Which is the best immune approach to replace ASCT?
CAR-T?

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DISCLOSURES

- Honoraria & Consulting:
  - BMS / Janssen / Takeda / Amgen / GSK
  - Karyopharm
  - Kadmon
  - Kite/ Gilead

Major disclosure – CARD CARRYING TRANSPLANTER

Questions to consider

- CAR-T or bispecific – which modality is likely to win?
- Transplant based Upfront Therapy in MM:
  - What's standard expectation in 2021?
  - Will improved induction and maintenance with ASCT move the goal post further?
- How do we know what is a win for CAR-T vs. ASCT?
  - MRD Assessment?
  - What should a trial look like?

CAVEAT:
All forward looking statements…..
No real comparative data

Benefits of Upfront ASCT …..

- Most reliable way to an **early MRD neg CR**
- Longest **upfront PFS** or PFS1 among current options
- A minority may never need any further therapy – **Cure Fraction**
- Long period **free of intense therapy** or any therapy
- Low Non-relapse mortality **(NRM)** - ~0.5% in RW studies
- **Safe** in elderly, dialysis dependent
- As Induction/maint improves – outcomes improve for the **"ASCT** package"
- **World-wide access** - arguably better than many drugs in MM

Front Runner CAR-Ts in RRMM

	KarMMa	Ciltacel	Orvacel
Med /Max Age	**61/78**	**61/78**	**61/77**
Median Prior	**6**	**5**	**6**
Bridging	**88**	**73**	**63**
ORR	**81%**	**97%**	**92%**
CR/sCR	**33%**	**67%**	**63%**
MRD- in evaluable	**94%**	**93%**	**84%**
PFS / DoR	**10.7**	**22.8/NR**	**NR**

	Ide-cel	Ciltacel
ORR	73%	97%
CR	33%	67%
MRD-, %	39%	54.6%
mPFS (all)	12.1*	23 mo
PFS in sCR	20.2*	Not reached

Main Messages:

Best single agent CR/ MRD/ ORR rates and PFS in RRMM

Non-curative modality .. At least in the RRMM setting

NRM : is not trivial (albeit in RR-MM population)

Idecel : 17 deaths unrelated to PD (N-140). **3 died within 8 weeks & 1 - 8 weeks – 6 mo. (Aspergillosis, GI Bleed, CRS, late onset CMV)**

Ciltacel: 9 deaths from non-PD related causes (N-113). ***Sepsis/CRS/HLH/Pneumonia/ AML***

