

## Supplementary Online Content

Pidala J, Martens M, Anasetti C, et al. Factors associated with successful discontinuation of immune suppression after allogeneic hematopoietic cell transplantation. *JAMA Oncol*. Published online September 26, 2019. doi:10.1001/jamaoncol.2019.2974

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This supplementary material has been provided by the authors to give readers additional information about their work.

## **eMethods. Detailed Methodology**

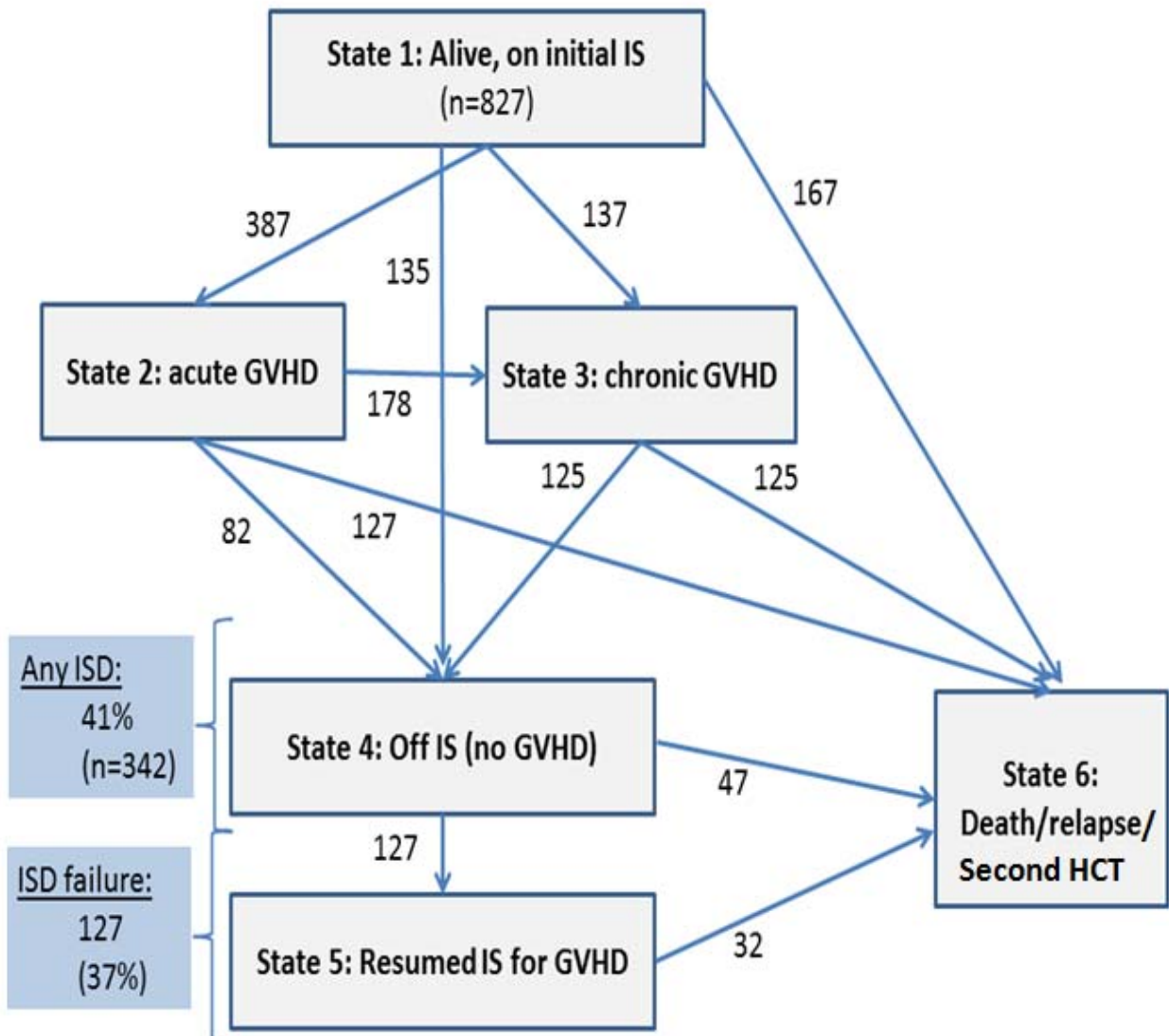
### Data collection schedule on BMT CTN 0201 and 0402 trials:

Weekly acute GVHD information was collected on both trials until day 98. For CTN 0201, acute GVHD and chronic GVHD information and IS data were collected at day 90, 120, 180, 365, 730, and 1095. For CTN 0402, acute GVHD and chronic GVHD information and IS data were collected at day 100, 120, 180, 270, 365, and 730. Data on acute GVHD, chronic GVHD, graft failure, relapse and death underwent review by an endpoint review committee as part of the primary analysis for both trials.

