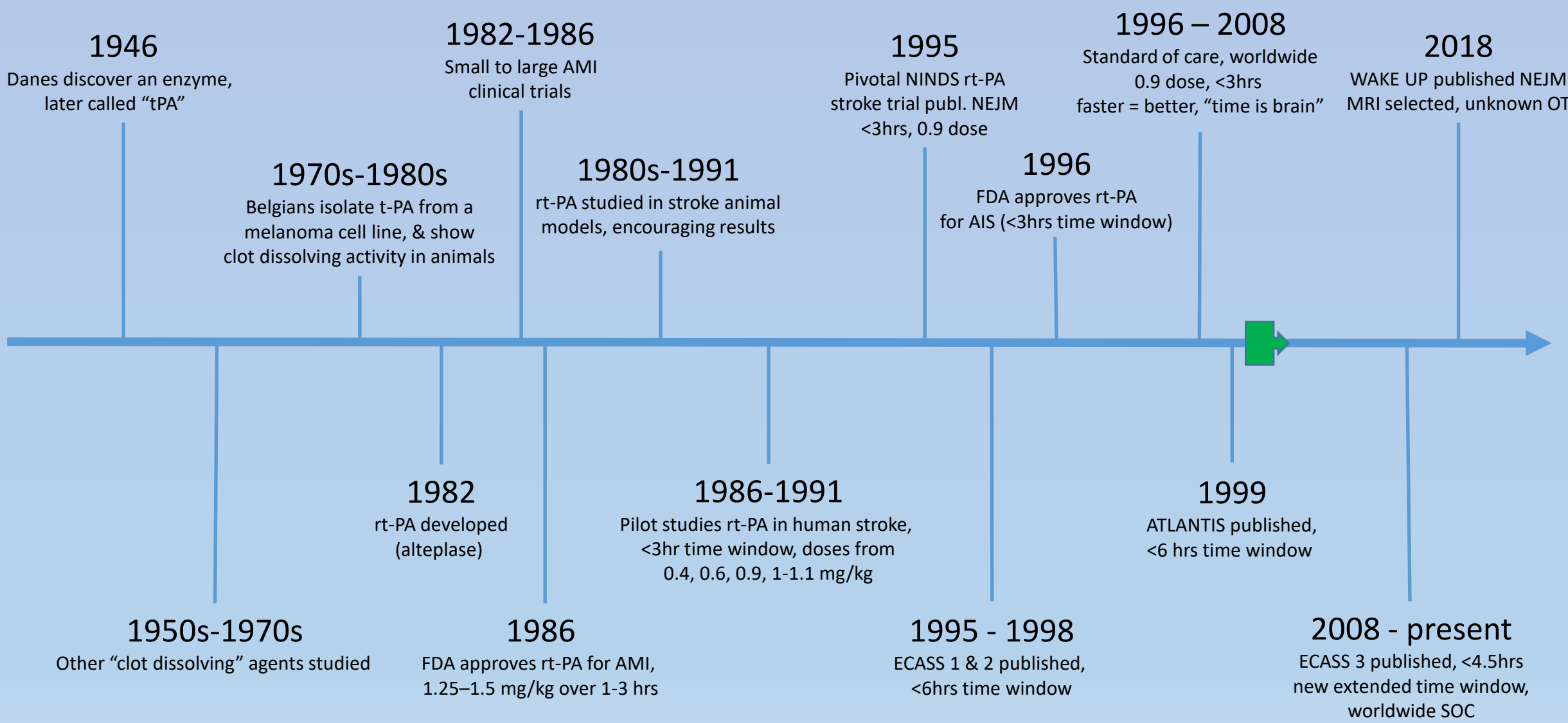
Gravanis et al. *Expert Opinion on Therapeutic Targets*, 2008





https://en.wikipedia.org/wiki/Tissue-type_plasminogen_activator

History of IV rt-PA (ALT)



History of IV rt-PA (ALT)

1946
Danes discover an e
later called "tP

2018
E UP published NEJM
elected, unknown OT

195
Other "clot di

- present
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The New England
Journal of Medicine

Volume 333 DECEMBER 14, 1995 Number 24

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

	alteplase	placebo	p
Disability-free recovery (mRS ≤ 1)	43%	27%	< .001
	NNT = 6		
Symptomatic intracerebral hemorrhage	6.4%	0.6%	< .001
	NNH = 17		

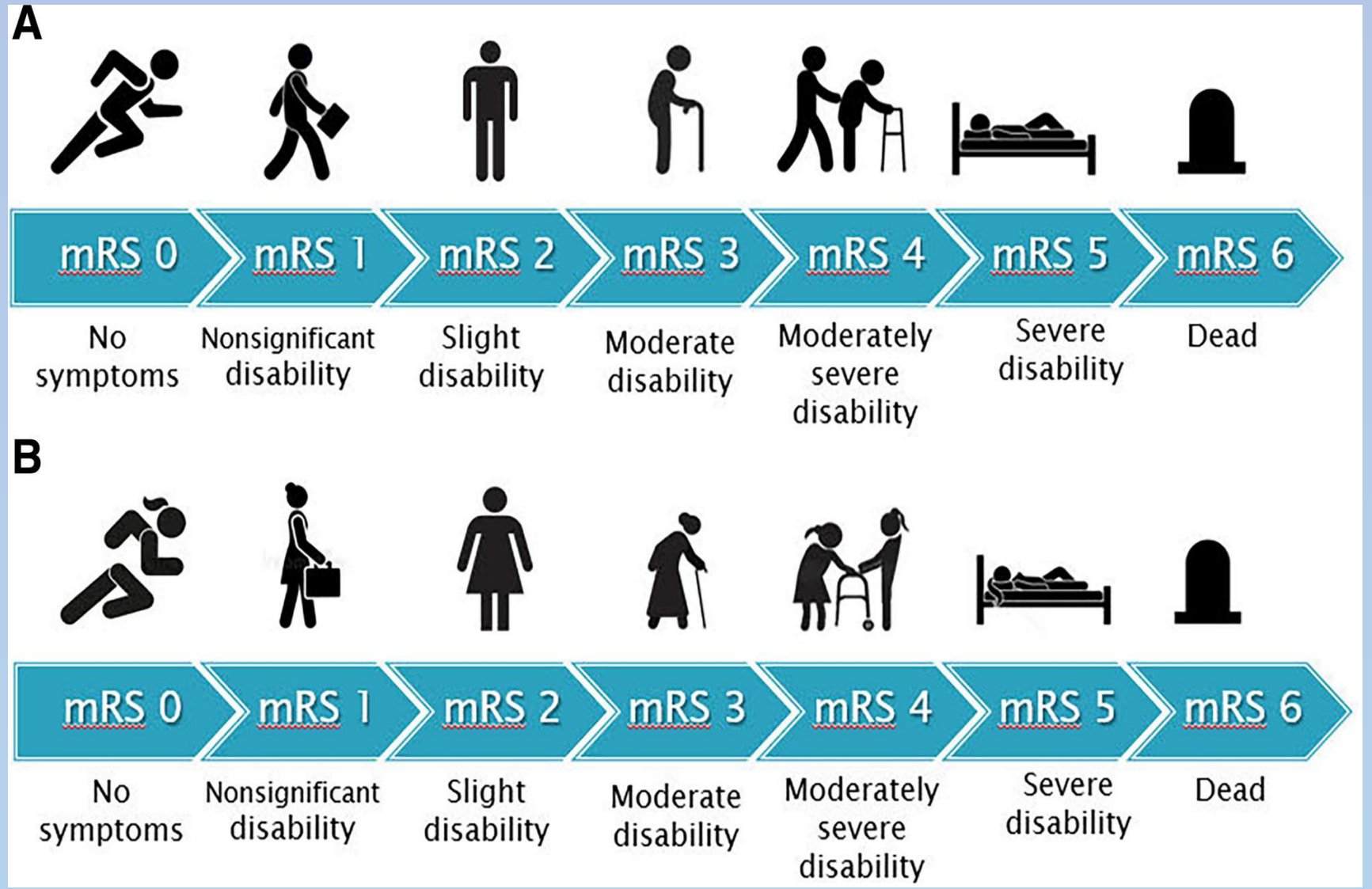
Quantifying Functional Outcome after Stroke

Modified Rankin Scale	
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

(added late 1980s) →

(added btwn 2005-8) →

Rankin, *Scott Med J* 1957
Wilson et. al., *Stroke* 2005

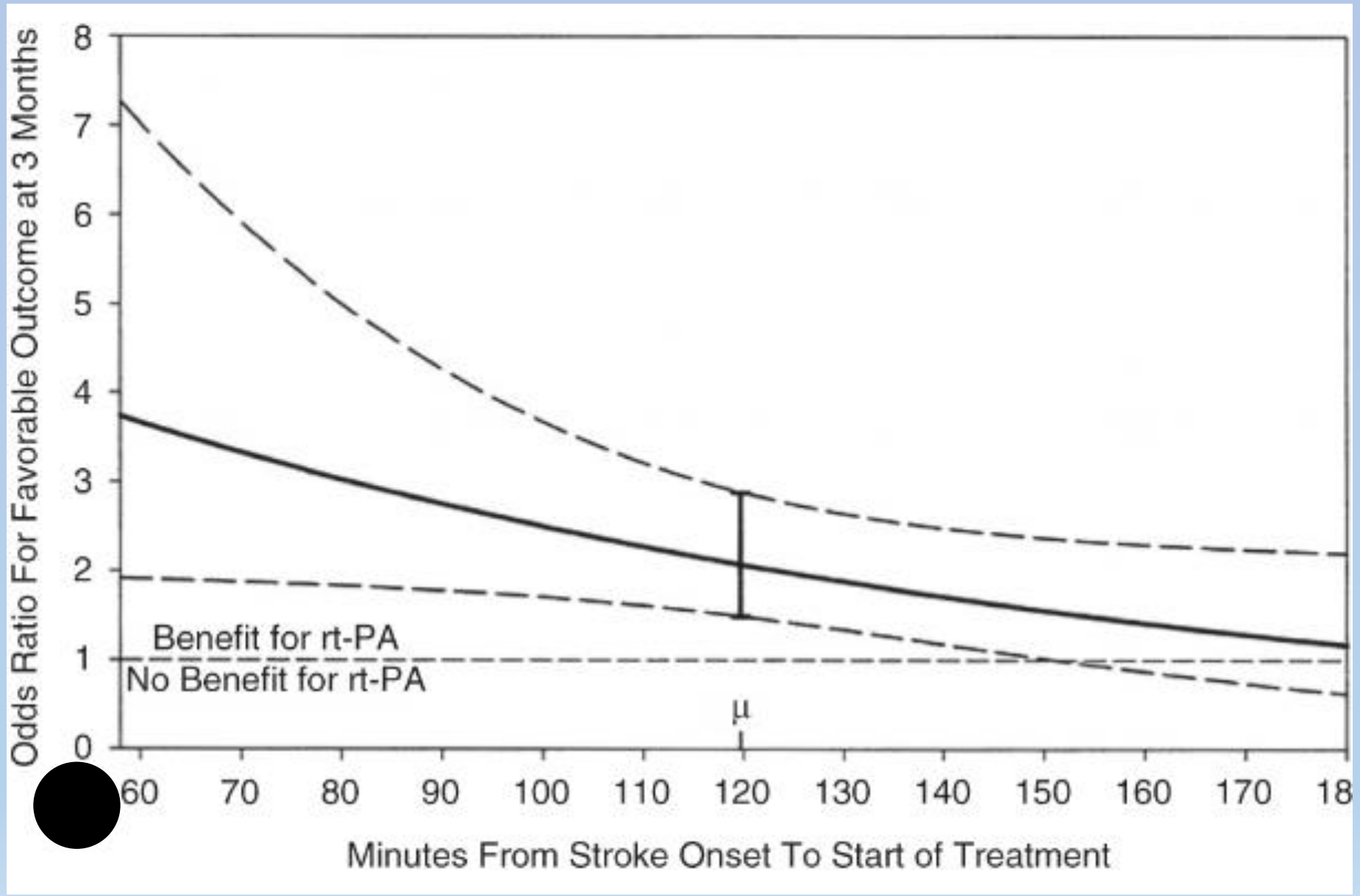


0 - 1 = *excellent* FO

0 – 2 = *good* FO

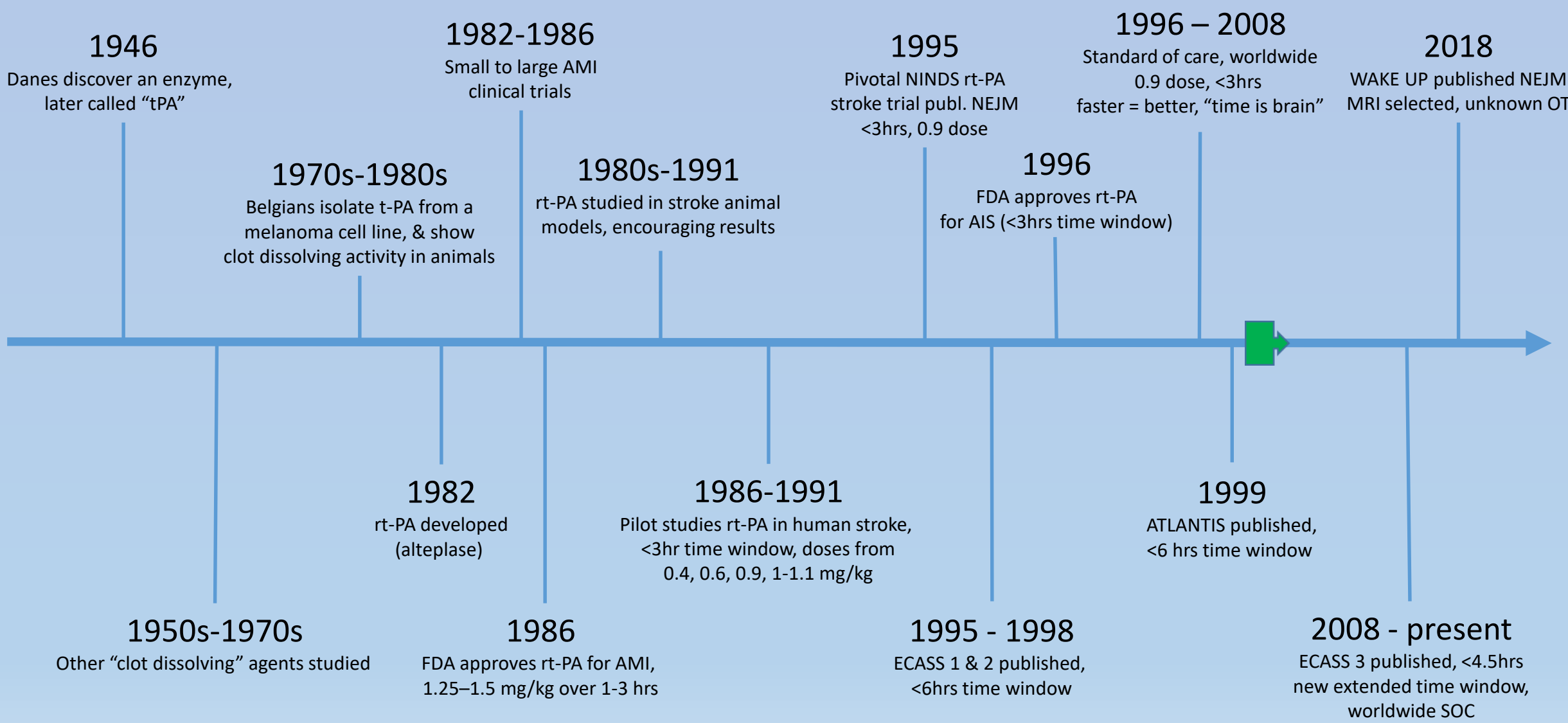
Jeffrey L. Saver. Stroke. Standardized Nomenclature for Modified Rankin Scale Global Disability Outcomes: Consensus Recommendations From Stroke Therapy Academic Industry Roundtable XI, Volume: 52, Issue: 9, Pages: 3054-3062, DOI: (10.1161/STROKEAHA.121.034480)

NINDS (<3 hrs)