Munshi N et al. N Engl J Med 2021; 384:705
Berdeja J et al Lancet 2021 398: P314

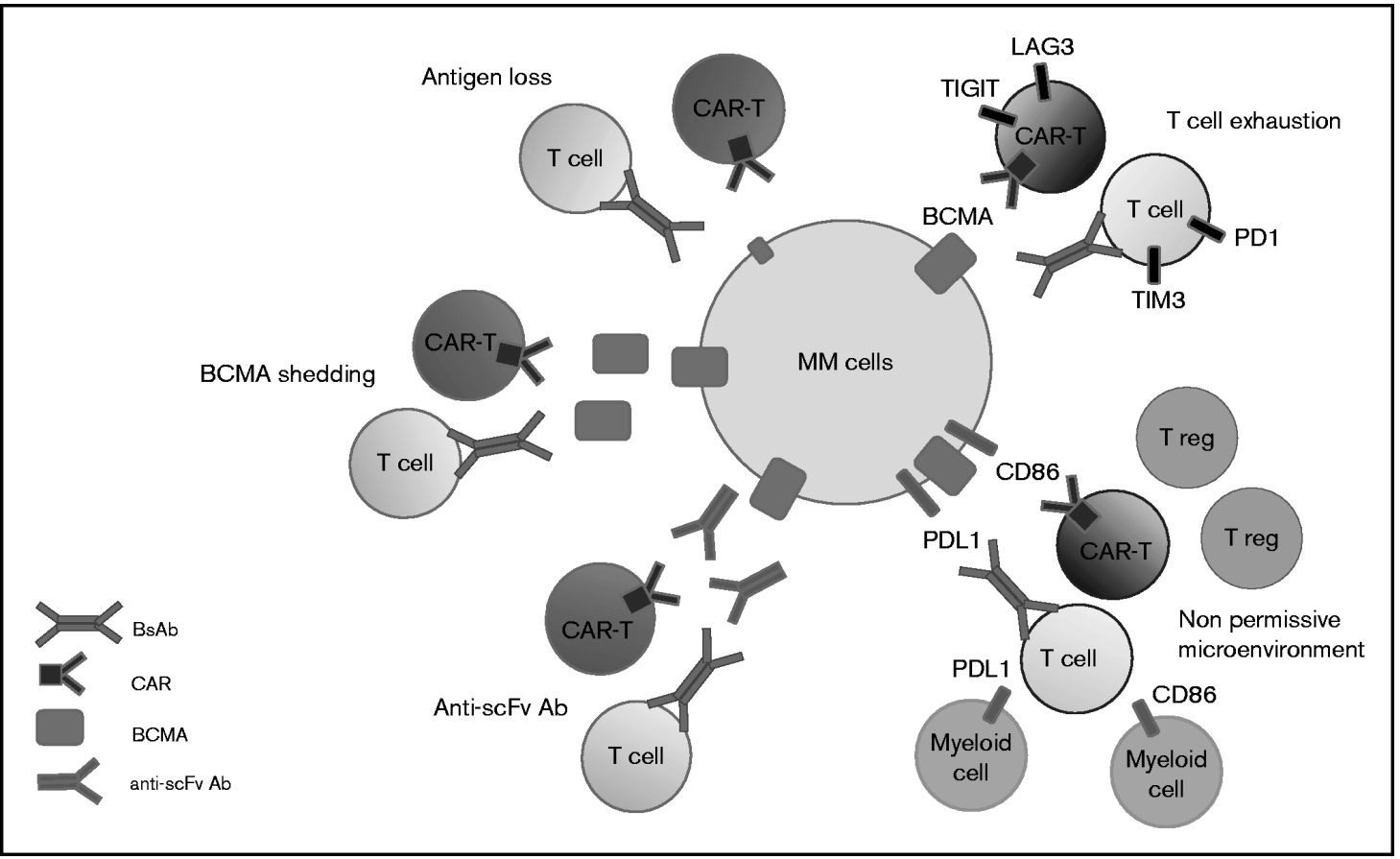
ASCT vs. CAR-T vs. BsAb –comparison

	ASCT	CAR-T (current data)	Bispecific BCMA Ab
Early MRD neg CR	REF	Better than ASCT	About the same as ASCT?
Disease free/ Rx free mo	~60 mo	Better if upfront ?	Unknown? BUT need Rx
Cure fraction?		Possible ? Better than ASCT?	**No idea; NEED continuous RX**
Hypogamma/ Immune Status	Reconst.	Worse than ASCT but improves?	**Ongoing issue; late hypogamma**
Access to center	World-wide	Manufacturer accredited	Easiest; off the shelf
NRM			Low /Late Infection risk?
Safety – Age/r comorbid			Safest
Effect on Cytogenetic HR		Better than ASCT?	
PFS	60 plus mo	UNKNOWN UNKNOWN	
Targets & Innovation	None	BCMA + …	BCMA/GPRC5D/FCRH5

Teclistamab in RRMM:
17 deaths unrelated to MM PD among 157 pts
Pneumonia/ Sepsis / Covid-19/ Gen deterioration
Profile of persistent hypogamma with rpt dosing
G≥3 infections in 45% of RP2D dosed pts

Usmani S et al Lancet 2021; Aug 10

Mechanisms of failure with CAR-T…



Will these be addressed by earlier use of CAR-T ?

T cell phenotype ?
Less clonally advanced MM responds better?

