Phase 2b Study of the Interferon-Free and Ribavirin-Free Combination of Daclatasvir, Asunaprevir, and BMS-791325 for 12 Weeks in Treatment-Naive Patients With Chronic HCV Genotype 1 Infection

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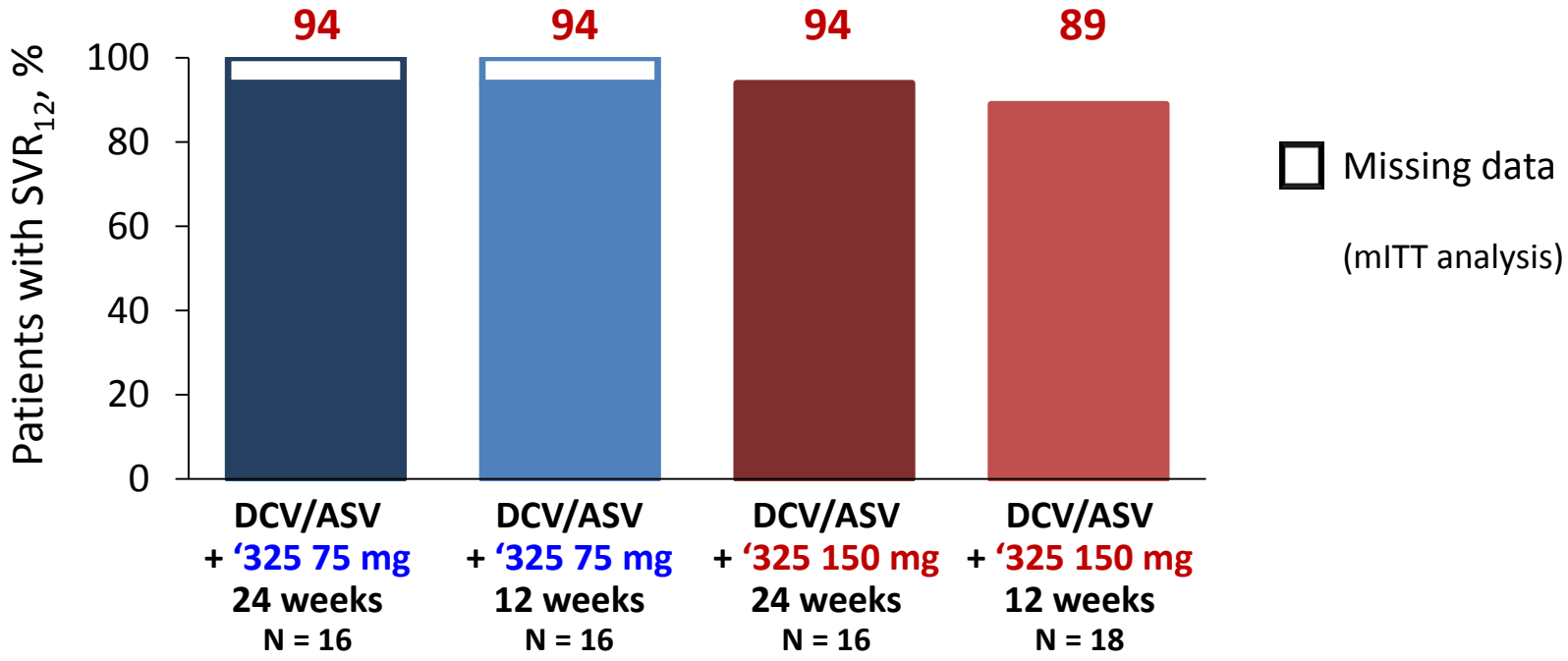
BMS Direct-Acting Antiviral Agents

- Daclatasvir (DCV)
  - NS5A replication complex inhibitor with potent, pan-genotypic activity *in vitro*[1]
  - Once-daily dosing, 60 mg tablet with no food restrictions
  - Studied in over 5500 patients in phase 1–3 studies[2] including all-oral, IFN alfa-free and ribavirin-free combinations
- Asunaprevir (ASV)
  - NS3 protease inhibitor active against genotypes (GT) 1, 4, 5, and 6 *in vitro*[3]
  - Twice-daily dosing, 200 mg tablet or 100 mg softgel capsule
  - Studied in over 2000 patients in phase 1–3 studies including all-oral combinations
- BMS-791325
  - Non-nucleoside, NS5B polymerase inhibitor active against GT 1, 3, 4, 5, and 6 *in vitro*[4]
  - Twice-daily dosing, either 75 or 150 mg tablet, with no food restrictions
  - Studied in over 500 patients in phase 1–2 studies including all-oral combinations

1. Gao M, *et al*. *Nature* 2010;465:96–100; 2. Pol S, *et al. Lancet Infect Dis* 2012;12:671–677; 3. McPhee F, *et al*. *Antimicrob Agents Chemother* 2012;56:5387–5396; 4. Kadow J, *et al. 243rd ACS National Meeting*; March 25–29, 2012. Abstract MEDI-23.