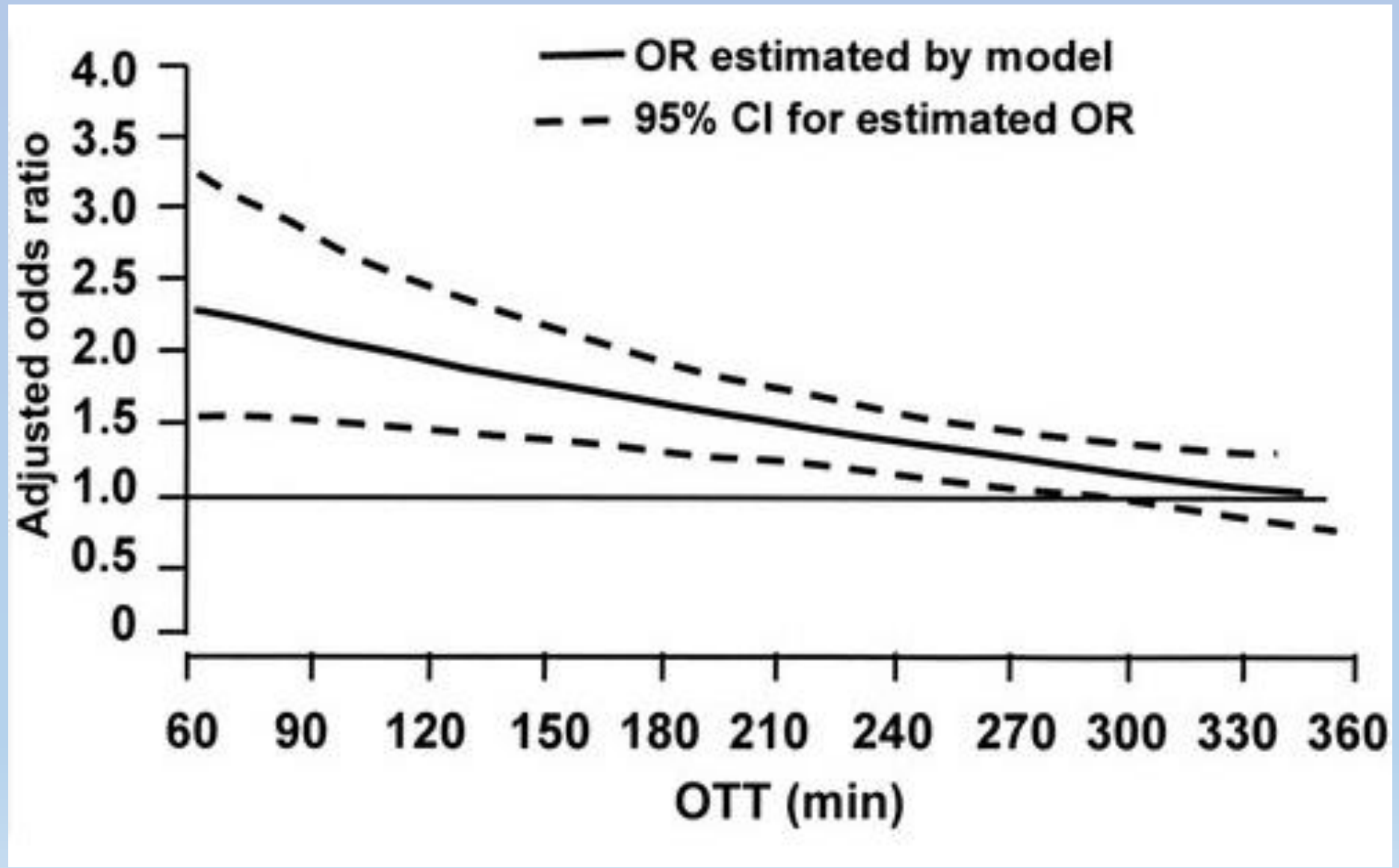


Marler, et al. *Neurology* 2000

History of IV rt-PA (ALT)



NINDS (<3hrs) + ECASS 1/2 (<6hrs) + ATLANTIS (<6hrs)



Hacke et al, *Lancet* 2004

Safety of acute stroke therapies: SICH

Supplemental Table I

	Clinical	Radiologic	Relation	
NINDS	Any	Any	Temporal	**6.4%**
ECASS 2	≥ 4 NIHSS	Any	None	**3.8%**
ECASS 3	≥ 4 NIHSS	Any	Causal	**2.4%**
SITS-MOST	≥ 4 NIHSS	PH 2	None	**1.9%**

Supplemental Table I: The varying definitions of SICH. NINDS definition of SICH was any ICH not seen on prior imaging with either a suspicion for hemorrhage or any decline in neurologic status. The European-Australian Cooperative Acute Stroke Study II (ECASS 2) definition of SICH was any hemorrhagic transformation and worsening by equal to or greater than 4 on the NIHSS. The ECASS 3 definition additionally required the establishment of a causal relationship between the hemorrhage and clinical neurologic deterioration. The Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) definition of SICH was restricted to local or parenchymal hematoma type 2 on imaging obtained 22 to 36 hours after treatment, accompanied by neurologic deterioration defined as worsening by 4 points or more on the NIHSS compared to baseline or lowest value between baseline and 24 hours, or hemorrhage leading to death.

Rao NM et al. *Stroke* 2014;45:2728-33

IV tPA (ALT) SICH independent risk factor evidence

Strongest:

- large pre-tPA head CT brain hypodensity or DWI volume
- signif elevated serum glucose and/or history of DM
- > 0.9 mg/kg dose ALT

different tPA?

Moderate:

- Stroke symptom/sign severity (NIHSS)

Weakest:

- Advanced patient age
- Increased treatment time
- Systolic HTN
- Low platelets
- H/o CHF

different tPA?

Other factors:

- CAA
- Endocarditis
- AVM
- Secondary TBI
- Intracranial dissection

Landsberg MG et al. 2007. *Cerebrovasc Dis.;* 24:1-10

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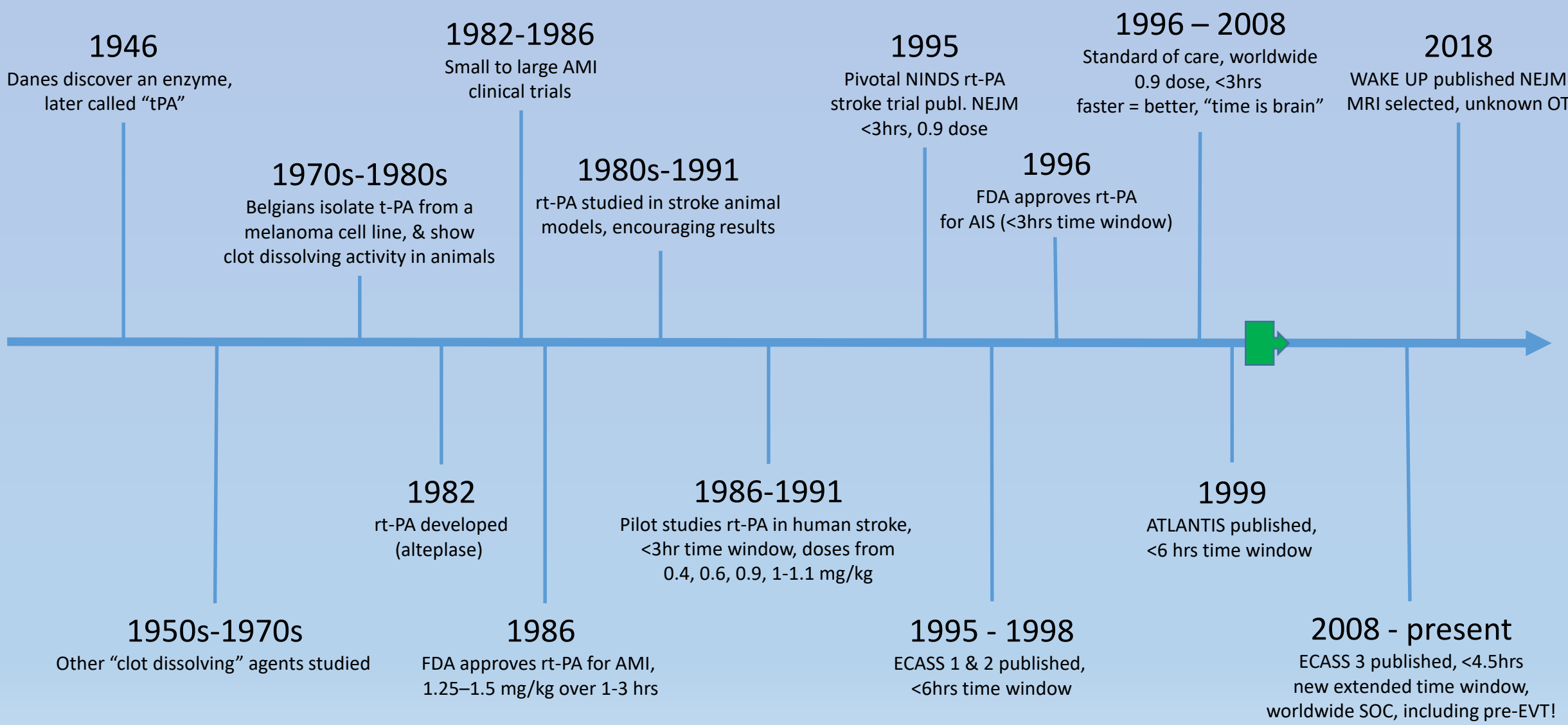
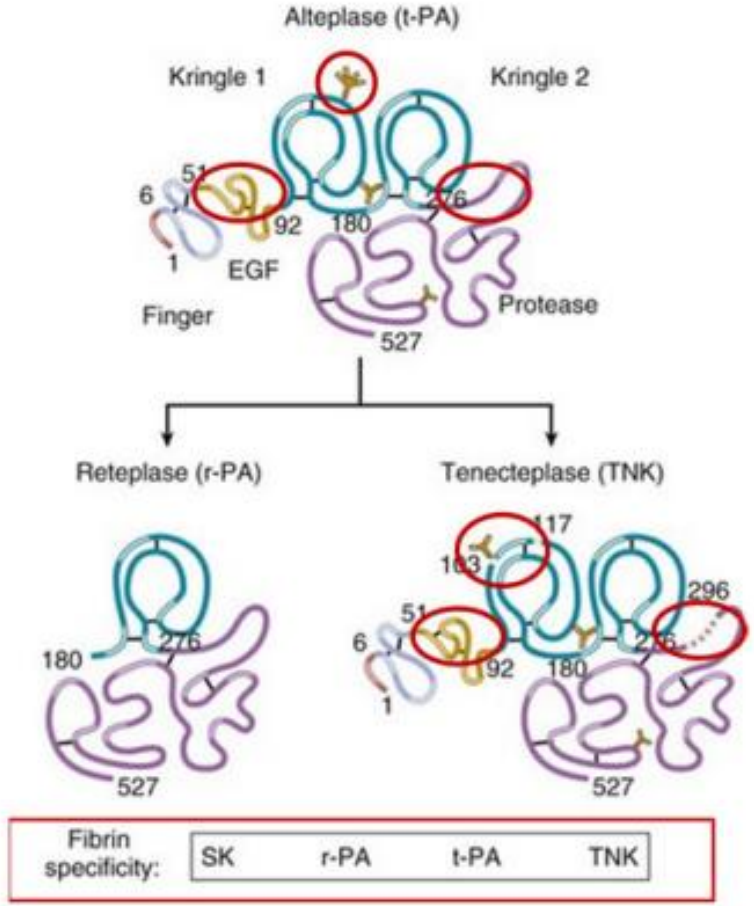


Is a different thrombolytic better (efficacy and/or safety) than alteplase?

- For approved/guideline supported standard, early IV treatment window (< 3-4.5 hrs) +/- EVT?
- For investigational late treatment window (4.5-24 hrs) IV +/- EVT?
- For investigational intrarterial use during EVT?

Tenecteplase (TNK)????

- Tenecteplase is a triple combination mutant variant of alteplase
- Has a high fibrin specificity (15x)→ theoretical risk of lower complications
- Higher resistance to plasminogen activator inhibitor-1 (80x)→ longer half-life (20 minutes)→ **Bolus dose administration**

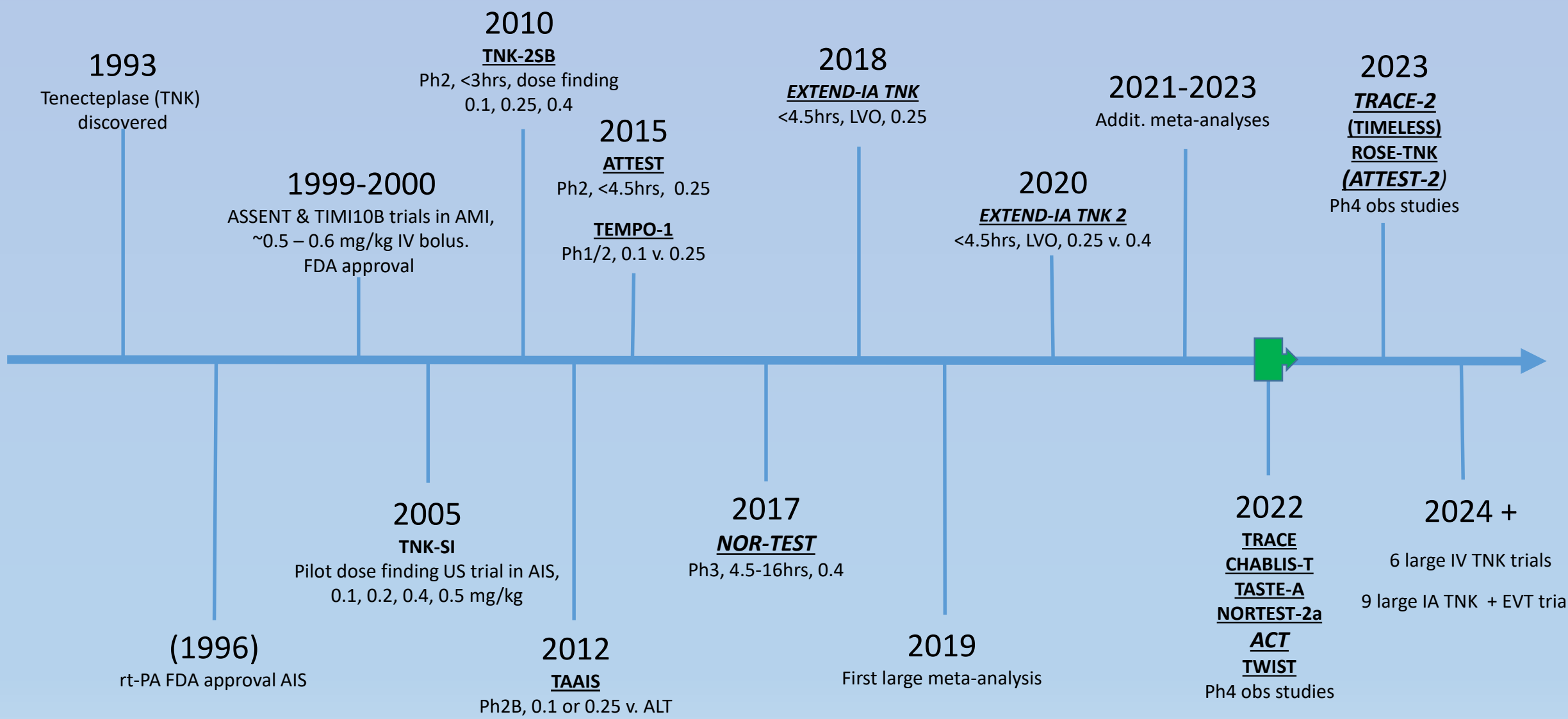


Dunn et al; Drug Evaluation, 2012.
Warrach et al; Stroke, 2020.

	Alteplase (ALT)	Tenecteplase (TNK)
Design/synthesis	Recombinant version naturally occurring tPA	Bioengineered triple mutant version of ALT
Binding Affinity	Fibrin **+** PAI-1 **++**	Fibrin **+++** PAI-1 **+**
Fibrinogen depletion	**++** to **++++**	**+** to **++**
Circulating half-life Terminal half-life	5 minutes 1 hour	20 minutes 2 hours
Preparation	More complex, typically 5-10 min (in pharmacy, by PharmD at WHHS)	Simple, ~ 1 min (in ED, by RN)
Administration	60 minute IV infusion, after 10% initial IV bolus	5-10 second single IV bolus
Average wholesale price	> $10,000 (100mg vial)	< $8,000 (50mg vial)
FDA indications	AIS < 3hr AMI AMPE CVC clearance	AMI (if PCI n/a or delayed)

Dunn et al. *Drug Eval* 1012; Nelson et al. *NEJM* 2019; Warach et al. *Stroke* 2020