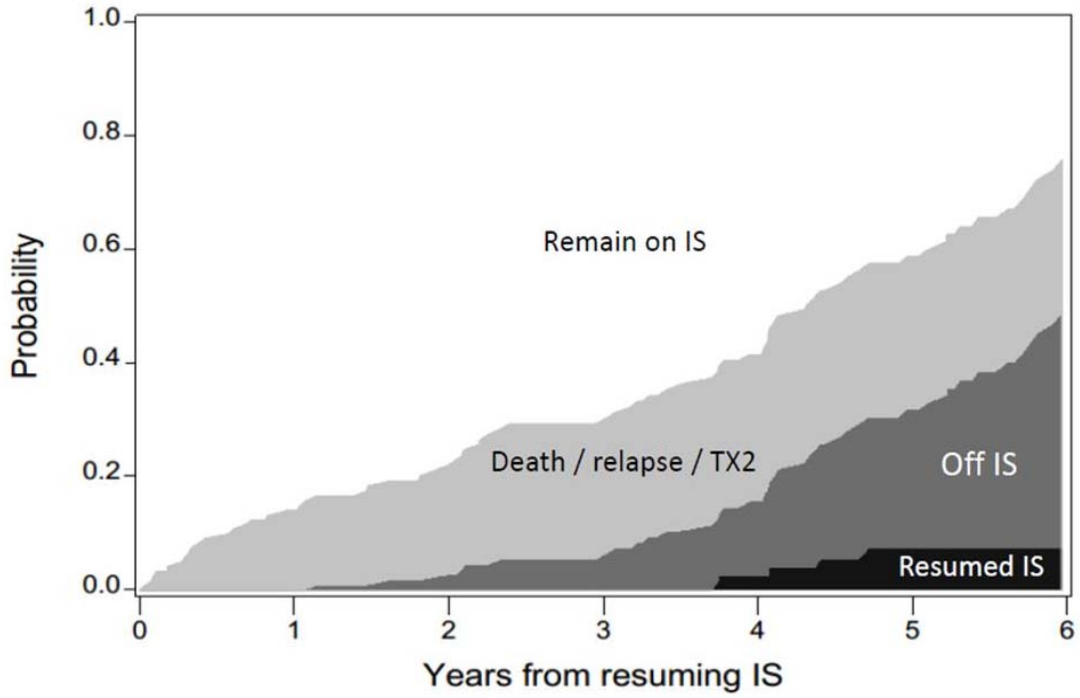
### IS taper recommendations on BMT CTN 0201 and 0402 trials:

The 0201 protocol recommended initiation of IS taper (either cyclosporine or tacrolimus) at 50 days post-HCT in the absence of GVHD with slow taper over a minimum of 20 weeks to complete ISD. The 0402 trial recommended sirolimus and tacrolimus taper initiation at 100 days post-HCT in the absence of GVHD and disease relapse with the goal of complete ISD by 6 months post-HCT.

**eFigure 1. Multistate model for discontinuation of IS. Numbers by each transition line indicate the number of patients undergoing that transition.**



**eFigure 2. State probability from time of ISD failure (resuming IS for GVHD occurring after failed ISD attempt).**



Remain on IS	86%	78%	71%	59%	41%	24%
Death / relapse / 2 <sup>nd</sup> transplant	14%	19%	24%	26%	27%	27%
Off IS	0%	3%	5%	13%	25%	41%
Resumed IS for GVHD	0%	0%	0%	2%	7%	7%