Hope of a cure with CAR-T… but

YES : T cells can mediate a cure – e.g. Allo HCT survivors; DLI
However – immune synapse is different
No active adaptation with CAR-T or bsAb
One modality may not cure

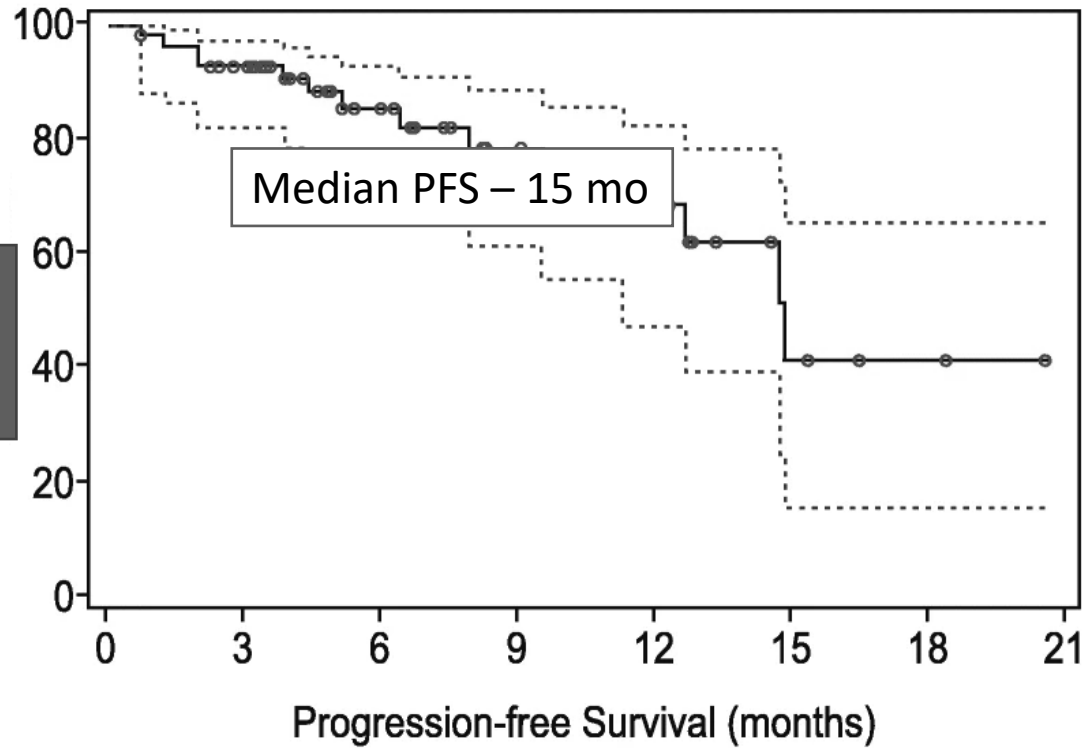
Gazeau N et al Effective anti-BCMA retreatment in multiple myeloma, Blood Adv, 2021

Earlier use of CAR-T leads to better PFS – can we assume?

LEGEND data from Chinese Study vs. CARTITUDE 1

Time from initial MM diagnosis, years	
Median (range)	4 (1 to 9)
Number of prior lines of therapy, n	
Median (range)	3 (1 to 9)
ASCT, n (%)	10 (18)
Prior therapies, n (%)	
Proteasome inhibitors	39 (68)
Immunomodulatory agents	49 (86)
Lenalidomide	25 (44)
Pomalidomide	2 (4)
Thalidomide	39 (68)
PI + IMIDs	34 (60)