Background

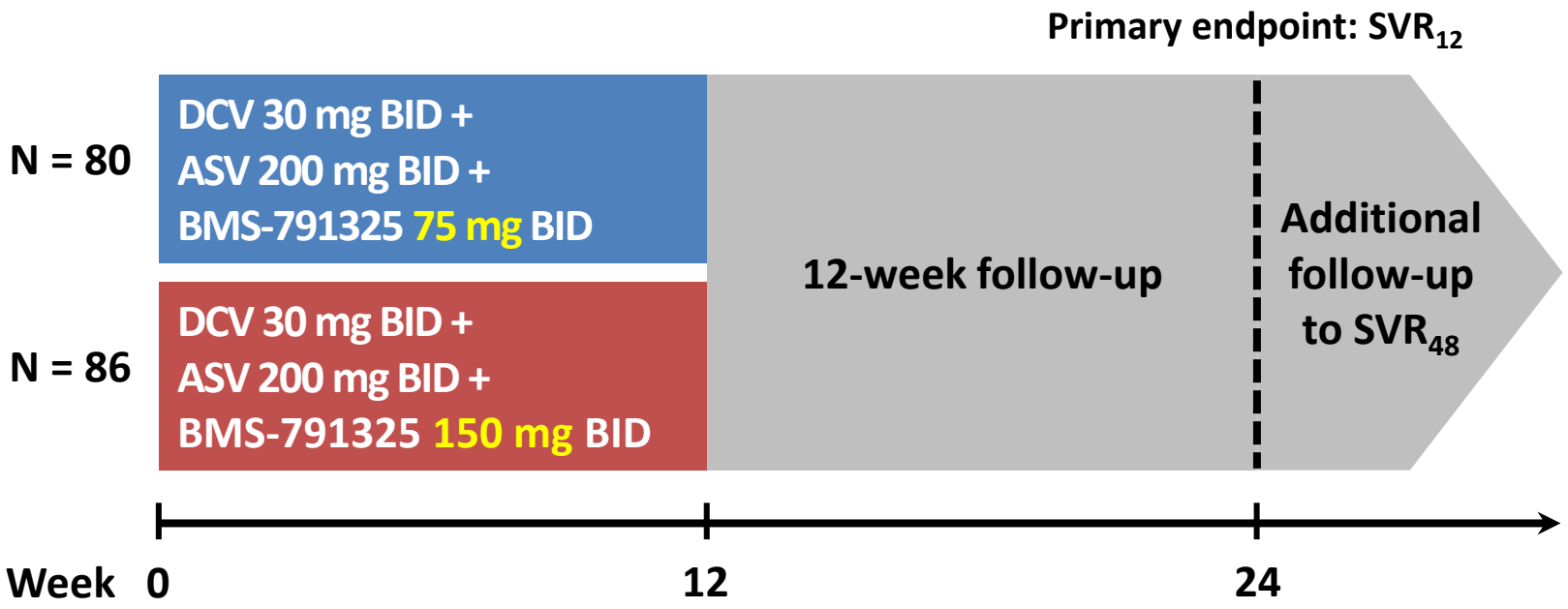
- In pilot cohorts, the all-oral, interferon-free and ribavirin-free combination of DCV, ASV, and BMS-791325 achieved comparable SVR rates after 12 or 24 weeks of therapy in patients with HCV GT 1 infection



- The present study expansion examines 12 weeks of therapy with this regimen in larger cohorts of patients with GT 1 infection, including cirrhotics
  - DCV dosed at 30 mg BID to support co-formulation development based on similar HCV GT 1 viral load reductions with 30 mg BID and 60 mg QD dosing[1]

1. Nettles RE, *et al. Hepatology* 2011;54:1956-1965.

Randomized, Phase 2b Open-Label Study (AI443-014)