History of IV TNK



History of IV TNK

1993
rt-PA FDA approval AIS

2010
TNK-2SB

TAAIS
Ph2B, 0.1 or 0.25 v. ALT

2018
First large meta-analysis

2023
TWIST
Ph4 obs studies

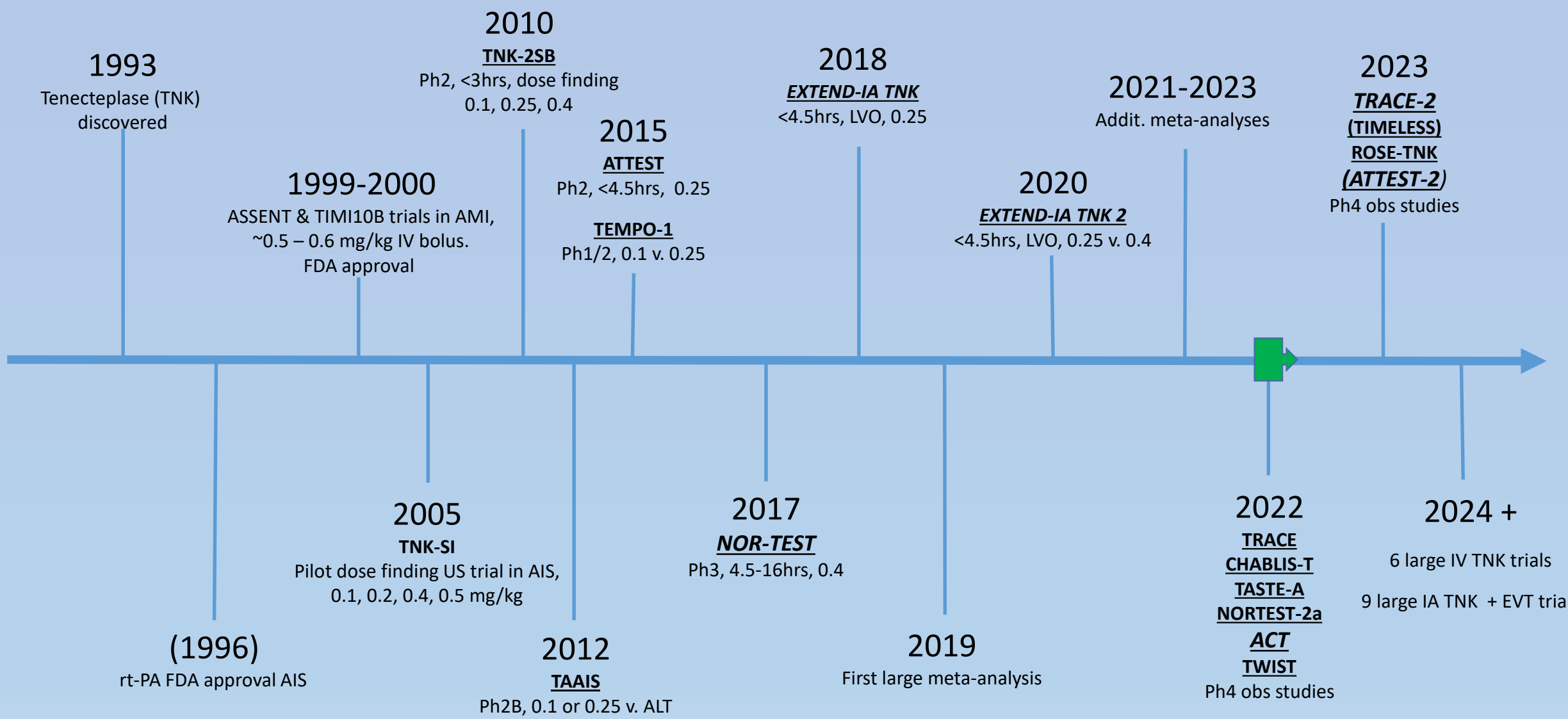
TNK-SI

Haley et al, *Stroke* 2005

- Phase 1/pilot, safety dose-escalation, USA (6 hosp), 2000-2003
- <3 hr time window, AIS, no EVT (same as NINDS ALT)
- Sequential tiered doses (0.1, 0.2, 0.4, 0.5 TNK), 125 pts planned (up to 0.6), but only 88 enrolled (stopped during 0.5)
- PO = SICH w/in 36hrs; SO = 90d FOs (all TNK doses and c/w historical ALT ctls)
- No SICH with 0.1, 0.2, 0.4 doses, but 15% SICH rate with 0.5
- 90d FOs → similar to historical ALT controls; no signif differences between TNK doses

Conclusion: TNK safe/future RCTs should proceed, up to 0.4 dose

History of IV TNK



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2023

TWIST
Ph4 obs studies

+

K trials

EVT trials

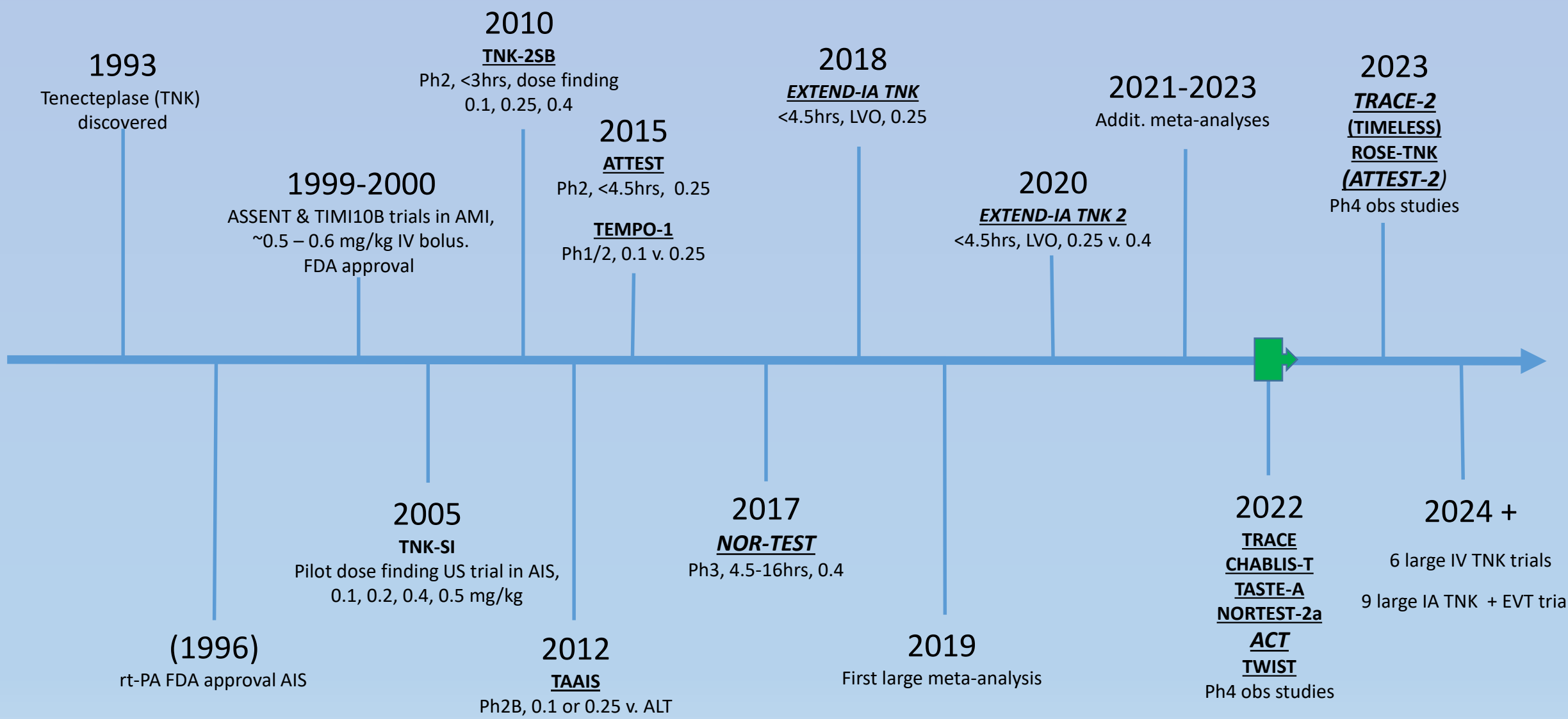
TNK-S2B

Haley et al, *Stroke* 2010

- Phase 2, small (112 pts), randomized, DB, USA (8 ctrs)
- Dose finding (0.1, 0.25, or 0.4 TNK vs ALT)
- <3 hr time window, AIS, no EVT
- PO= Composite MNI @24hrs + SICH rate; SO= 90d eFO, pFO, mort
- Prematurely terminated (slow enrollment; Ph3 part abandoned)
- 0.4 TNK dose discarded as inferior d/t excessive SICH (16% v. 0%, 6%, 3%)
- No signif differences (0.1 v. 0.25 TNK v. ALT) in MNI or 90d eFO
  - However, 0.25 TNK arm had best results of all 4 groups

Conclusion: none definitive, further study needed, 0.25 dose may be best

History of IV TNK



History of IV TNK

TAAIS

Parsons et al, *NEJM* 2012

- Phase 2, small (75 pts), PROBE, Australia (3 ctrs)
- TNK 0.1 v. 0.25 v. ALT
- <6 hr time window, AIS-LVO w/ fav CTP, no EVT
- PEO = NIHSS or MRI perf improvements @24hrs
- SEO = eFO; SSO = SICH rate, mort
- Combined TNK pts v. ALT
  - *Better clinical (8% v. 3%) & imaging (79% v 55%) PEOs*
  - Numerically lower SICH rate (4% v. 12%)
  - Numerically higher 90d eFO (54% v. 40%)
  - Numerically lower mortality rate (8% v. 12%)

Conclusion: TNK → better reperfusion & clinical outcomes in select AIS-LVO patients c/w ALT

Ten

1 +

NK trials

+ EVT trials

(1996)
rt-PA FDA approval AIS

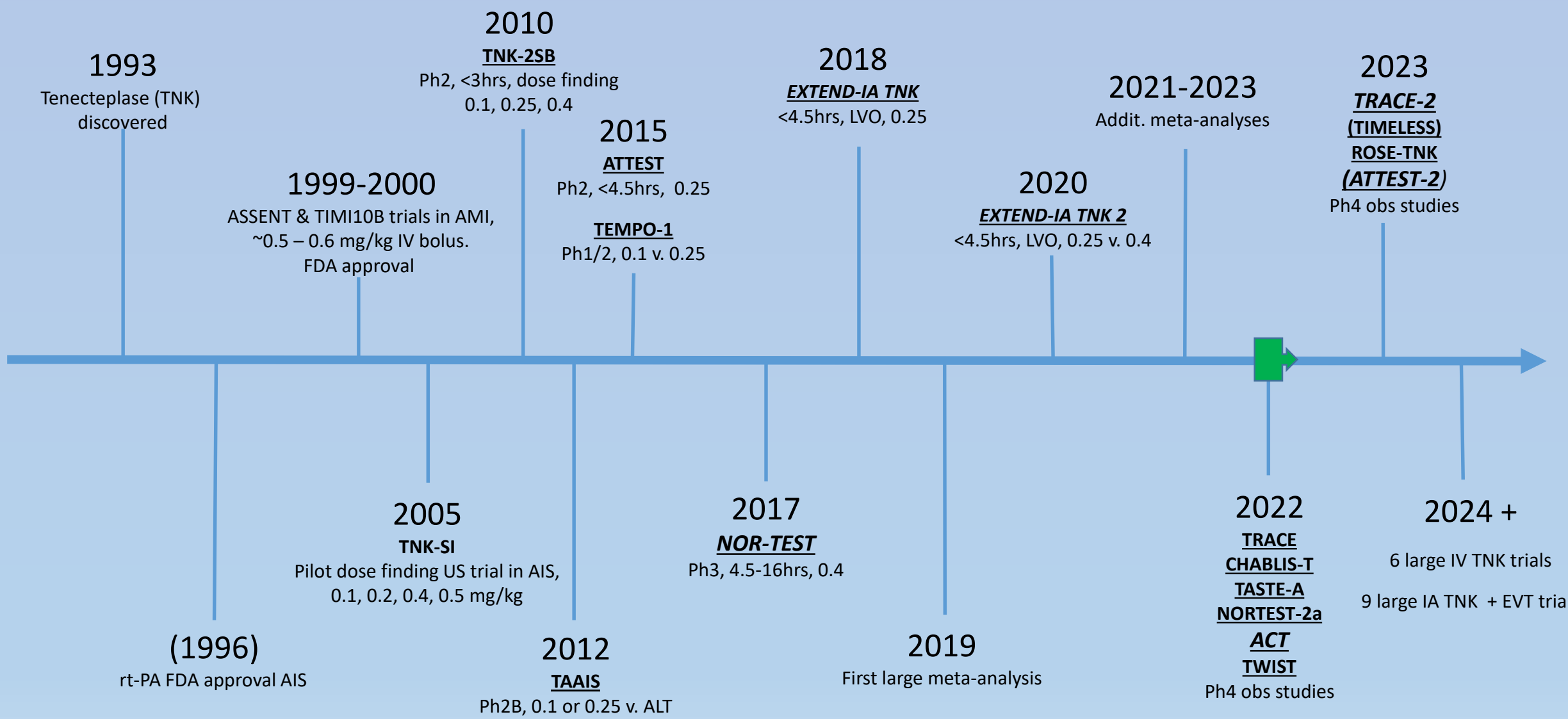
2010
TNK-2SB

2012
TAAIS
Ph2B, 0.1 or 0.25 v. ALT

2019
First large meta-analysis

TWIST
Ph4 obs studies

History of IV TNK



History of IV TNK

2010
TNK-2SB

2018

Tenecte
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rt-PA FDA approval AIS

TAAIS
Ph2B, 0.1 or 0.25 v. ALT

First large meta-analysis

TWIST
Ph4 obs studies

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T trials

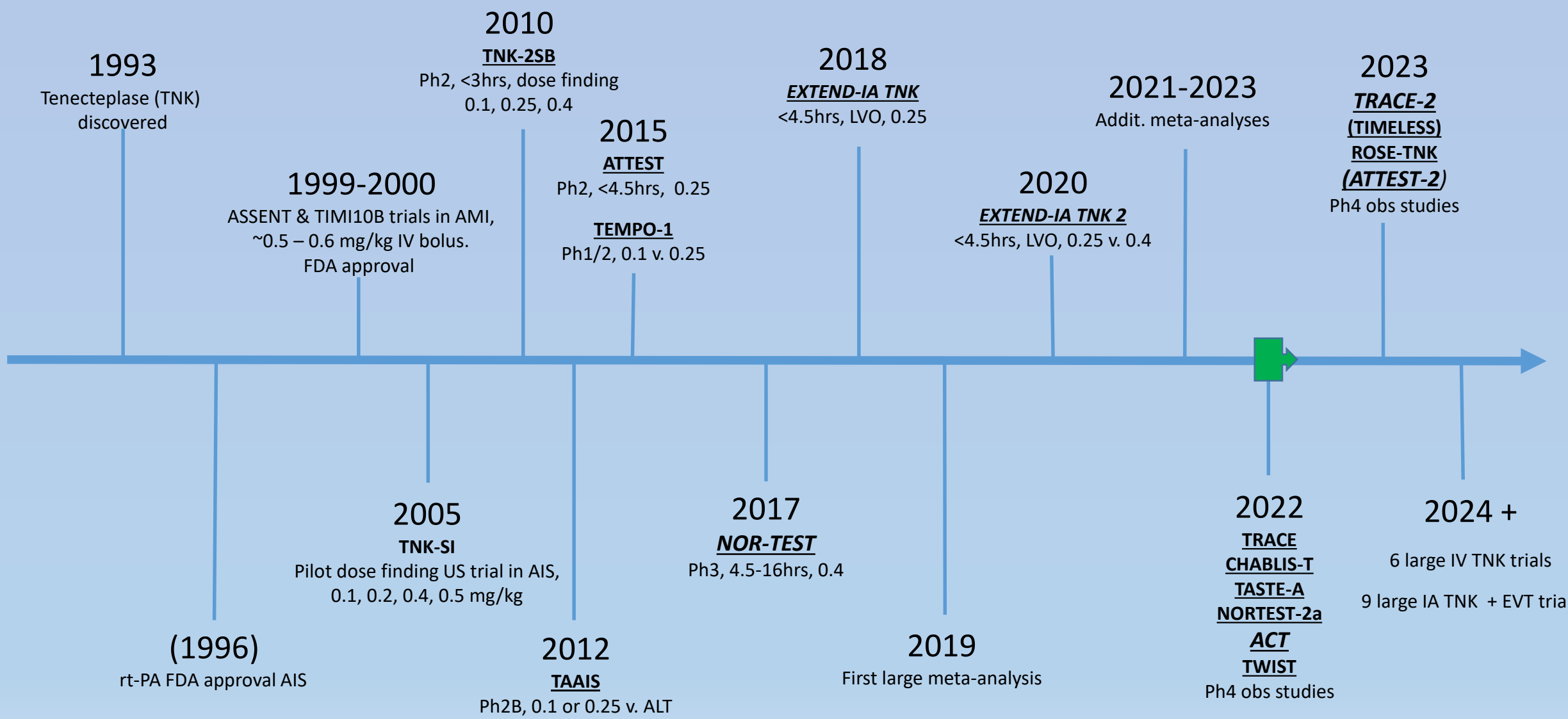
ATTEST

Huang et al, *Lancet Neurol* 2015

- Phase 2, small, PROBE, single ctr in Scotland, 2012-2013
- <4.5 hr time window, AIS, no EVT, CTA/P used for outcomes only
- TNK 0.25 v. ALT, 104 pts (52 + 52)
- PO = % penumbra saved @24-48hrs; SO = SICH/all ICH
- No diff in PO btwn TNK & ALT (both 68% salvage)
- 1 SICH TNK (2%), 2 SICH ALT (4%), not s.s.