ORR – 88%
CR – 63%
MRD Neg – 68%



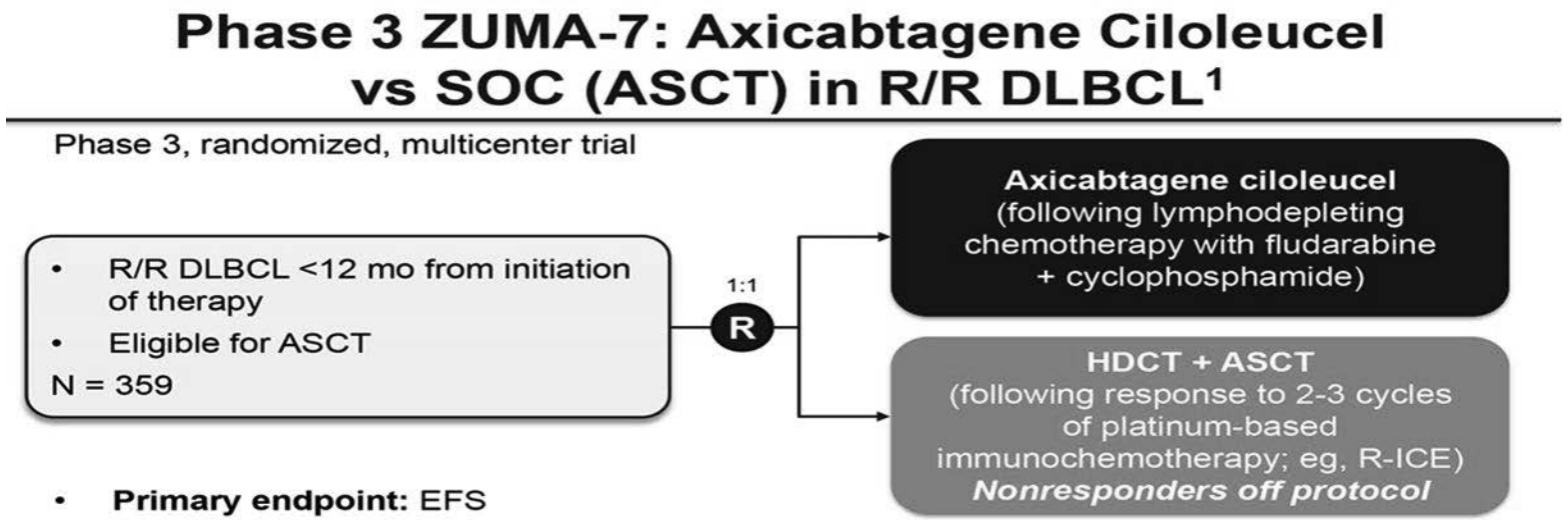
CARTITUDE-2 cohort A, Median 2 lines of prior therapy
ORR and MRD neg rates similar to CARTITUDE-1 at early time points

PFS will be better for single agent CAR-T consolidn post induction – Are we sure?

Zhao, WH et al. A phase 1, open-label study of LCAR-B38M.J Hematol Oncol 11, 141 (2018).

CAR-T vs. ASCT … What can lymphoma teach us?

- ZUMA-7 trial recently reported as “win” for CAR-T over ASCT in DLBCL



Study designed for a quick win!!
May not be the best option for pts or society

An MRD based study is easy to perform for upfront CAR-T in MM too …

Unlike in DLBLCL:

Neither modality is truly curative

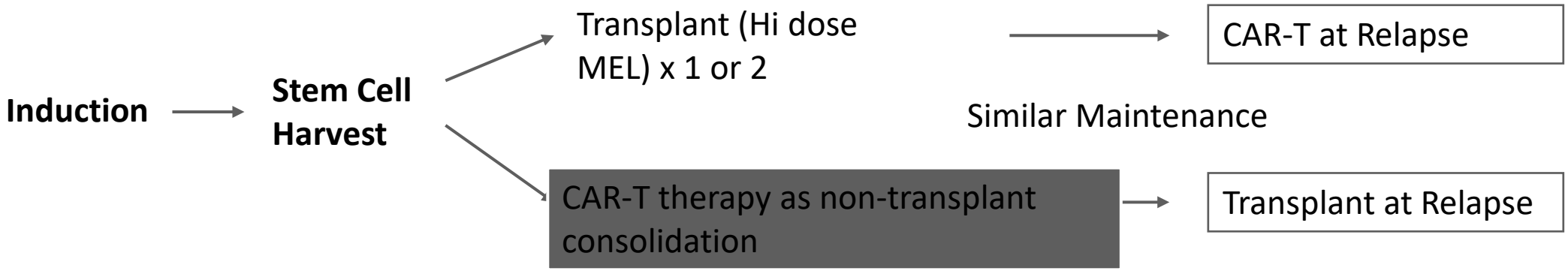
After induction very few pts will progress early and both groups will likely make it to CAR-T & ASCT

PFS / EFS will be defined by early relapsers who benefit from disease control in CAR-T arm i.e. HR-MM

So … should we limit a MM study to HR-MM only?