**eTable 1. Characteristics of Patients From CTN 0201 and CTN 0402**

	<b>CTN 0201</b>	<b>CTN 0402</b>	<b>TOTAL</b>
Variable	N (%)	N (%)	N (%)
<b>Total number of patients</b>	<b>526</b>	<b>301</b>	<b>827</b>
Age at transplant, years			
Median	44 (<1-67)	44 (13-59)	44 (<1-67)
Karnofsky performance score			
≥90	328 (62)	215 (71)	543 (66)
<90	142 (27)	86 (29)	228 (28)
Unknown	56 (11)	0 (0)	56 (7)
Disease			
AML	252 (48)	134 (45)	386 (47)
ALL	111 (21)	117 (39)	228 (28)
CML	63 (12)	22 (7)	85 (10)
MDS	87 (17)	26 (9)	113 (14)
Acute Biphenotypic Leukemia	0 (0)	2 (1)	2 (<1)
CMML	7 (1)	0 (0)	7 (1)
Agnogenic Myeloid Metaplasia with Myelofibrosis	6 (1)	0 (0)	6 (1)
Patient race/ethnicity			
White-non Hispanic	444 (84)	215 (71)	659 (80)
Any race-Hispanic	22 (4)	49 (16)	71 (9)
Black-non Hispanic	21 (4)	13 (4)	34 (4)
Others/unknown	39 (7)	24 (8)	63 (8)
Disease risk			
Early	241 (46)	235 (78)	476 (58)
Intermediate	131 (25)	46 (15)	177 (21)
Advanced	154 (29)	20 (7)	174 (21)
Conditioning regimen			
Cy+TBI	248 (47)	243 (81)	491 (59)
Bu+Cy	160 (30)	0 (0)	160 (19)
VP16+TBI	0 (0)	58 (19)	58 (7)
Fludarabine+Melphalan	40 (8)	0 (0)	40 (5)
Fludarabine+Bu+ATG	78 (15)	0 (0)	78 (9)
Donor type			
Matched sibling donor	0 (0)	301 (100)	301 (36)
Unrelated 8/8	409 (78)	0 (0)	409 (49)
Unrelated 7/8	105 (20)	0 (0)	105 (13)
Unrelated <7/8	12 (2)	0 (0)	12 (1)
Unrelated donor age at transplant, years			
Median	33 (18-61)	NA	33 (18-61)

Recipient/donor gender match			
M-M	225 (43)	85 (28)	310 (37)
M-F	71 (13)	63 (21)	134 (16)
F-M	140 (27)	78 (26)	218 (26)
F-F	90 (17)	49 (16)	139 (17)
M (donor unknown)	0 (0)	12 ( 4)	12 ( 1)
F (donor unknown)	0 (0)	14 ( 5)	14 ( 2)
Donor parity			
Parous female	65 (12)	83 (28)	148 (18)
Non-parous female	90 (17)	29 (10)	119 (14)
Female-unknown parity	6 ( 1)	0 (0)	6 ( 1)
Male	365 (69)	163 (54)	528 (64)
Donor gender unknown	0 (0)	26 ( 9)	26 ( 3)
Graft type			
Bone marrow	264 (50)	0 (0)	264 (32)
Peripheral blood stem cell	262 (50)	301 (100)	563 (68)
ATG use			
No ATG	376 (71)	301 (100)	677 (82)
ATG	137 (26)	0 (0)	137 (17)
Unknown	13 ( 2)	0 (0)	13 ( 2)
GVHD prophylaxis			
CSA/MTX	121 (23)	0 (0)	121 (15)
Tacrolimus/MTX	378 (72)	152 (50)	530 (64)
Tacrolimus/Sirolimus	3 ( 1)	149 (50)	152 (18)
Other	24 (5)	0 (0)	24 (3)
Duration of follow up among survivors, months (median, range)	79 (11-124)	61 (24-97)	72 (11-124)

\***Disease:** AML – acute myelogenous leukemia, ALL – acute lymphoblastic leukemia, MDS – myelodysplastic syndrome, CMML – chronic myelomonocytic leukemia, **Disease risk** per CIBMTR classification: Early-stage disease includes AML and ALL in first complete remission, CML in first chronic phase, and MDS subtype refractory anemia. Intermediate-stage disease includes AML or ALL in second or subsequent complete remission or in first relapse or CML in accelerated phase or second chronic phase. Advanced-stage disease includes AML in second or greater relapse or primary induction failure, CML in blast phase, MDS subtype refractory anemia with excess blasts or in transformation, or MDS not otherwise classified. **Conditioning regimen:** Cy – cyclophosphamide, TBI – total body irradiation, Bu – busulfan, VP16 – etoposide, ATG – anti-thymocyte globulin. **Gender match:** M - male, F – female. **GVHD prophylaxis:** CSA – cyclosporine, MTX – methotrexate.