Conclusion: Larger TNK RCTs warranted; 0.25 dose safe

History of IV TNK



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First large meta-analysis

2023

TWIST
Ph4 obs studies

ials

T trials

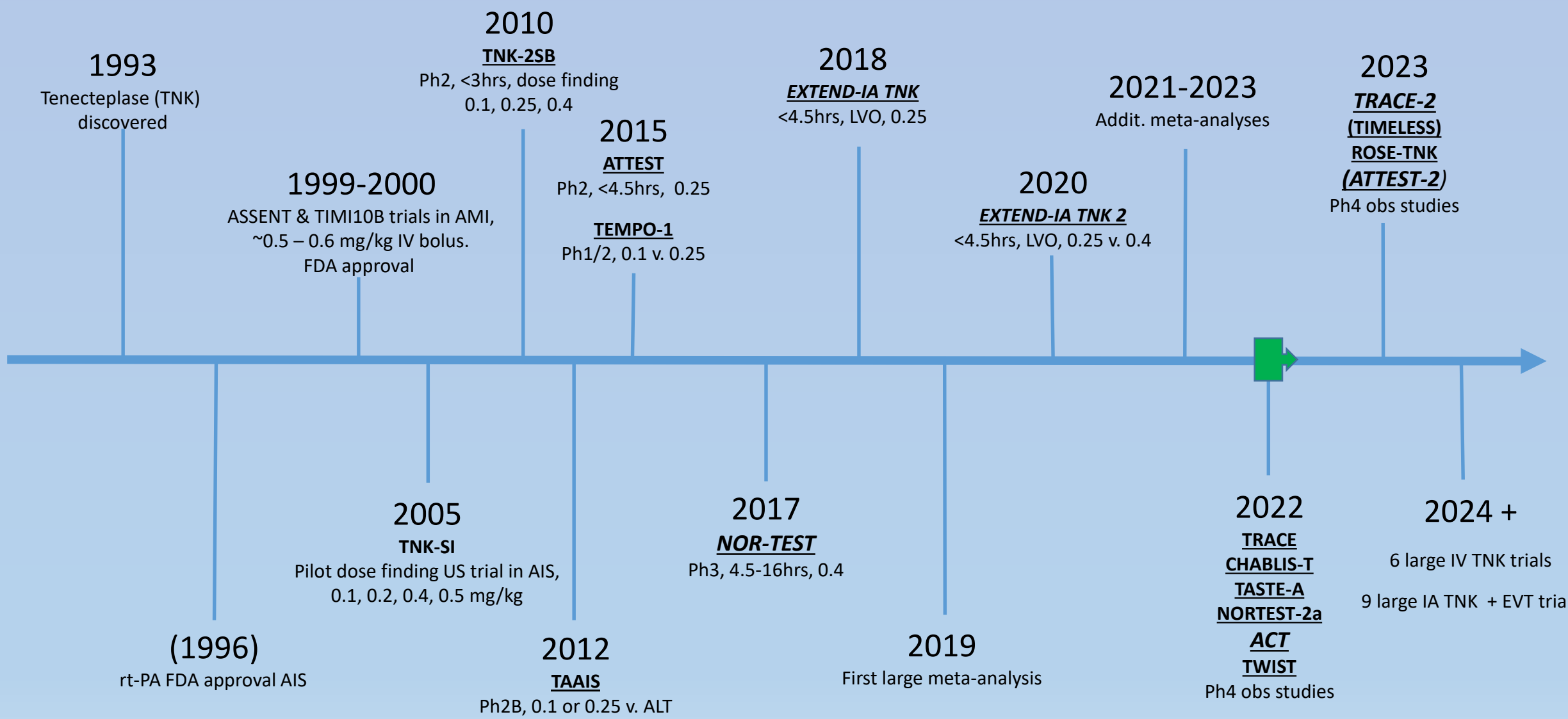
NOR-TEST

Logallo et al, *Lancet Neurol* 2017

- Phase 3, large, PROBE, superiority, 13 ctrs in Norway, 2012-2016
- AIS, <4.5 hr since LSN or WOS, +/- EVT, median NIHSS = 4, ~20% mimics
- TNK 0.4 v. ALT, 1100 pts (T 549; A 551)
- PEO = 90 d mRS 0-1 (eFO); SO = SICH, mort
- No diff in eFO (T 64%, A 63%), SICH, SAE (26% each), or mort (both 5%)
- Severe (NIHSS>15) subgroup → incr mort with TNK

Conclusion: TNK not superior to ALT; has a similar safety profile

History of IV TNK



History of IV TNK

EXTEND-IA TNK

Campbell et al, *NEJM* 2018

- Phase 2, medium, PROBE, non-inferiority, 13 ctrs in Aus/NZ, 2015-2017
- AIS, <4.5 hr, + LVO w/ fav CTP pre-EVT
- TNK 0.25 v. ALT, 202 pts (101 each)
- PEO = “subst. reperfusion” initial DSA ; SEO = FOs, MNI @72hrs; SO = SICH, mort
- PEO (T 22% > A 10%); eFO (51% v. 43%), gFO (64% > 51%); SICH (each 1%), mort (10% v. 18%)
- Median tPA to GP 46min! T only decr this time by 5 or 10 min (transfers)

Conclusion: pre-EVT TNK not inferior to ALT (efficacy/safety); may be superior (reperf & FO)

1993
Tenecte
disc

2010
TNK-2SB

2018

rt-PA FDA approval AIS

2012
TAAIS
Ph2B, 0.1 or 0.25 v. ALT

First large meta-analysis

TWIST
Ph4 obs studies

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History of IV TNK

1993
Tenecteplase (TNK) discovered

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(1996)
rt-PA FDA approva

3.6. Other IV Fibrinolytics and Sonothrombolysis

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	**IIb**	**B-R**	New recommendation.
IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).[178] This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (P=0.002 for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; P=0.04) but less robustly for the proportion who achieved an mRS score of 0 to 1 (P=0.23) or 0 to 2 (P=0.06). sICH rates were 1% in both groups.			See Table XLIII in online Data Supplement 1.
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	**IIb**	**B-R**	New recommendation.
IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[179–182] In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.[182] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XLIII in online Data Supplement 1.

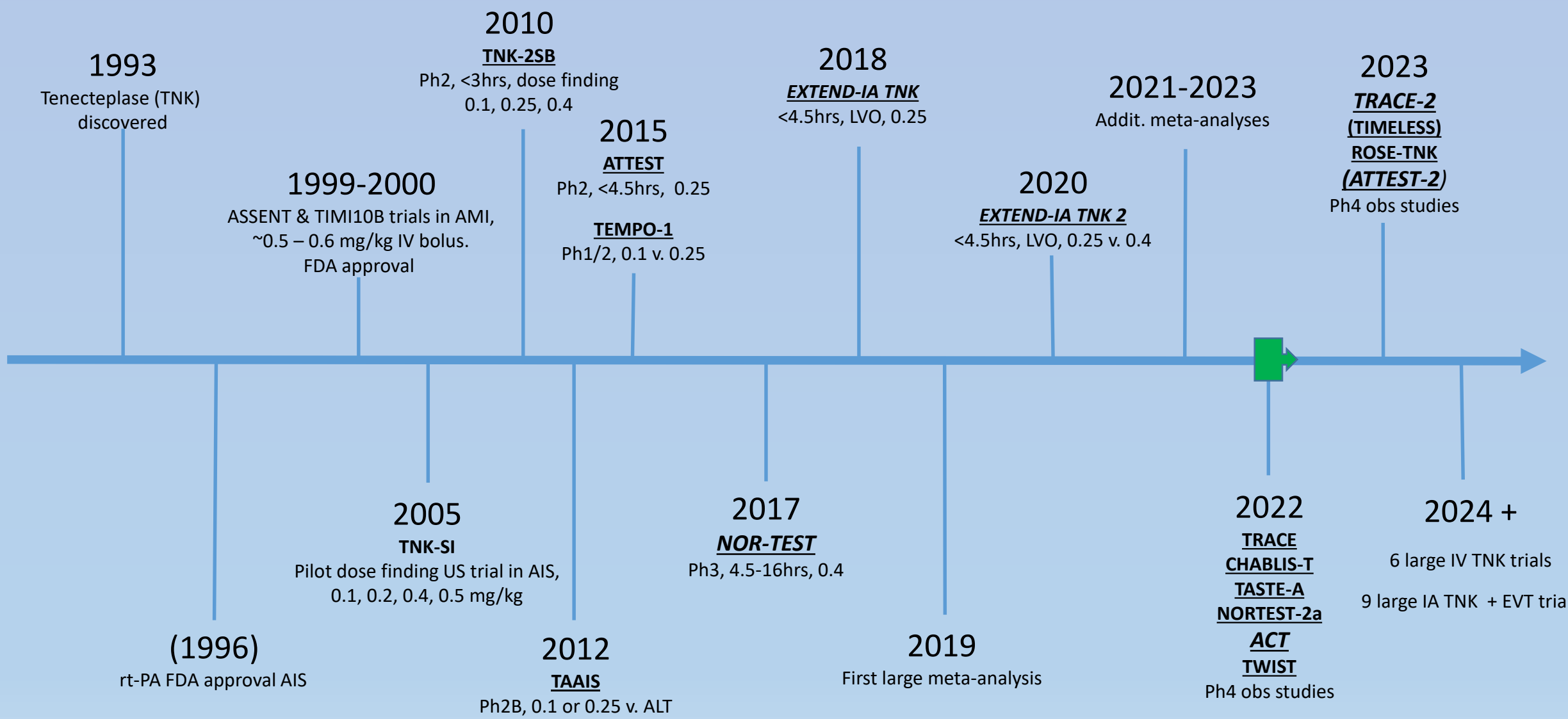
2023
TRACE-2
(TIMELESS)
ROSE-TNK
(ATTEST-2)
h4 obs studies

2024 +

6 large IV TNK trials

9 large IA TNK + EVT trials

History of IV TNK



History of IV TNK

1993

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rt-PA FDA approval AIS

2010

TNK-2SB

Ph2, <3hrs, dose finding

TAAIS

Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2021-2022

TWIST

Ph4 obs studies

2023

trials

VT trials

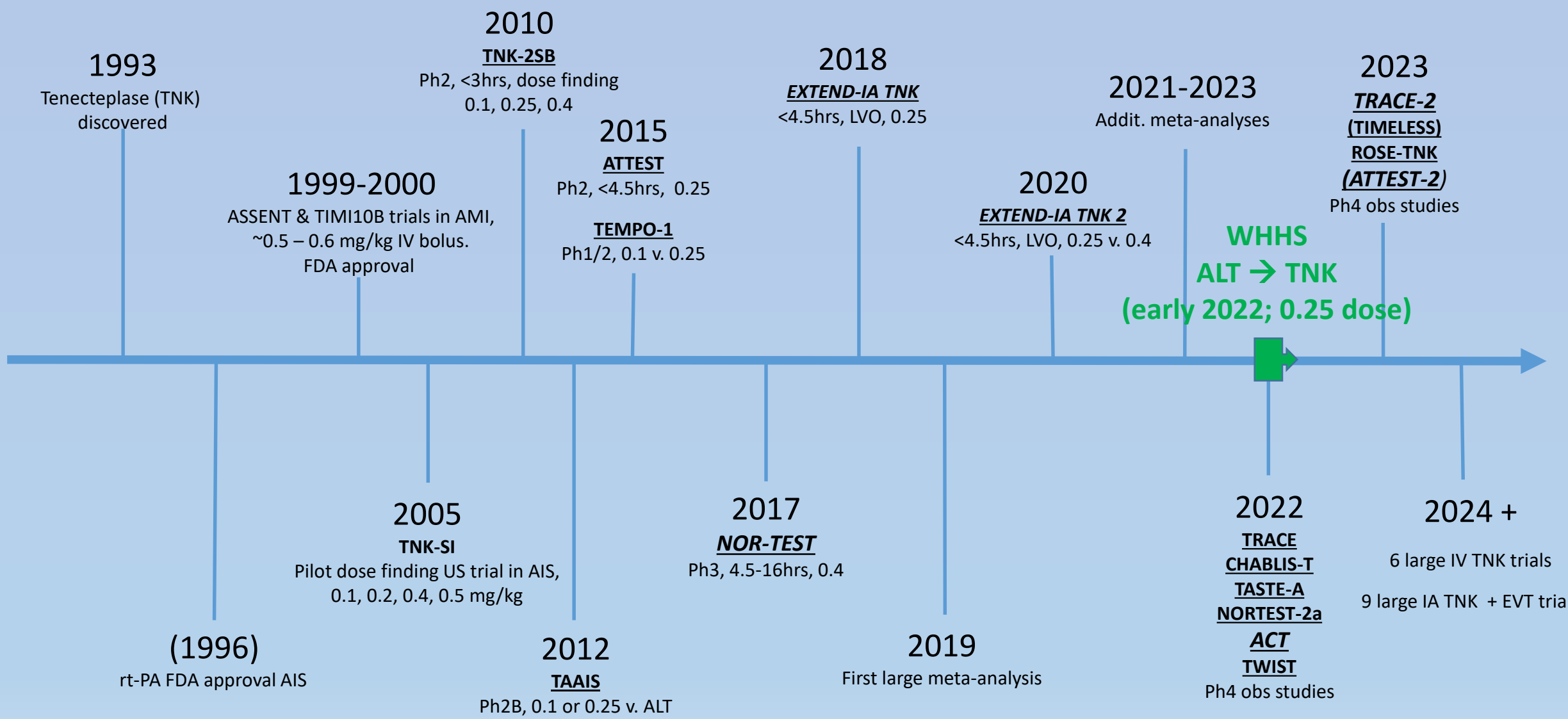
EXTEND-IA TNK 2

Campbell et al, *JAMA* 2020

- Phase 2, medium, PROBE, non-inferiority, 28 ctrs in Aus/NZ, 2017-2019
- AIS, <4.5 hr, + LVO w/ fav CTP pre-EVT
- TNK 0.4 v. TNK 0.25, 300 pts (150 each)
- PEO = >50% brain reperfusion initial DSA ; SEO = FOs; SO = SICH, mort
- PEO (both doses 19%); nearly = FOs and mort; SICH (4.7% v. 1.3%)
- Rural v. metroTNK to GP (152min v. 41min), no outcome differences

Conclusion: Standard IV window, pre-EVT 0.4 TNK not advantageous over 0.25 TNK

History of IV TNK



History of IV TNK

2010

TRACE

Li et al, *Stroke Vasc Neurol* 2022

- Phase 2, medium, PROBE, 22 ctrs in China, 2018-2020
- AIS, <3 hr
- TNK 0.1, 0.25, 0.3 v. ALT, 236 pts (~60 each 4 arms)
- PEO = signif improv NIHSS @14d; SO = SICH, mort
- PEO→ no differences (but 0.25 79% v. other 3 arms 65-69%)
- SO→ SICH (5%, 0%, 3%, 2%)

Conclusion: <3hr TNK from 0.1 to 0.3 well tolerated, similar to ALT in Chinese pts; 0.25 may be best

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+
trials
EVT trials

(1996)
rt-PA FDA approval AIS

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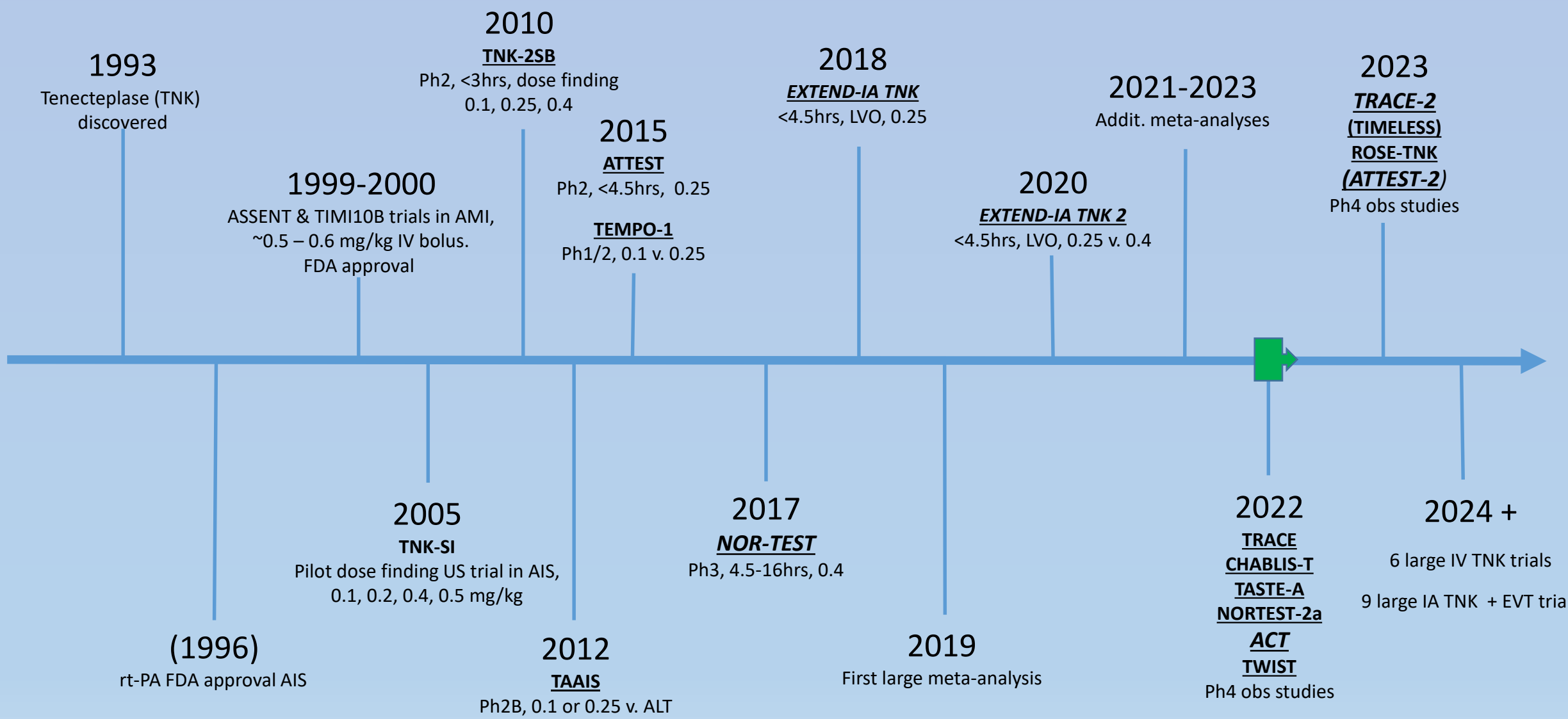
2019
First large meta-analysis