NOVEL AGENTS HAVE NOT ELIMINATED TRANSPLANT SO FAR .. Will CAR-T do it?

Resounding win so far for transplant – higher PFS/ RR/ MRD neg rates
(DETERMINATION II yet to read out)

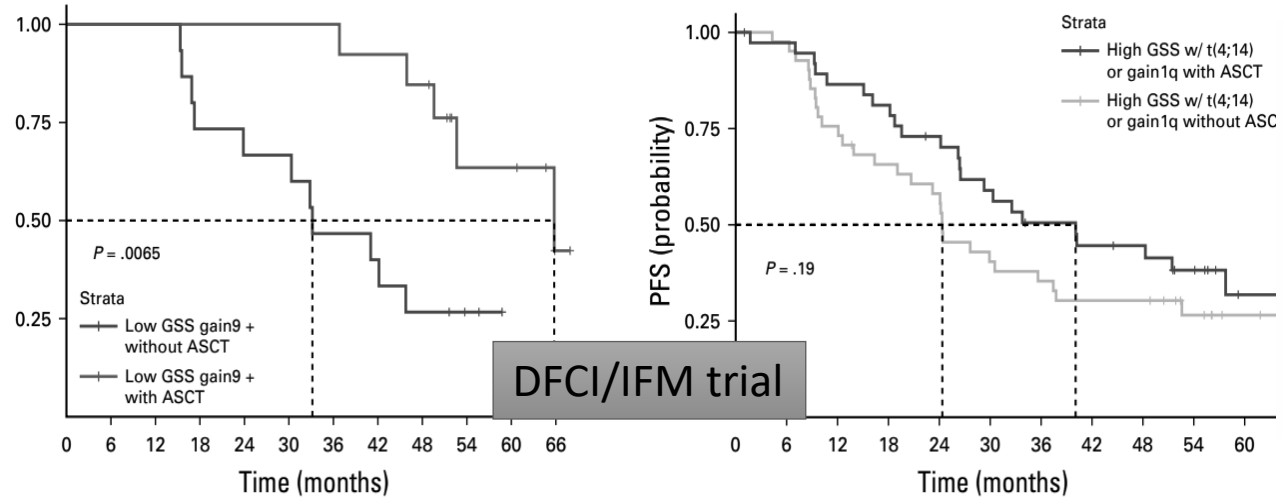


This design can answer the PFS qn for CAR-T replacing UPFRONT ASCT
But is that the right question for a million dollar therapy?
Sequencing ASCT-CAR-T or CAR-T-ASCT?
Reserve upfront CAR-T for pts predicted to NOT benefit from ASCT?

Even this design cannot answer
utility qn of CAR-T replacing ASCT
sequencing qn …. needs OS