**eTable 2. Dynamic Prediction Model of Likelihood of Being off IS Without GVHD at 1 Year Time Horizon.**

Effect	LN(OR)	OR	95% CI	p-value
<b>Intercept</b>	-1.031	0.357	(0.251 , 0.591)	0.0001
<b>ltime (years)</b>	1.238	3.449	(2.314 , 5.140)	0.0000
<b>ltime*ltime</b>	-0.156	0.856	(0.794 , 0.922)	0.0000
<b>Graft type (unrelated only)</b>				
Bone marrow	0.000	1.000	-	-
Peripheral blood	-0.710	0.492	(0.329 , 0.735)	0.0005
<b>Donor type</b>				0.0718 (2 df)
Matched related	0.000	1.000	-	-
Matched unrelated	0.015	1.015	(0.671 , 1.534)	0.9445
Mismatched unrelated	-0.565	0.569	(0.313 , 1.033)	0.0638
<b>Age (years)</b>				
0-50	0.000	1.000	-	-
> 50	-0.508	0.601	(0.420 , 0.860)	0.0054
<b>Disease risk</b>				
Early	0.000	1.000	-	-
Intermediate or advanced	-0.463	0.629	(0.454 , 0.872)	0.0054
<b>State history</b>				0.0000 (4 df)
On IS, no chronic GVHD	0.000	1.000	-	-
Chronic GVHD, no current skin involvement	-1.669	0.189	(0.107 , 0.333)	0.0000
Chronic GVHD, current skin involvement	-2.668	0.069	(0.036 , 0.134)	0.0000
ISD, short duration spent on IS <sup>1</sup>	1.296	3.654	(2.326 , 5.740)	0.0000
ISD, long duration spent on IS <sup>2</sup>	2.274	9.722	(5.418 , 17.444)	0.0000

<sup>1</sup> Short duration spent on IS

- IS discontinued ≤ 180 days after transplant if no post-transplant GVHD
- IS discontinued ≤ 240 days from acute GVHD onset if history of prior acute GVHD
- IS discontinued ≤ 640 days from chronic GVHD onset if history of prior chronic GVHD

<sup>2</sup> Long duration spent on IS

- IS discontinued > 180 days after transplant if no post-transplant GVHD
- IS discontinued > 240 days from acute GVHD onset if history of prior acute GVHD
- IS discontinued > 640 days from chronic GVHD onset if history of prior chronic GVHD

**eTable 3: Dynamic prediction model of likelihood of being off IS without GVHD at 3 year time horizon.**

Effect	LN(OR)	OR	95% CI	p-value
<b>Intercept</b>	-0.732	0.481	(0.281 , 0.824)	0.0077
<b>ltime (years)</b>	1.851	6.366	(3.961 , 10.233)	0.0000
<b>ltime*ltime</b>	-0.373	0.688	(0.608 , 0.780)	0.0000
<b>Graft type (unrelated only)</b>				
Bone marrow	0.000	1.000	-	-
Peripheral blood	-1.045	0.352	(0.225 , 0.550)	0.0000
<b>Donor type</b>				0.0406 (2 df)
Matched related	0.000	1.000	-	-
Matched unrelated	0.139	1.149	(0.725 , 1.823)	0.5545
Mismatched unrelated	-0.670	0.512	(0.247 , 1.060)	0.0715
<b>Age (years)</b>				
0-50	0.000	1.000	-	-
> 50	-0.691	0.501	(0.327 , 0.768)	0.0015
<b>State history</b>				0.0000 (4 df)
On IS, no chronic GVHD	0.000	1.000	-	-
Chronic GVHD, no current skin involvement	-1.135	0.321	(0.195 , 0.531)	0.0000
Chronic GVHD, current skin involvement	-1.699	0.183	(0.100 , 0.336)	0.0000
ISD, short duration spent on IS <sup>1</sup>	0.223	1.25	(0.736 , 2.123)	0.4089
ISD, long duration spent on IS <sup>2</sup>	1.379	3.97	(2.103 , 7.494)	0.0000

<sup>1</sup> Short duration spent on IS

- IS discontinued ≤ 180 days after transplant if no post-transplant GVHD
- IS discontinued ≤ 240 days from acute GVHD onset if history of prior acute GVHD
- IS discontinued ≤ 640 days from chronic GVHD onset if history of prior chronic GVHD

<sup>2</sup> Long duration spent on IS

- IS discontinued > 180 days after transplant if no post-transplant GVHD
- IS discontinued > 240 days from acute GVHD onset if history of prior acute GVHD
- IS discontinued > 640 days from chronic GVHD onset if history of prior chronic GVHD