ACT
TWIST
Ph4 obs studies

History of IV TNK



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2023
TWIST
Ph4 obs studies

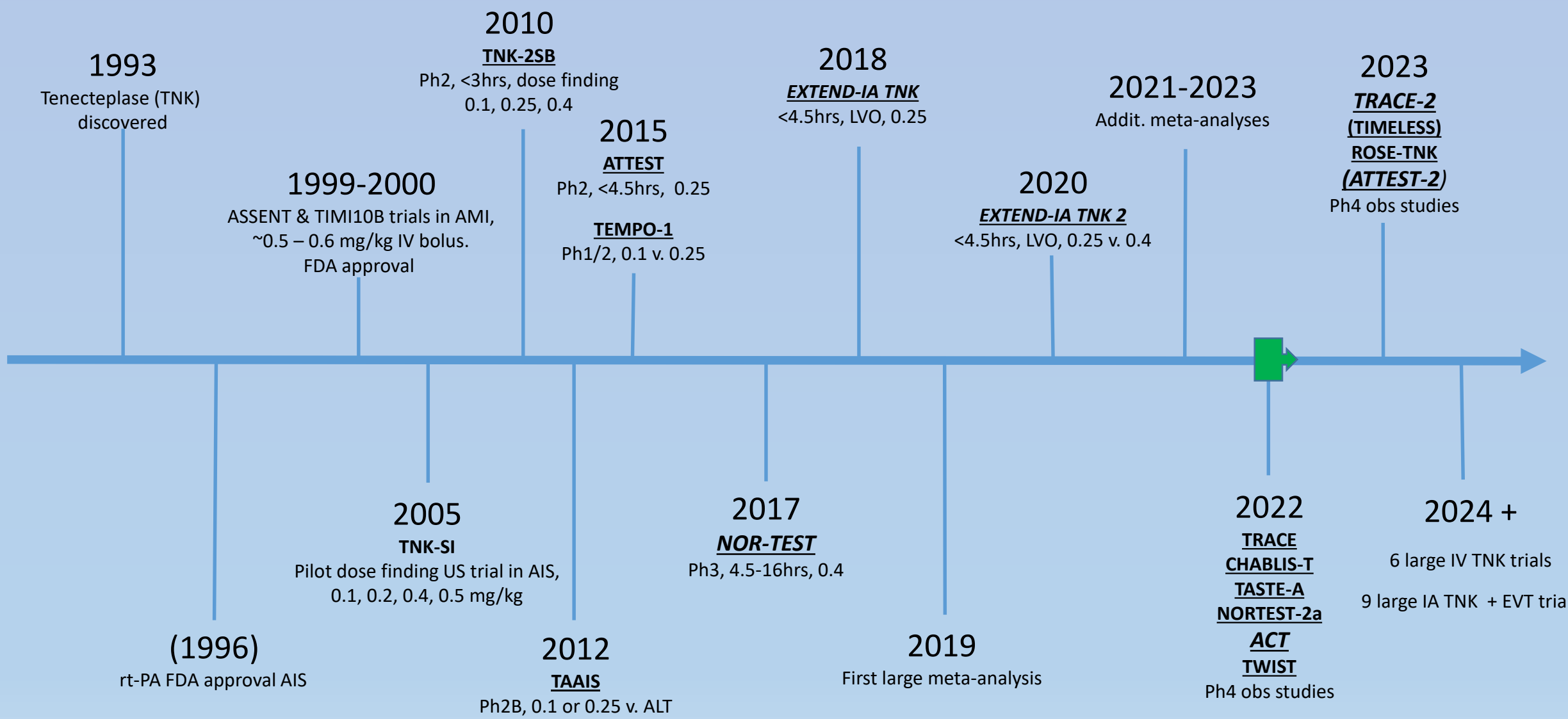
CHABLIS-T

Cheng et al, ISC 2022

- Phase 2, small, PROBE, 13 ctrs in China
- AIS, + LVO w/ fav CTP, IV TNK given 4.5 – 24 hrs LSN, +/- EVT
- TNK 0.25 v. 0.32, 86 pts
- PO = reperf w/o SICH; SO = SICH
- PO→ 33% v. 23% but eFO 28% v. 49% (similar gFO)
- SO→ SICH (12% v. 9%); SICH both T doses 6% (w/o EVT) 18% (w/ EVT)

Conclusion: late window IV TNK 0.25 & 0.32 similar results, highest SICH rate + EVT

History of IV TNK



History of IV TNK

1993

rt-PA FDA approval AIS

2010

TNK-2SB

TAAIS
Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2023

TWIST
Ph4 obs studies

trials

EVT trials

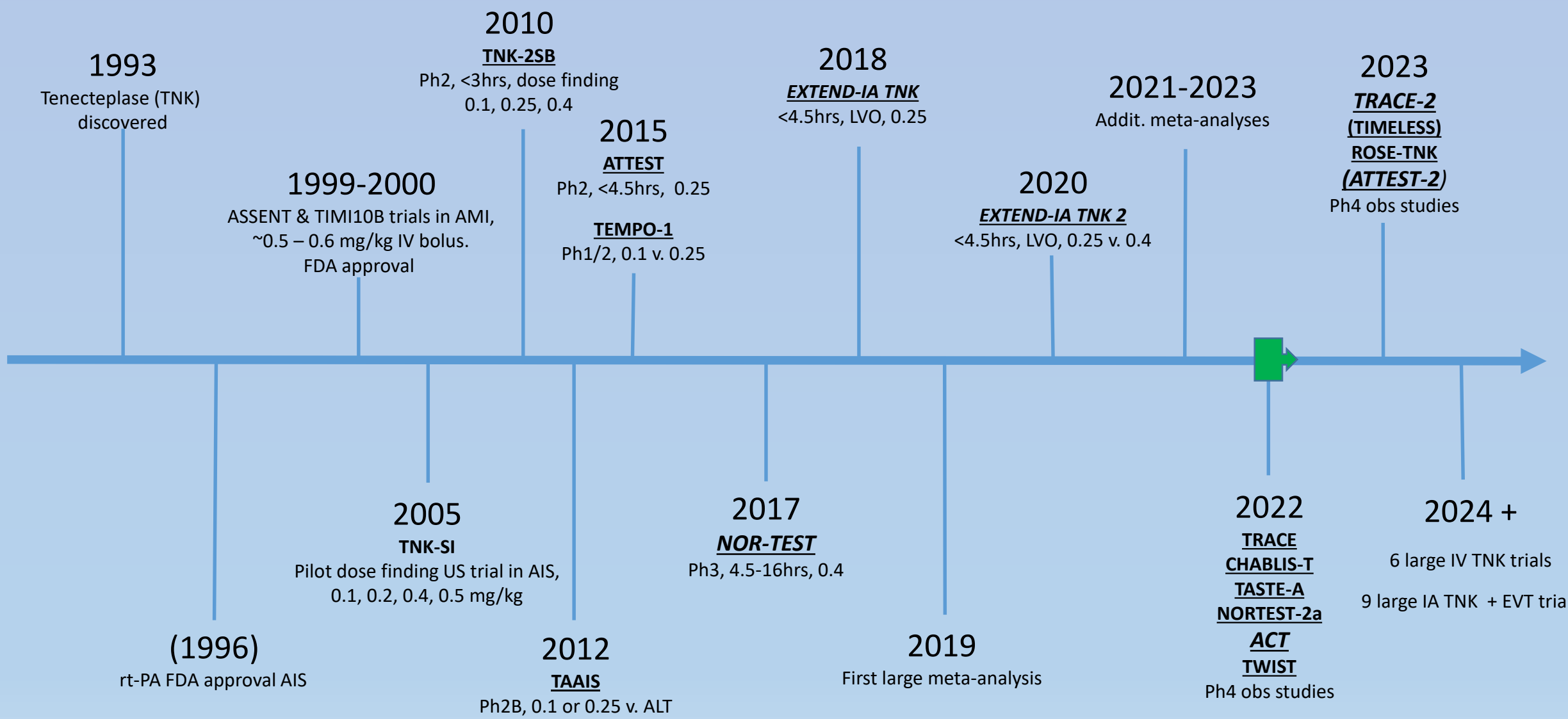
TASTE-A

Bivard et al, *Lancet Neurol* 2022

- Phase 2, small, PROBE, 5 MSU affiliated ctrs in Australia
- AIS, <4.5 hrs, IV TNK v. ALT given in MSU
- TNK 0.25 v. ALT, 104 pts
- PO = CTP lesion vol at hosp arrival; SO = SICH, mort, SAE
- PO→ T 12ml < A 35 ml
- SO→ no SICHs, 9% v. 10% mort, 5% v. 8% SAE

Conclusion: MSU TNK superior early reperfusion c/w ALT, no safety concerns

History of IV TNK



History of IV TNK

1993

rt-PA FDA approval AIS

2010

TNK-2SB

TAAIS
Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2023

TWIST
Ph4 obs studies

+

K trials

EVT trials

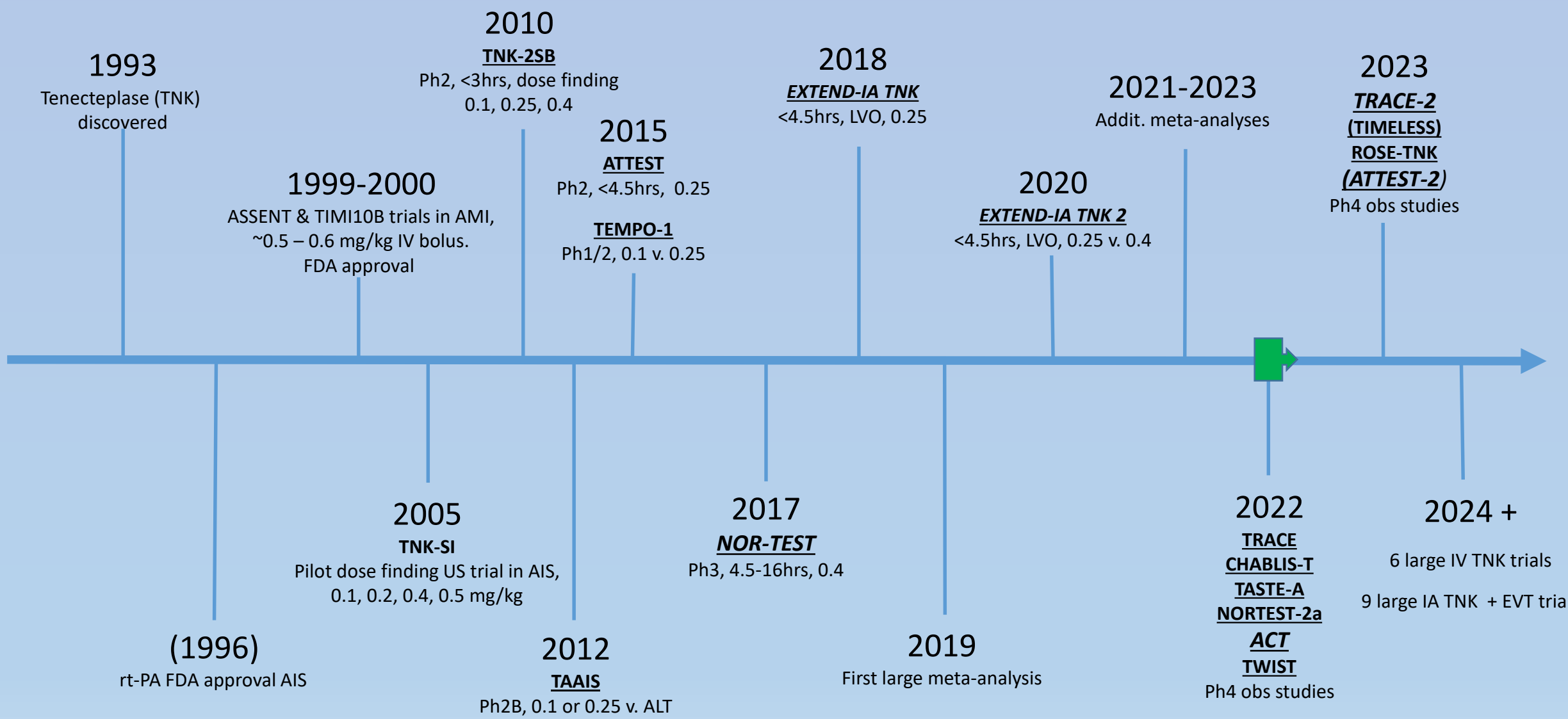
NOR-TEST 2(a)

Kvistad et al, *Lancet Neurol* 2022

- Phase 3, medium, PROBE, non-inferiority, 11 ctrs in Norway, 2019-2021
- AIS, <4.5 hr, NIHSS >5, 57% LVO
- TNK 0.4 v. ALT, 204 pts (T 100; A 104), terminated early d/t harm concerns
- PEO = 90 d mRS 0-1 (eFO); SO = SICH, mort
- PEO→ 32% < 51%
- SICH → 6% > 1%; mort→ 16% > 5%

Conclusion: TNK 0.4 worse safety and FO c/w ALT, non-inferiority not established, future trials should select lower TNK doses

History of IV TNK



History of IV TNK

2010
TNK-2SB

2018

Tenecte
disc

rt-PA FDA approval AIS

TAAIS
Ph2B, 0.1 or 0.25 v. ALT

First large meta-analysis

TWIST
Ph4 obs studies

ials

T trials

ACT

Menon et al, *Lancet* 2022

- Phase 3, large, PROBE, 22 ctrs in Canada, 2019-2022 (COVID)
- AIS, <4.5 hr, 1577 pts, 33% LVO, +/- EVT, only 6% from PSC
- TNK 0.25 v. ALT; PEO = 90-120d mRS 0-1 (eFO); SO = SICH, mort
- PEO→ 37% v. 35%
- SICH → both 3%; mort→ both 15%

Conclusion: TNK 0.25 is a reasonable alternative to ALT

History of IV TNK

1993

Tenecte
disc

rt-PA FDA approval AIS

2010

TNK-2SB

Ph2, <3hrs, dose finding

TAAIS

Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2021-2022

TWIST

Ph4 obs studies

2023

ACT (LVO subgroup)

Bala et al, *JAMA Neurol* 2022

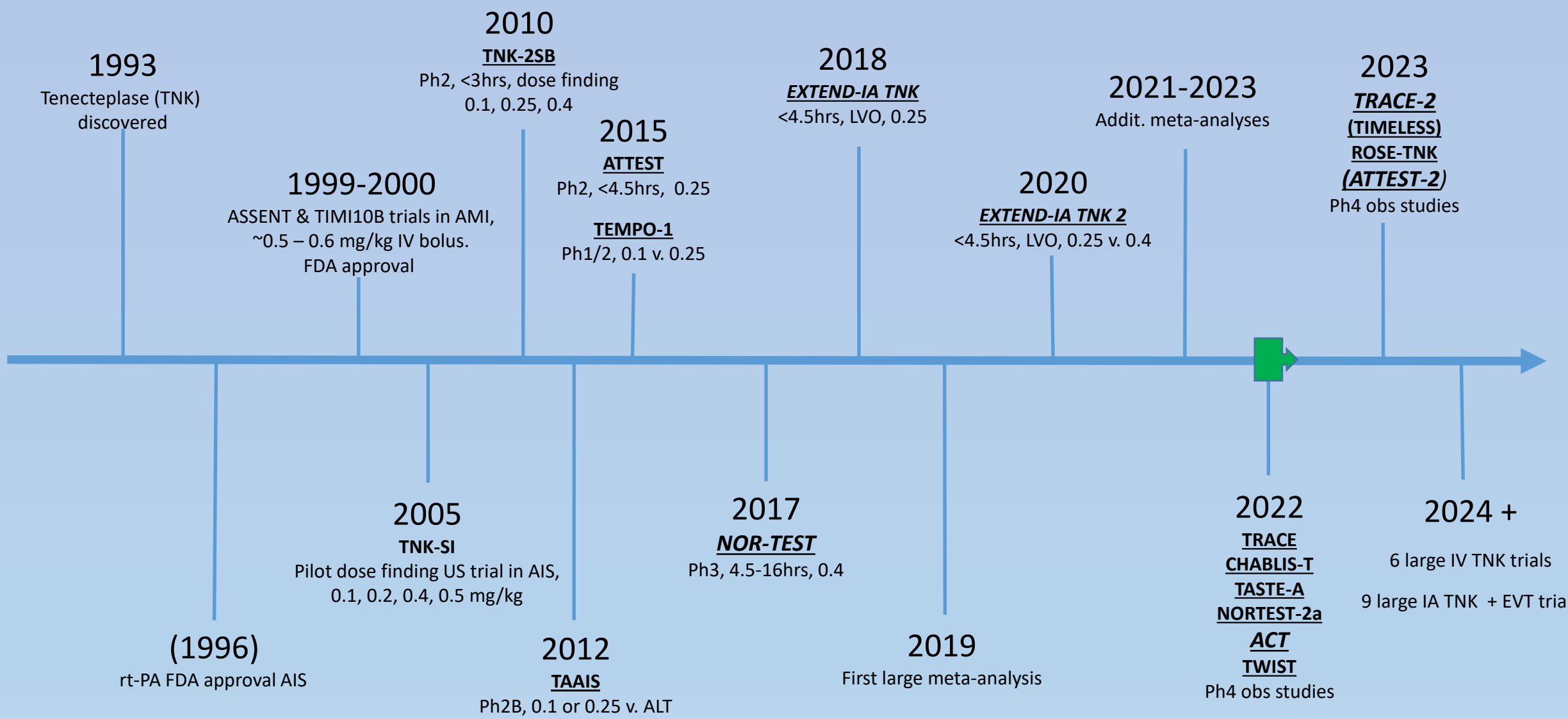
- Secondary subgroup analysis of Phase 3, large, PROBE, 22 ctrs in Canada, 2019-2022 (COVID)
- AIS, <4.5 hr, 530 LVO pts; 405 + EVT, TNK 0.25 v. ALT
- PEO = 90-120d mRS 0-1 (eFO), mRS 0-2 (gFO), EVT success reperf; SO = SICH, mort
- eFO→ 33% v. 30%; gFO→ 49% v. 51%; reperf 9% v. 10%
- SICH → 6% v. 4%; mort→ 20% v. 18%