ASCT- PFS– MRD in current era

Samur et al JCO 2020

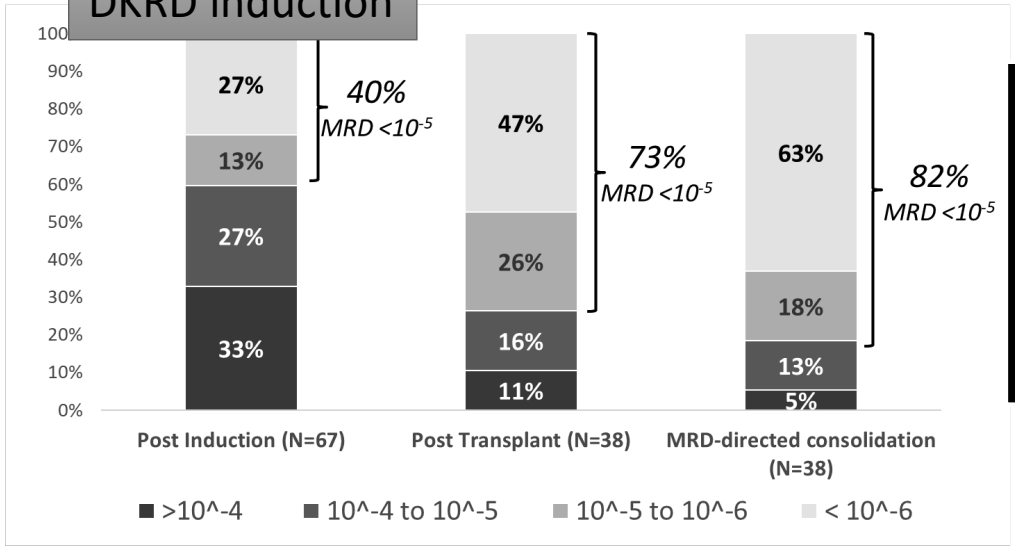


DFCI/IFM trial

UK MRC XI data – de Tute et al IMW 2021

	ASCT+3 PFS			ASCT+9 PFS		
	HR	95%CI	P	HR	95%CI	P
MRD (-ve vs +ve)	0.401	0.271-0.592	<0.0001	0.220	0.102-0.472	0.0001
Treatment (len vs obs)	0.388	0.268-0.561	<0.0001	0.218	0.102-0.463	<0.0001
Cytogenetics (UHiR+HR vs SR)	2.576	1.770-3.748	<0.0001	2.357	1.084-5.126	0.0305
	ASCT+3 OS			ASCT+9 OS		
MRD (-ve vs +ve)	0.457	0.246-0.849	0.0132	0.242	0.055-1.073	0.0619
Treatment (len vs obs)	0.528	0.297-0.938	0.0294	0.252	0.070-0.906	0.0347
Cytogenetics (UHiR+HR vs SR)	4.286	2.272-8.086	<0.0001	6.658	1.311-33.82	0.0222

DKRD induction



Costa L et al ASH 2019

ASCT helps PFS even in extremely good risk pts
ASCT improves MRD Neg Rates even with good induction
Even with MRD neg post ASCT – maintenance helps
New Induction + ASCT + consolidation – limited upward MRD room
HR & UHR pts with MRD neg still do poorly vs. SR-MM

MASTER trial

UPFRONT CAR-T projects

Industry led projects

Practical Issues :
SYNERGISTIC or Mutually exclusive?

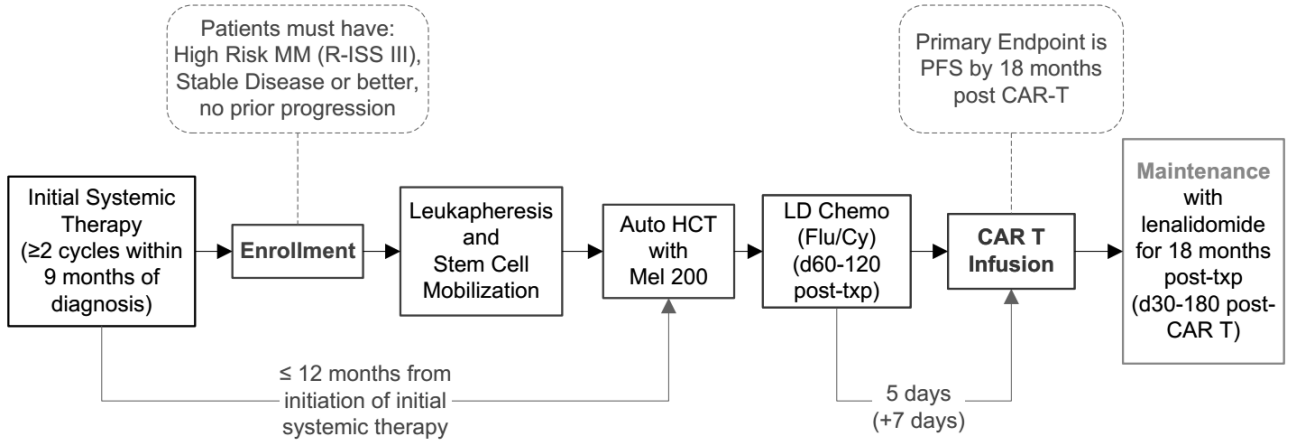
CAR-T after ASCT –
MRD convert those pos after ASCT &
Cure for SR-MM patients?