**eTable 4: Dynamic prediction model of likelihood of being off IS without GVHD at 5 year time horizon.**

Effect	LN(OR)	OR	95% CI	p-value
<b>Intercept</b>	-0.698	0.497	(0.277 , 0.894)	0.0195
<b>ltime (years)</b>	1.784	5.951	(3.877 , 9.135)	0.0000
<b>ltime*ltime</b>	-0.509	0.601	(0.398 , 0.908)	0.0157
<b>Graft type (unrelated only)</b>				
Bone marrow	0.000	1.000	-	-
Peripheral blood	-0.948	0.388	(0.237 , 0.634)	0.0002
<b>Donor type</b>				0.0079 (2 df)
Matched related	0.000	1.000	-	-
Matched unrelated	0.306	1.358	(0.831 , 2.220)	0.2219
Mismatched unrelated	-0.760	0.468	(0.213 , 1.028)	0.0587
<b>Age (years)</b>				
0-50	0.000	1.000	-	-
> 50	-0.867	0.420	(0.257 , 0.686)	0.0005
<b>State history</b>				0.0007 (4 df)
On IS, no chronic GVHD	0.000	1.000	-	-
Chronic GVHD, no current skin involvement	-0.384	0.681	(0.421 , 1.102)	0.1174
Chronic GVHD, current skin involvement	-0.622	0.537	(0.295 , 0.977)	0.0417
ISD, short duration spent on IS <sup>1</sup>	-0.169	0.845	(0.488 , 1.462)	0.5462
ISD, long duration spent on IS <sup>2</sup>	1.052	2.864	(1.421 , 5.770)	0.0032

<sup>1</sup> Short duration spent on IS

- IS discontinued ≤ 180 days after transplant if no post-transplant GVHD
- IS discontinued ≤ 240 days from acute GVHD onset if history of prior acute GVHD
- IS discontinued ≤ 640 days from chronic GVHD onset if history of prior chronic GVHD

<sup>2</sup> Long duration spent on IS

- IS discontinued > 180 days after transplant if no post-transplant GVHD
- IS discontinued > 240 days from acute GVHD onset if history of prior acute GVHD
- IS discontinued > 640 days from chronic GVHD onset if history of prior chronic GVHD

**eTable 5: Proposed Scoring Algorithm for each landmark time.**

Variable	Level	Score		
		1 year horizon	3 year horizon	5 year horizon
Graft type	BM	0	0	0
	PB	-1	-2	-2
Donor type	Matched related	0	0	0
	Matched unrelated	0	0	0
	Mismatched unrelated	-1	-2	-2
Age	0-50	0	0	0
	>50	-1	-1	-2
Disease risk	Early	0	0	0
	Intermediate/Advanced	-1	0	0
Current state	On IS, no chronic GVHD	0	0	0
	Chronic GVHD, no current skin involvement	-3	-2	-1
	Chronic GVHD, current skin involvement	-5	-3	-1
	ISD, short duration spent on IS <sup>1</sup>	3	0	0
	ISD, long duration spent on IS <sup>2</sup>	5	3	2

<sup>1</sup> Short duration spent on IS

- IS discontinued ≤ 180 days after transplant if no post-transplant GVHD
- IS discontinued ≤ 240 days from acute GVHD onset if history of prior acute GVHD
- IS discontinued ≤ 640 days from chronic GVHD onset if history of prior chronic GVHD

<sup>2</sup> Long duration spent on IS

- IS discontinued > 180 days after transplant if no post-transplant GVHD
- IS discontinued > 240 days from acute GVHD onset if history of prior acute GVHD
- IS discontinued > 640 days from chronic GVHD onset if history of prior chronic GVHD

As an example of using this scoring system, consider a 55 year old patient with an early disease risk status that received a peripheral blood, matched related HCT and is still on IS at two years post-transplant. Suppose that interest lies in predicting the patient's chance of being off IS at three years post-transplant given their current status at two years. The three-year post-TX prediction time lies one year subsequent to the two-year post-TX landmark time. Therefore, the 1-year landmark model displayed in Figure 3a and Table S5 is applicable. Applying the 1-year horizon column on Table S5 gives a risk score of  $(-1) + 0 + (-1) + 0 + 0 = -2$  for this patient. Examining the curve in Figure 3a corresponding to a score of -2, we see that at the 2-year landmark time on the x-axis, the predicted chance that this patient is off IS at 3 years post-transplant is 40%.