Conclusion: Standard window IV TNK 0.25 → similar reperfusion, safety, and functional outcomes vs. ALT for AIS-LVO patients

ials

T trials

History of IV TNK



1993
Tenecteplase (TNK) discovered

1999
ASSENT & TIMI1
~0.5 – 0.6 mg
FDA ap

Pilot do
0.1,

(1996)
rt-PA FDA approval AIS

	Haley et al.	Parsons et al.	Huang et al.	Logallo et al.	Campbell et al.	Li et al.	Bivard et al.	Menon et al.	Kvistad et al.
Year	2010	2012	2015	2017	2018	2021	2022	2022	2022
Countries	United States	Australia	Scotland	Norway	Australia and New Zealand	China	Australia	Canada	Norway
Patients, *n*	112	75	96	1,100	202	236	104	1,577	204
TNK dose (s), mg/kg	0.1/0.25/0.4	0.1/0.25	0.25	0.4	0.25	0.1/0.25/0.32	0.25	0.25	0.4
Age, years, mean (SD) or median (IQR)	TNK 0.1: 67 (19); TNK 0.25: 69 (15); TNK 0.4: 68 (16); tPA: 72 (16)	TNK 0.1: 72 (6.9); TNK 0.25: 68 (9.4); tPA: 70 (8.4)	TNK: 71 (12); tPA: 71 (13)	TNK: 70.8 (14.4); tPA: 71.2 (13.2)	TNK: 70.4 (15.1); tPA: 71.9 (13.7)	TNK 0.1: 62.4 (11.1); TNK 0.25: 64.3 (12.8); TNK 0.32: 64.8 (12.1); tPA: 66.5 (12.6)	TNK: 76 (60–84); tPA: 73 (61–80)	TNK: 74 (63–83); tPA: 73 (62–83)	TNK: 73.2 (12.6); tPA: 68.6 (15.6)
Sex, male	58 (51.8%)	38 (50.7%)	61 (63.5%)	660 (60%)	110 (54.5%)	170 (72%)	63 (60.6%)	822 (52.1%)	98 (48.0%)
Severity (NIHSS), mean (SD) or median (IQR)	TNK 0.1: 8 (5–11); TNK 0.25: 10 (6–15); TNK 0.4: 9 (5–17); tPA 13 (5–17)	TNK 0.1: 14.5 (2.3); TNK 0.25: 14.6 (2.3); tPA: 14.0 (2.3)	TNK: 12 (9–18); tPA: 11 (8–16)	TNK: 5.6 (5.4); tPA: 5.8 (5.2)	TNK: 17 (12–22); tPA: 17 (12–22)	TNK 0.1: 7 (5–10); TNK 0.25: 8 (5–12); TNK 0.32: 7.5 (6–12); tPA: 8 (5–12)	TNK: 8 (5–14); tPA: 8 (5–17)	TNK: 9 (6–16); tPA: 10 (6–17)	TNK: 13.4 (6.6); tPA: 13.2 (6.4)
Permitted time window	<3 h	<6 h	<4.5 h	<4.5 h	<4.5 h	<3 h	<4.5 h	<4.5 h	<4.5 h
Onset to treatment, min, median (IQR) or mean (SD)	–	Overall: 174 (48); TNK 0.1: 186 (54); TNK 0.25: 180 (42) tPA: 162 (48)	TNK: 180 (156–215); tPA: 200 (160–220)	TNK: 118 (79–180); tPA: 111 (80–174)	TNK: 125 (102–156); tPA: 134 (104–176)	TNK 0.1: 154 (56–195); TNK 0.25: 149 (80–179); TNK 0.32: 147 (69–220); tPA: 153 (18–187)	TNK: 45 (34–66); tPA: 50 (32–69)	TNK: 128 (93–186); tPA: 131 (95–188)	TNK: 92.5 (74–143); tPA: 99 (73–143)
Atrial fibrillation	–	28 (37.3%)	34 (35.4%)	119 (10.8%)	–	32 (13.6%)	15 (14.6%)	–	17 (8.3%)
Hypertension	89 (79.5%)	47 (62.7%)	48 (50%)	482 (43.8%)	–	157 (66.5%)	61 (58.7%)	–	104 (51.0%)
Dyslipidemia	56 (50%)	37 (49.3%)	11 (11.5%)	126 (11.5%)	–	51 (21.6%)	43 (41.3%)	–	63 (30.9%)
Diabetes mellitus	21 (18.8%)	15 (20.0%)	14 (14.6%)	144 (13.1%)	–	49 (20.8%)	28 (27.2%)	–	28 (13.7%)
Current smoker	16 (14.2%)	15 (20.0%)	23 (24.0%)	346 (31.5%)	–	95 (40.2%)	17 (16.5%)	–	49 (24%)
sICH definition	NINDS study	SITS-MOST	ECASS II	ECASS III	SITS-MOST	ECASS III	SITS-MOST	SITS-MOST	ECASS III

23
yses

2022
TRACE
HABLIS-T
TASTE-A
ORTEST-2a
ACT
TWIST
obs studies

2023
TRACE-2
(TIMELESS)
ROSE-TNK
(ATTEST-2)
Ph4 obs studies

2024 +
6 large IV TNK trials
9 large IA TNK + EVT trials

Kobeissi et al. *Front Neurol*, 2023

History of IV TNK

1993
Tenecteplase (TNK) discovered

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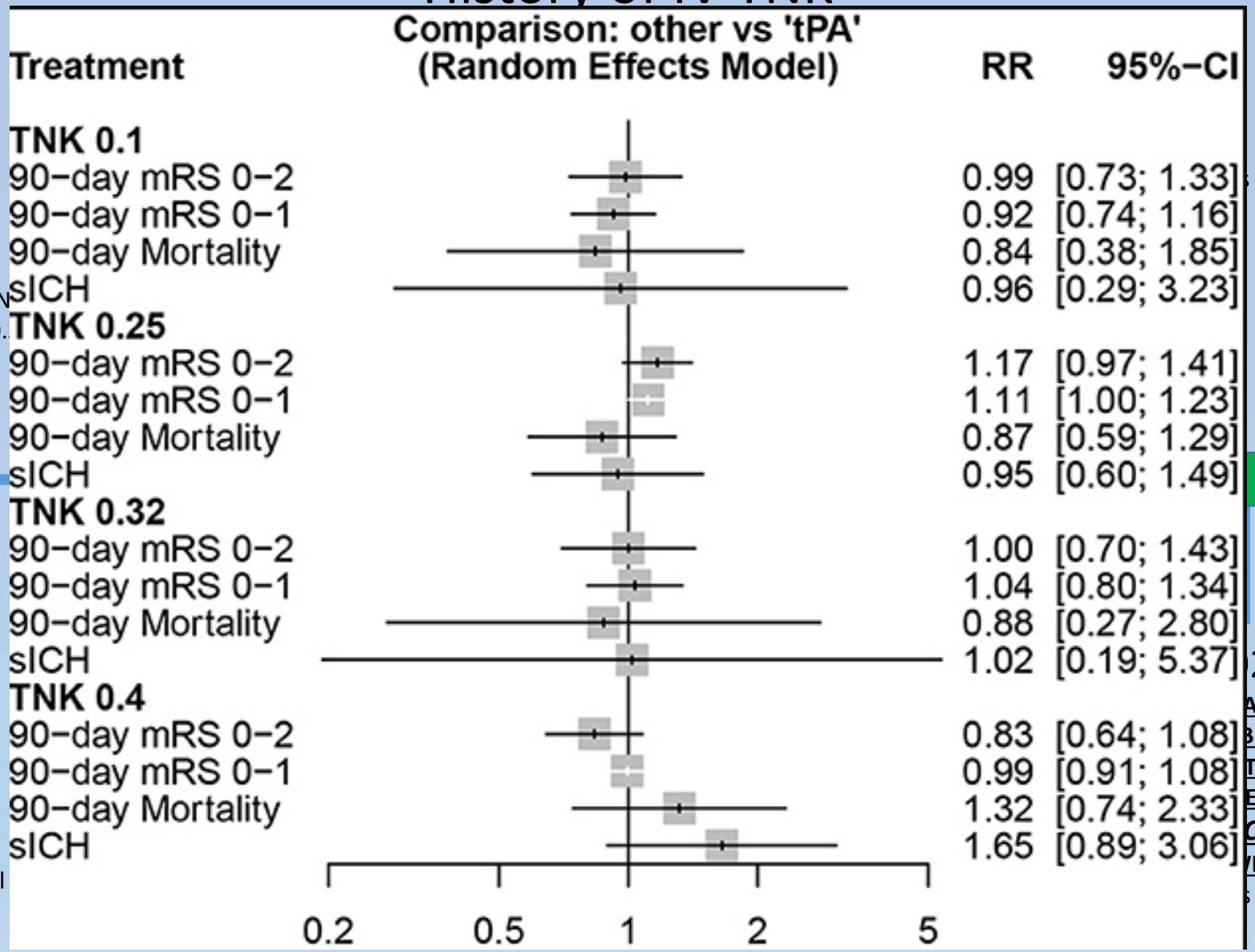
~0.

(1996)
rt-PA FDA approval



22
ACE
BLIS-T
TE-A
EST-2a
CT
IST
s studies

2023
TRACE-2
(TIMELESS)
ROSE-TNK
(ATTEST-2)
Ph4 obs studies

2024 +

6 large IV TNK trials

9 large IA TNK + EVT trials

Kobeissi et al. *Front Neurol*, 2023

History of IV TNK

1993

Tenecte
disc

rt-PA FDA approval AIS

2010

TNK-2SB

TAAIS
Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2023

TWIST
Ph4 obs studies

ials

T trials

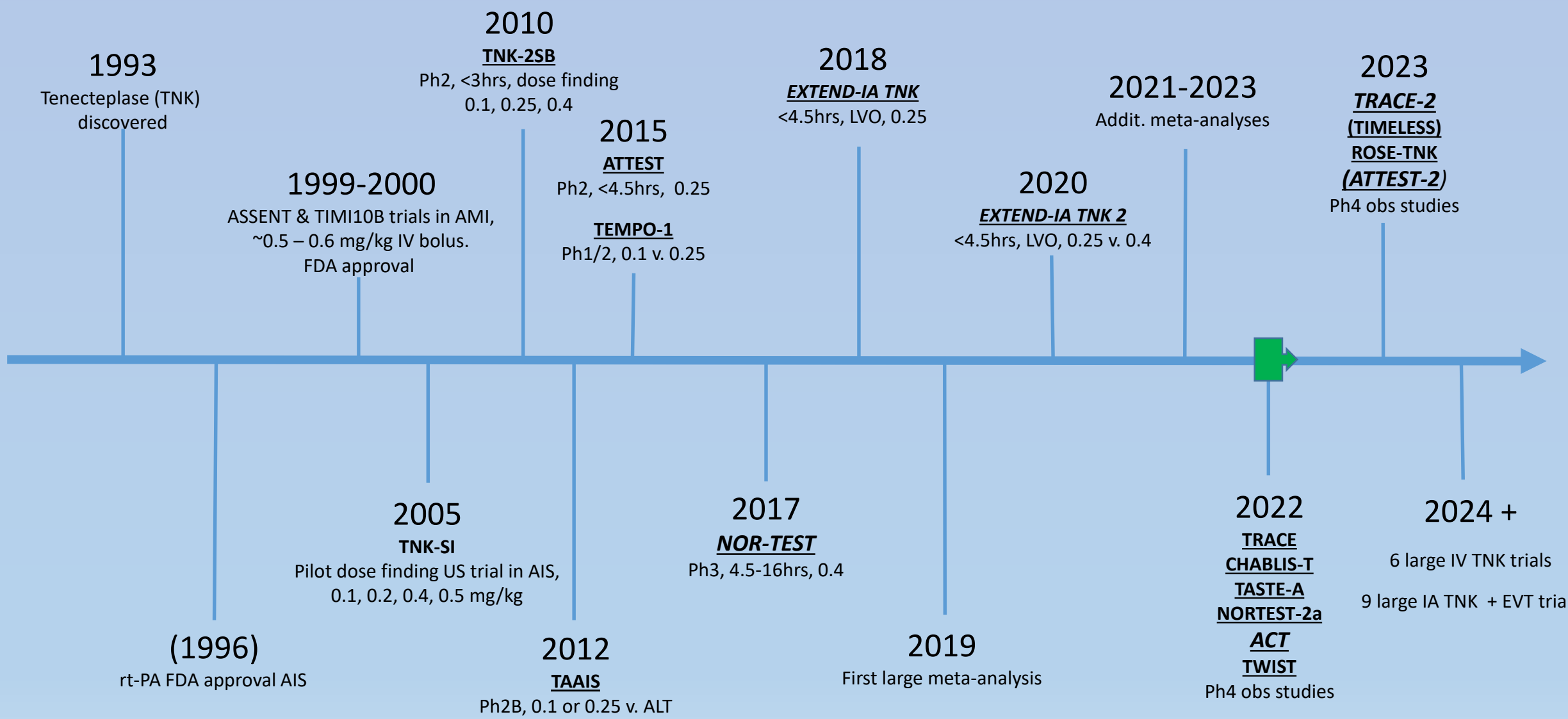
TWIST

Roaldsen et al, *Lancet Neurol* 2022

- Phase 3, medium, PROBE, 77 ctrs/10 countries (EU and Aus/NZ), 2017-2021
- Wake up AIS symptoms (incl. limb weakness & aphasia or NIHSS>2), (-) head CT, IV TNK 0.25 v. Placebo (w/in 4.5 hrs of w.u.), +/- EVT
- 578 patients (288 T; 290 P)
- PEO = improved 90d mRS FO; SO = SICH, mort
- FO→ OR 1.2 (0.88 – 1.6)
- SICH → 2% v. 1%; mort→ 10% v. 8%

Conclusion: Late window IV TNK 0.25 not assoc with better functional outcomes for select wake up AIS patients, with similar safety profile vs. no thrombolysis. Not recommended.

History of IV TNK



History of IV TNK

1993
Tenect
di

2010
TNK-2SB
Ph2. <3hrs. dose finding

2018

2021-2023

2023

ASCENSION NETWORK STUDY

Warach et al, *Stroke*, 2022

- Medium, retrospective, obs, non-randomized, study, 10 Ascension Seton hosp in TX, from 9/2017 – 12/2020. Switch to TNK 9/2019
- "Routine clinical practice" use of TNK vs. ALT for AIS, CSC & PSCs, 22/24% EVT, ~60% Class 1 criteria
- TNK 243 v. ALT 354 pts. Outcomes: Times (<45 min DTN, <90 min DIDO), FO, SICH, Cost
  - DTN → 41% > 29%; DIDO 37% > 14%
  - GFO → OR 1.26 (0.89 – 1.8); UFO OR 0.77 (0.42 – 1.37)
  - SICH→ 1.7% v. 2.8%; OLAG → 1.3% v. 0.3%
  - Cost → $13.3K < $15.8K

Conclusion: TNK for AIS in RCP 10 hosp system→ improved DTN/DIDO times, non-inferior functional clinical outcomes and reduced hosp costs

+

trials

EVT trials

(1996)
rt-PA FDA approval AIS

2012
TAAIS
Ph2B, 0.1 or 0.25 v. ALT

2019
First large meta-analysis

ACT
TWIST
Ph4 obs studies

History of IV TNK

1993

(1996)
rt-PA FDA approval AIS

2010
TNK-2SB
Ph2, <3hrs, dose finding

Pilot dose finding US trial in AIS,
0.1, 0.2, 0.4, 0.5 mg/kg

2012
TAAIS
Ph2B, 0.1 or 0.25 v. ALT

2018

PhIII, 4.5-16hrs, 0.4

2019
First large meta-analysis

2021-2022
TASTE-A
NORTEST-2a
ACT
TWIST
Ph4 obs studies

2023

+

trials

9 large IA TNK + EVT trials

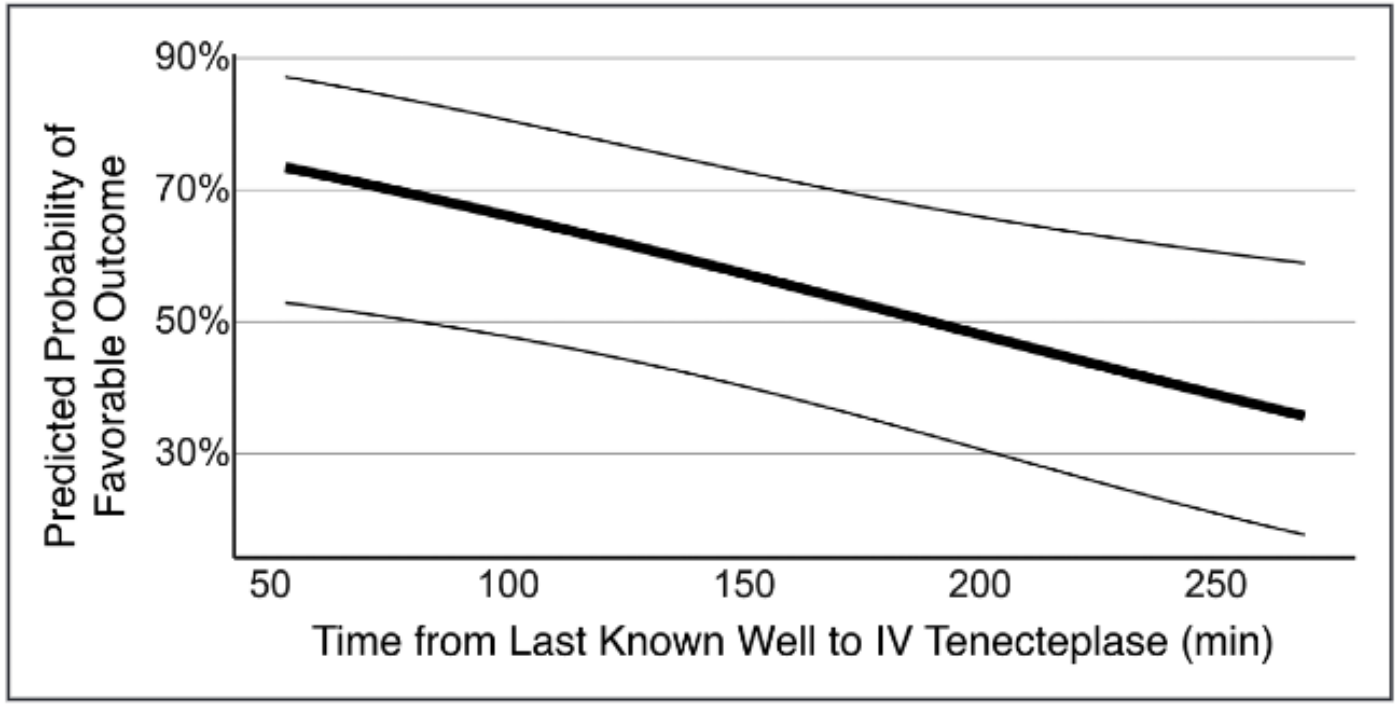


Figure. Relationship of time to treatment to probability of favorable outcome at discharge for tenecteplase treated patients.