CAR-T before ASCT – wipe out persistence?

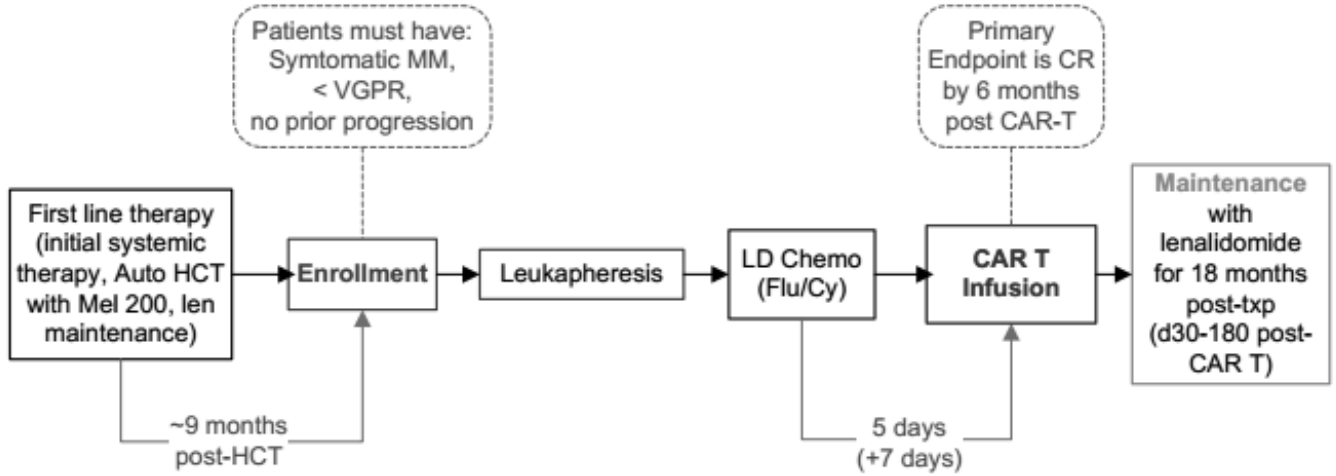
CAR-T using ASCT as a lymphodepleting tool?

Can we assess treatment discontinuation after 2 cell therapy modalities?