An inverse relationship was observed in the time from stroke onset to the favorable discharge outcome of discharge to home walking independently, with adjusted odds ratio, 0.993 (0.987–0.998), *P*=0.01. The Figure plots this relationship with the 95% CI, holding the covariates constant at their average values: age (66.09 y), National Institutes of Health Stroke Scale (9.27), blood glucose on arrival (152 mg/dL), history of hypertension (no), dyslipidemia (no), and diabetes (no).

WHHS experience – Use & DTNs

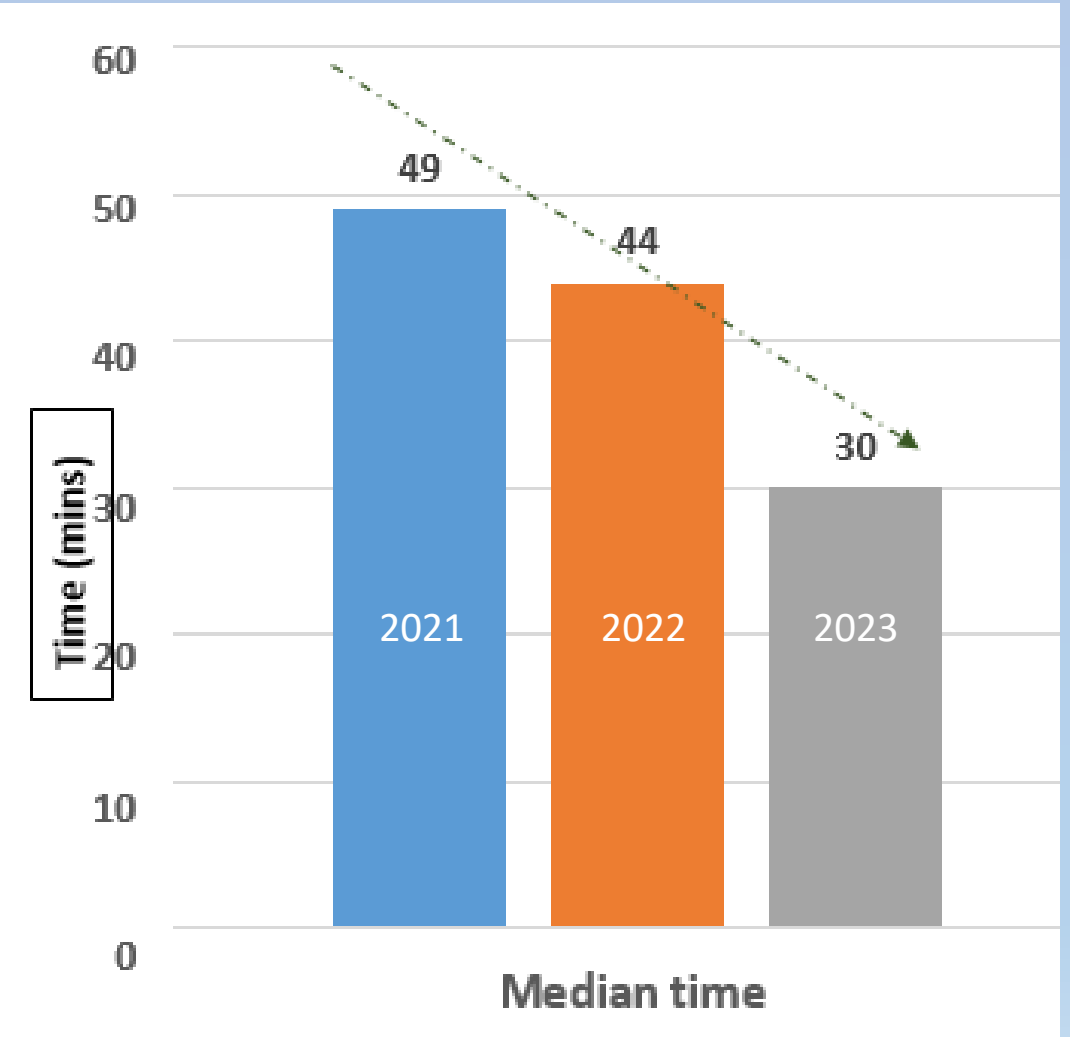
GWTG targets: ≥85% ≥75% ≥50%

Year	Total Ischemic strokes	tPA given* (%)	tPA DTN <60 min (%)	tPA DTN <45 min (%)	tPA DTN <30 min (%)
2021	297	31 (10%)	12 (39%)	5 (15%)	0 (0%)
2022	293	39 (13%)	25 (64%)	14 (36%)	5 (13%)
2023	237	38 (16%)	30 (79%)	24 (63%)	15 (39%)

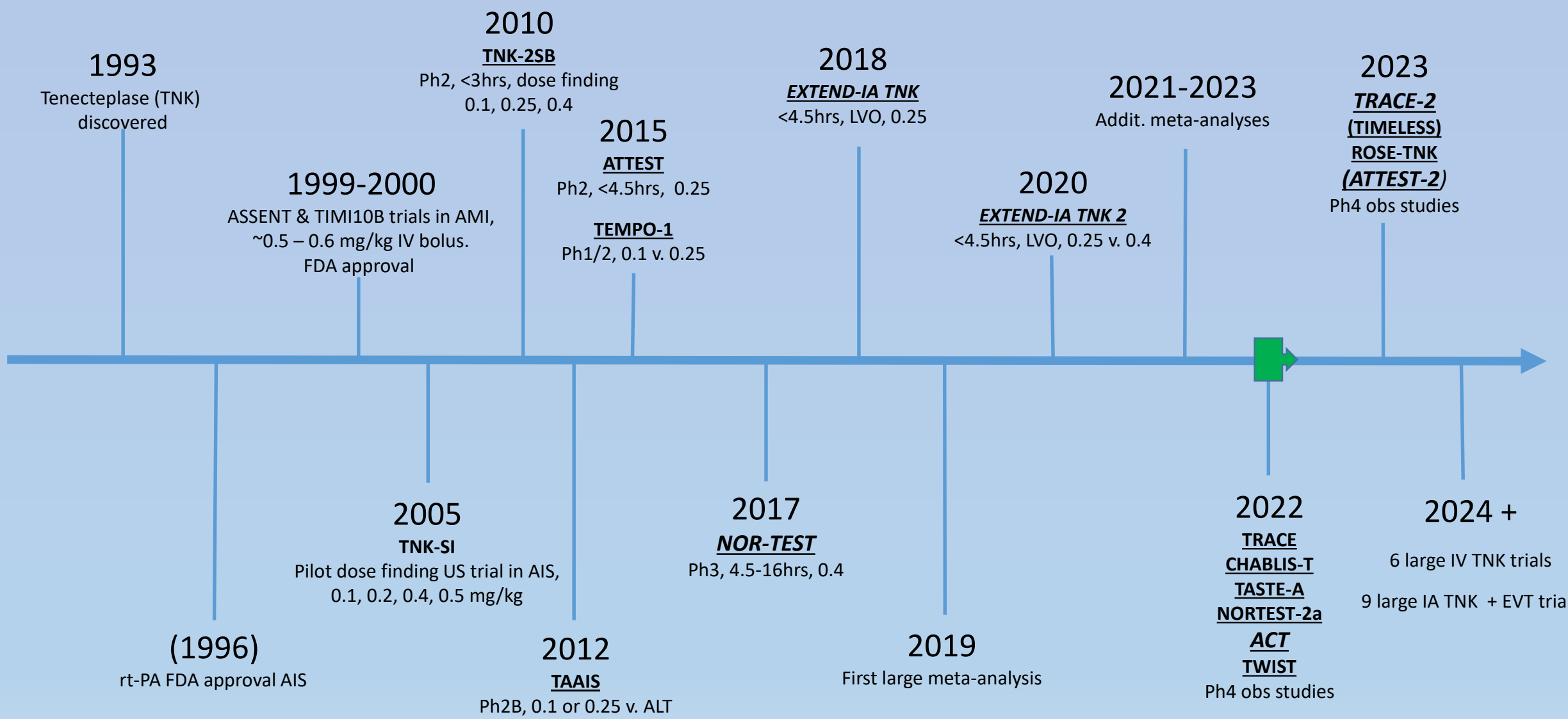
A T

* = given in ED

WHHS median tPA door-to-needle times: 2021 - 2023



History of IV TNK



History of IV TNK

1993

rt-PA FDA approval AIS

2010

TNK-2SB

TAAIS

Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2023

TWIST

Ph4 obs studies

trials

VT trials

CERTAIN sICH

Warach et al, *JAMA Neurol*, 2023

- Large, retrospective, obs, non-randomized, study, interN CERTAIN collab, >100 hosp USA/Aus/NZ, 2018-2021
- "Real world" use of TNK vs. ALT for AIS, mix CSC & PSCs, 9238 pts, 24% EVT
- 21% TNK; 79% ALT. T cases older, higher NIHSS, more EVT
- First project looked at safety (SICH rates)
- SICH→ T 1.8% < A 3.6%; adj.OR 0.42 (0.3-0.6)
  - (-) EVT → T 1.4 % < A 3% ; (+) EVT → 2.4% < 5.9%

Conclusion: Recent, non-randomized real world TNK use for AIS is associated with (~half) lower rate of SICH vs. ALT, regardless of +/- EVT.

WHHS experience – SICH

Year	Total Ischemic Strokes	tPA given	tPA percentage	SICH cases	SICH percentage
2017	279	41	15%	0	0
2018	247	45	18%	**2**	**4.4%**
2019	271	47	17%	**2**	**4.2%**
2020	270	37	14%	0	0
2021	297	31	10%	0	0
2022	293	40	14%	0	0
2023	237	39	16%	0	0

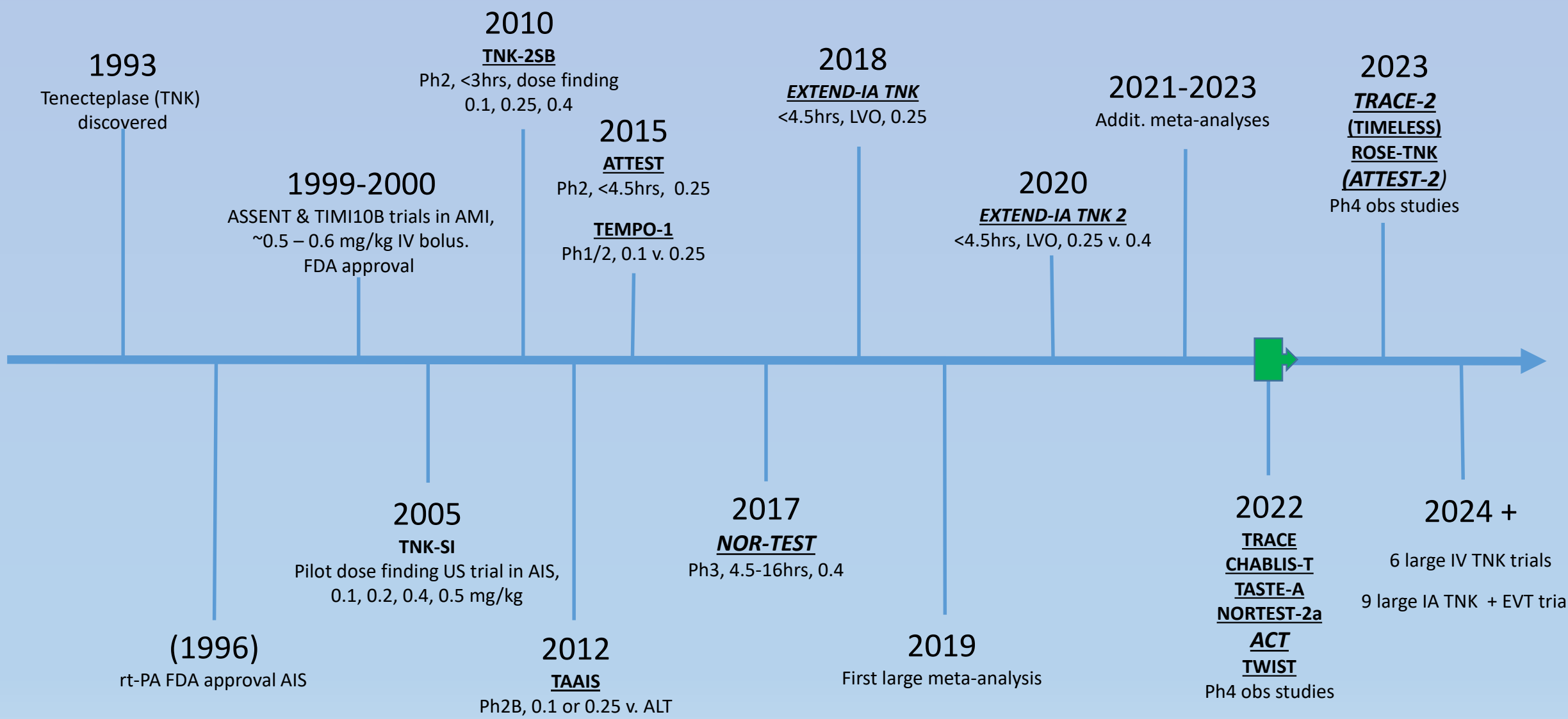
A

T

2%

0%

History of IV TNK



History of IV TNK

1993

Tenecte
disc

rt-PA FDA approval AIS

2010

TNK-2SB

Ph2, <3hrs, dose finding

TAAIS

Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2021-2022

TWIST

Ph4 obs studies

2023

TRACE-2

Wang et al, *Lancet* 2023

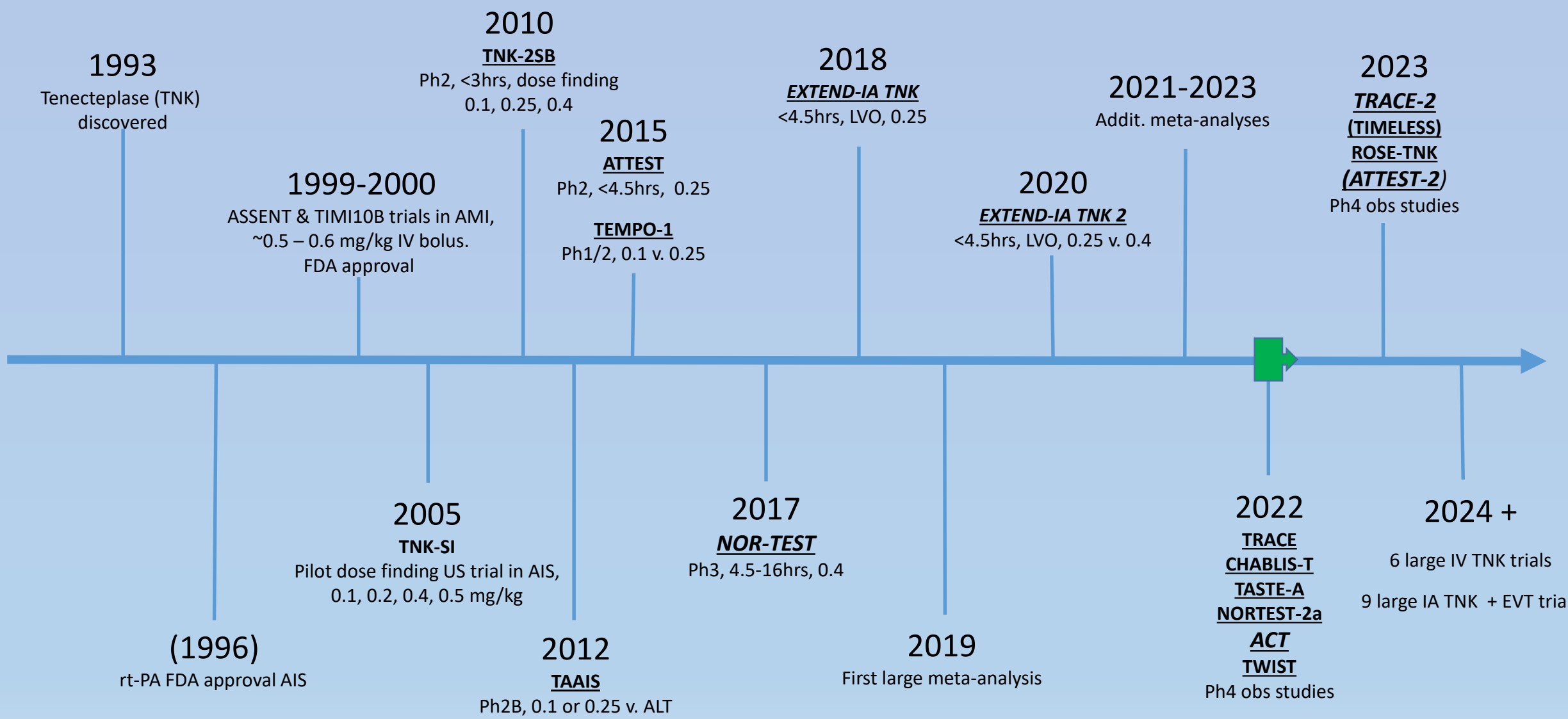
- Phase 3, large, PROBE, non-inferiority, 53 ctrs in China, 2021-2022
- AIS, <4.5 hrs, ineligible or refused EVT, IV TNK 0.25 v. ALT, 1430 pts
- PEO = 90d mRS 0-1 (eFO); SO = SICH, mort
- eFO→ 62% v. 58%
- SICH → both 2%; mort→ 7% v. 5%

Conclusion: Standard early IV 0.25 TNK is non-inferior to ALT for AIS pts not treated with EVT

ials

T trials

History of IV TNK



History of IV TNK

1993

Tenecte
disc

rt-PA FDA approval AIS

2010

TNK-2SB

Ph2, <3hrs, dose finding

TAAIS

Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2021-2022

2023

Albers et al, ESOC, 5/2023

TIMELESS

- Phase 3, medium, PRDBPCT, >100 ctrs USA/Canada, 2019-2023
- AIS, + LVO & fav CTP, IV TNK 0.25 v. placebo, 4.5 -24 hrs, 458 pts (~80% EVT)
- PEO = 90d mRS shift, full reperf; SO = SICH, mort. Avg time from TNK to EVT = 20min
- FO→ OR 1.1 (0.8-1.6), reperf 77% > 64%
- SICH → 3% v. 2%; mort→ both 20%
- M1 subgroup (~50% pts) → gFO 46% > 31%; M2 occl pts seemed to do worse

Prelim conclusion: Late window IV 0.25 TNK did not improve overall FO in AIS-LVO (mostly EVT treated) pts, but appeared relatively safe, and may benefit M1 occlusion pts (further study)

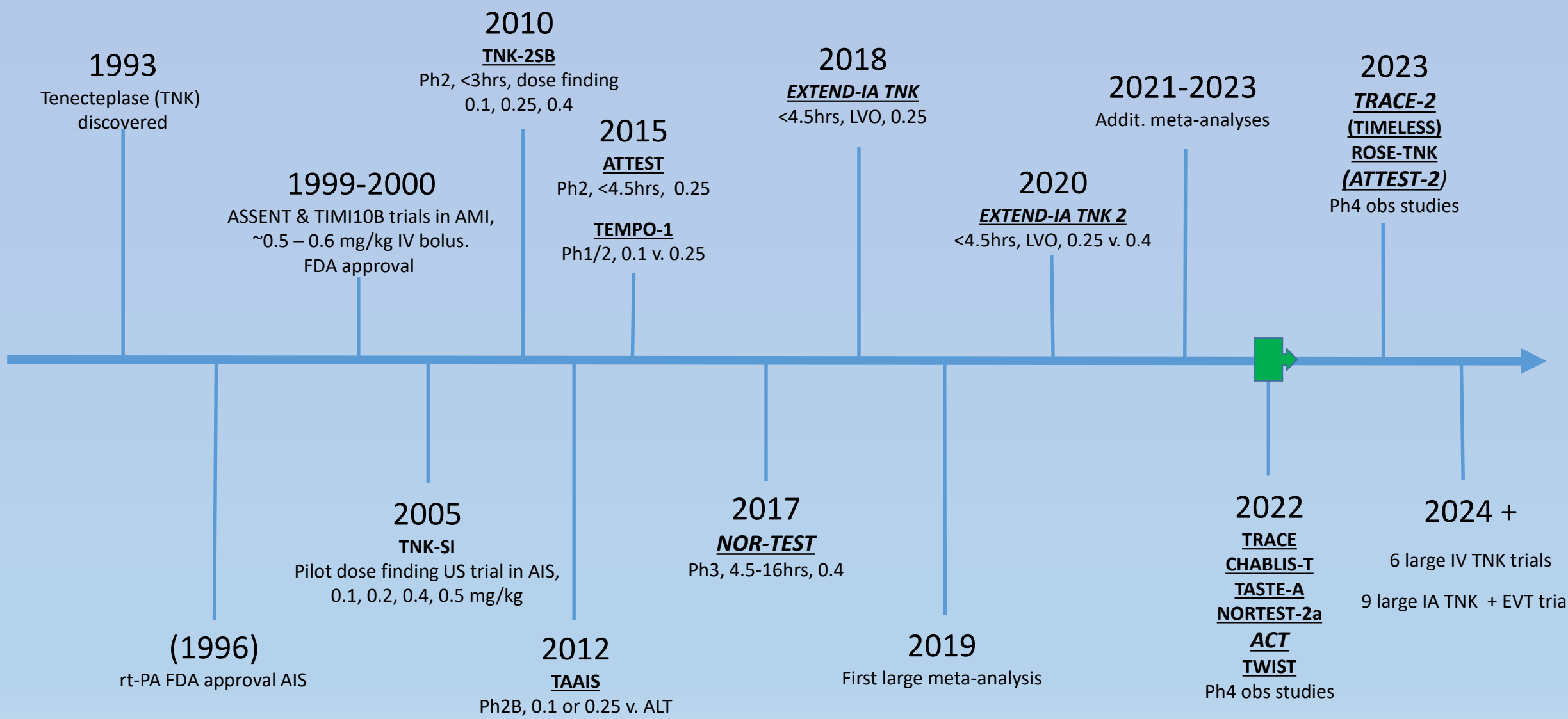
TWIST

Ph4 obs studies

ials

T trials

History of IV TNK



History of IV TNK

2010
TNK-2SB

1993
Tenecte
disc

2018

2023

rt-PA FDA approval AIS

TAAIS
Ph2B, 0.1 or 0.25 v. ALT

First large meta-analysis

TWIST
Ph4 obs studies

ials

T trials

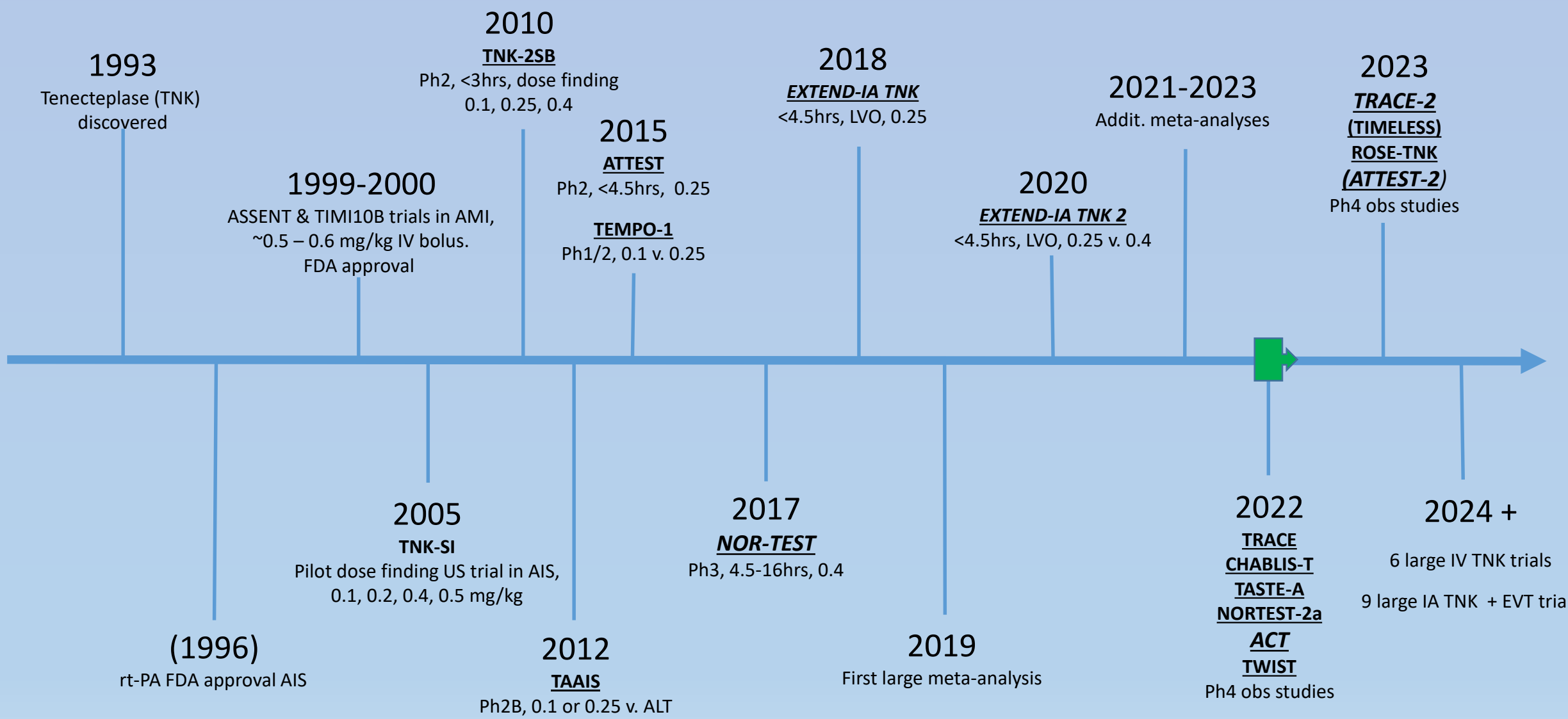
ROSE-TNK

Wang et al, *J Stroke*, 9/2023

- Phase 2, small, PROBE, 14 ctrs in China, 2021-2022
- AIS, 4.5 -24hrs & DWI +/FLAIR – MRI result, IV TNK 0.25 (vs. control), no EVT, 80 pts
- PEO = 90d mRS 0-1 (eFO), gFO; SO = SICH
- eFO→ 52% v. 50%; SICH → each 0%

Conclusion: Late window IV 0.25 TNK did not improve FO in MRI selected AIS pts, but showed no safety concerns

History of IV TNK



History of IV TNK

1993

Tenect
di

2010

TNK-2SB

Ph2, <3hrs, dose finding

2018

2021-2022

2023

ATTEST-2

Muir et al, WSC, 2023

- Phase 3, large, hierarchical PROBE, 40 ctrs in the UK, 2017-2023 (COVID pause)
- <4.5 hr time window, AIS, no EVT
- TNK 0.25 v. ALT, 1858 pts
- PEO = 90d mRS distribution; SO = SICH/all ICH, mort
- eFO→ 2% abs T>A benefit; gFO→ 3.4% abs T>A benefit (both n.i., not sup.)
- No signif safety differences

Prelim conclusion: For non-EVT AIS, <4.5hr IV 0.25 TNK is non-inferior to ALT

trials

VT trials

rt-PA FDA approval AIS

TAAIS

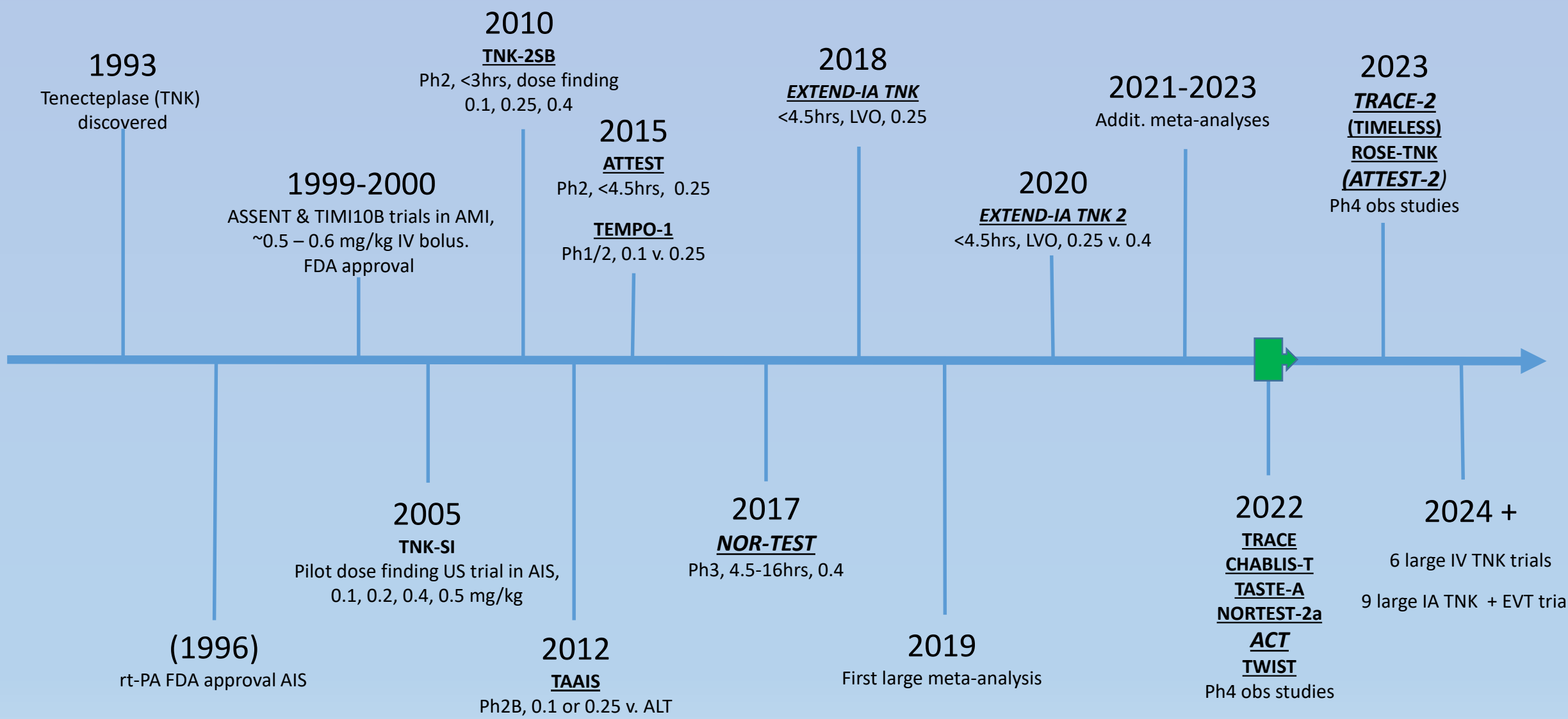
Ph2B, 0.1 or 0.25 v. ALT

First large meta-analysis

TWIST

Ph4 obs studies

History of IV TNK



History of IV TNK

1993

Tenectep
disc

2010

TNK-2SB

Ph2, <3hrs, dose finding

2018

2021-2022

2023

Active large IV TNK clinical trials

- NORTEST-2b (Norway) → <4.5hrs, AIS, NIHSS>5, 0.25 v. ALT, >800-1000 pts
- TASTE (AUS, EU, China) → <4.5hrs, AIS, 0.25 v. ALT, >1000 pts
- TEMPO-2 (Canada) → <12hrs, minor AIS or TIA, 0.25 v. AP, >1000 pts
- RESILIENT EXT IV (Brazil) → 4.5-24hrs, AIS, 0.25 v. P, >600 pts
- DIRECT-TNK (Brazil) → <4.5hrs, AIS-LVO, 0.25 + EVT v EVT, >500 pts
- EXTERNAL LVO (Aus) → <24hrs, AIS-LVO, 0.25 v. ALT v. P pre EVT, >700 pts
- POST-ETERNAL (Aus) → <24hrs, AIS-BAO, 0.25 v. ALT v. P pre EVT, >600 pts

als

trials

rt-PA FDA approval AIS

TAAIS

Ph2B, 0.1 or 0.25 v. ALT

First large meta-analysis

TWIST

Ph4 obs studies

History of IV TNK

1993

Tenecte
dis

rt-PA FDA approval AIS

2010

TNK-2SB

Ph2, <3hrs, dose finding

TAAIS

Ph2B, 0.1 or 0.25 v. ALT

2018

First large meta-analysis

2021-2022

TWIST

Ph4 obs studies

2023

trials

VT trials

Active IA TNK + EVT clinical trials

- TECHNO (EU)
- BRETIS-TNK2 II (China)
- INSIST-IT (China)
- RESCUE-TNK (China)
- ATTENTION-IA (China)
- ALLY (USA)
- EXTEND-AGNES TNK (Aus)
- ANGEL-TNK (China)
- ARTERIAL TNK BAO (China)

Conclusions

- Based on multiple RCTs, 0.25 mg/kg TNK ***is*** clinically non-inferior to ALT for < 4.5 hr standard AIS IV time window, +/- EVT
- TNK has many practical advantages over ALT, and published RWE supports significant decreased DTN times and decreased SICH rates
- Our 1.5+ year WHHS experience also demonstrates these benefits
- 0.4 mg/kg TNK dose should be avoided, given increased potential harm w/o additional efficacy benefit
- The FDA should approve 0.25 TNK as an alternative treatment for AIS <4.5 hours and the ASA should strengthen/expand their guidelines supporting TNK
- I strongly encourage stroke centers who haven't switched from ALT → TNK to do so!
- Use of IV TNK > 4.5 hrs IV or IA cannot yet be supported or discouraged until further RCTs are completed

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