CTN 1901 Study Schema – HR-MM concept

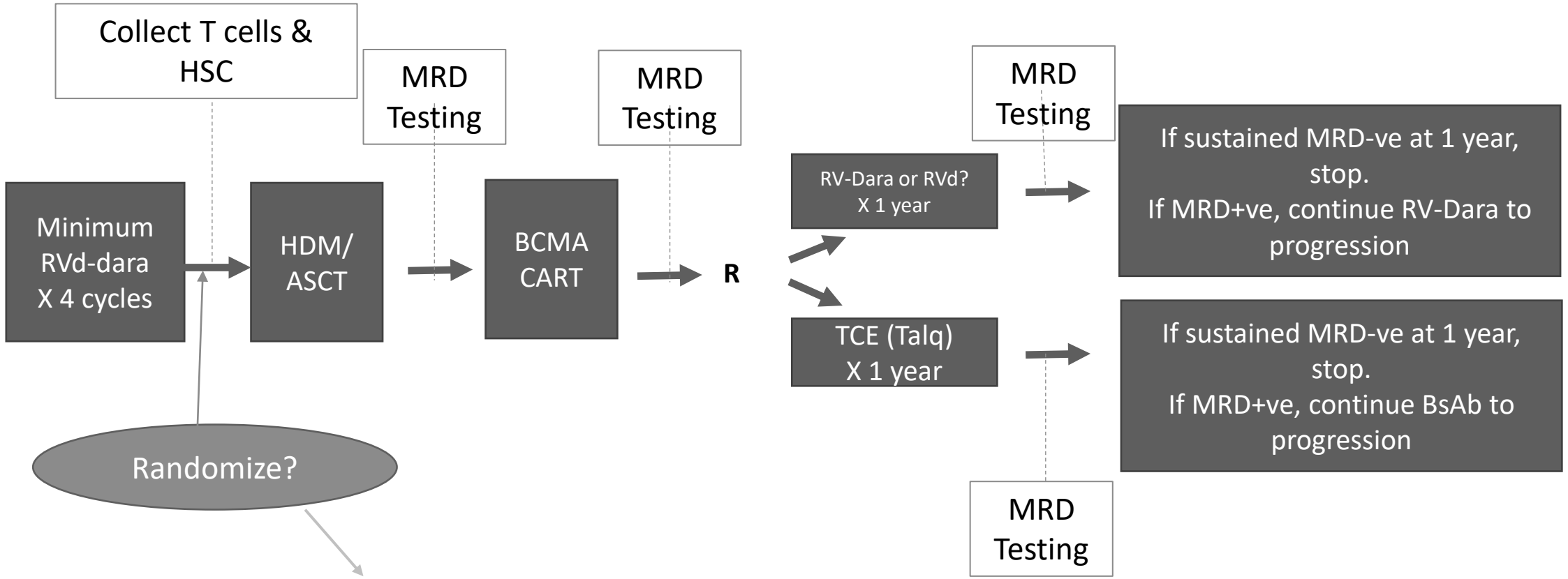


CTN 1902 Study Schema – Response upgrade concept



BMT CTN State of the Science
MM concept

- **HR and U HR disease ONLY**



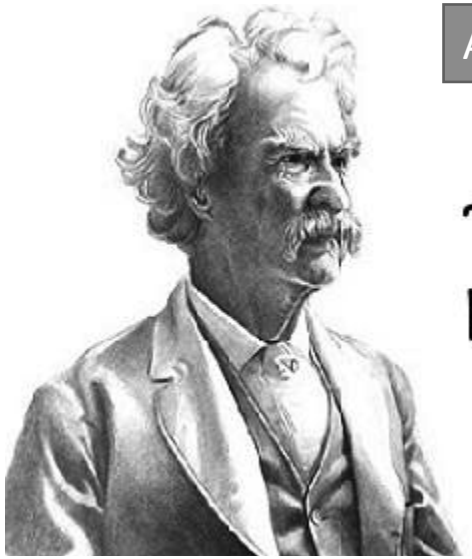
CONTROL POPULATION:
RVD-Dara x 4 → ASCT → RVd maintenance per Emory protocol

CAR-T BsAb & ASCT & some points to ponder

- CAR-T : Durable MRD Neg remissions (in RRMM setting)
  - Best option to replace / work with ASCT to get long upfront remissions
  - Best option for limiting therapy and increasing cure fraction without excess treatment
- Manufact
- Affordabi
- Competir
  - PBSC Collection after CAR-T possible?
  - Second CAR-T of the same kind does not usually work
- What got us here : Synergistic/ Additive use of all modalities:
  - Need trials of early CAR-T (before / instead of and after ASCT)
  - **Goal sus-MRD & Rx discontinuation**
  - **Cautious Optimism that BCMA CAR-T will do this**

For now - I will still collect & store PBSC in every TE pt
Equipoise on CAR-T vs. ASCT trials with crossover
Outcome of ASCT after CAR-T or BsAb -big unknown
Sustained use BsAb worry about immune reconstitution

Auto transplant in Myeloma 2021



The reports of my death have been greatly exaggerated.