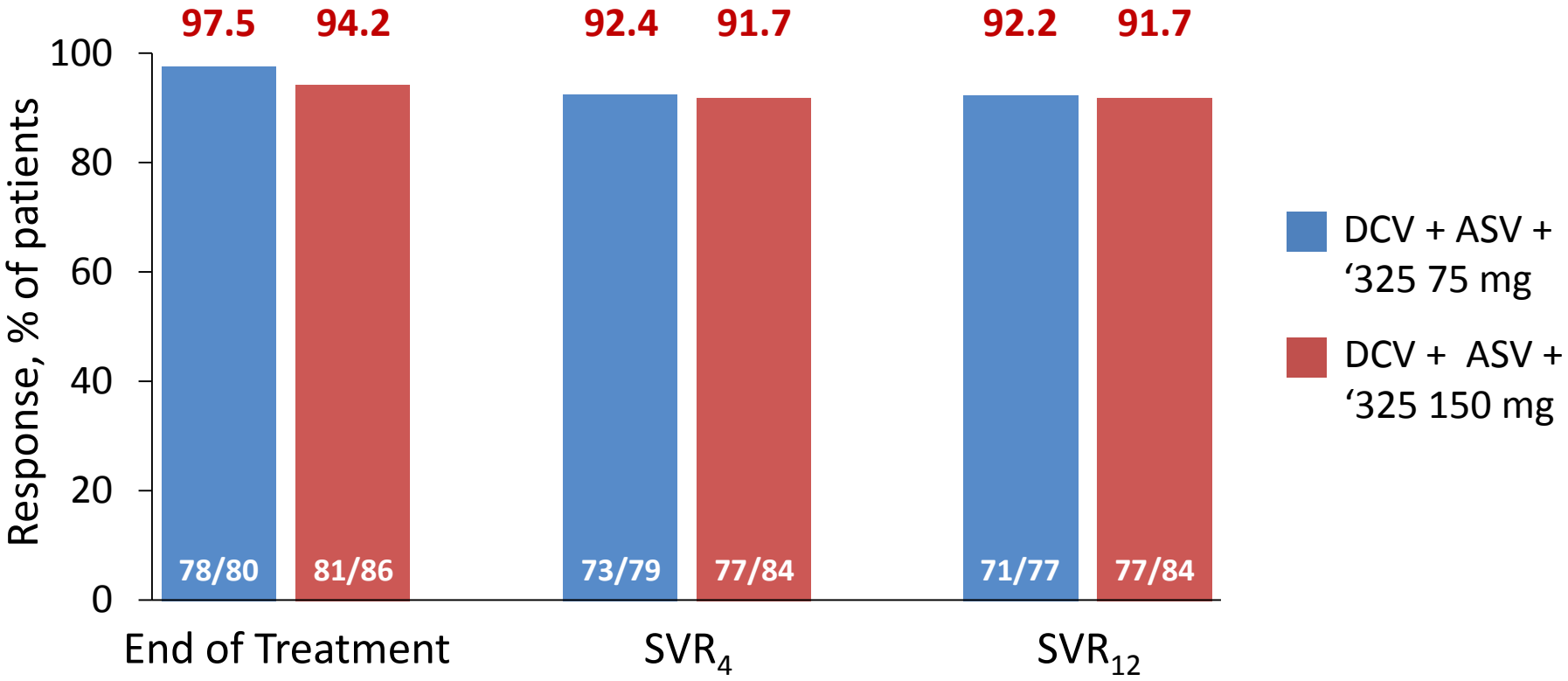
- **Patients:** treatment-naive, stratified by GT 1a/1b and presence of biopsy-confirmed cirrhosis (≈ 10% cirrhotics per group)
- **HCV RNA end points:** lower limit of assay quantitation, target detected ($LLOQ_{TD}$; 25 IU/mL), and below LLOQ and target not detected ($LLOQ_{TND}$; ≈ 10 IU/mL)
- **Primary end point:** HCV RNA < LLOQ 12 weeks post-treatment (SVR_{12})
  - Observed analysis: breakthrough, relapse, addition of pegIFNα/RBV = failure
  - Modified intent-to-treat analysis: missing, breakthrough, relapse or addition of pegIFNα/RBV = failure

Demographic and Baseline Disease Characteristics

Parameter		DCV + ASV + ‘325 75 mg N = 80	DCV + ASV + ‘325 150 mg N = 86	Total N = 166
Age, median years (range)		54 (23-68)	54 (23-69)	54 (23-69)
Male sex, n (%)		55 (69)	57 (66)	112 (67)
Race, n (%)	White	61 (76)	76 (88)	137 (83)
	Black/African American	17 (21)	10 (12)	27 (16)
	Other	2 (3)	0	2 (1)
HCV genotype, n (%)	1a	67 (84)	69 (80)	136 (82)
	1b	13 (16)	17 (20)	30 (18)
HCV RNA, mean $\log_{10}$ IU/mL (SD)		6.3 (0.80)	6.4 (0.69)	
IL28B genotype, n (%) (rs12979860)	CC	25 (31)	29 (34)	54 (33)
	CT	44 (55)	39 (45)	83 (50)
	TT	9 (11)	17 (20)	26 (16)
	Not reported	2 (3)	1 (1)	3 (2)
Cirrhosis (biopsy-confirmed), n (%)		8 (10)	7 (8)	15 (9)
Derived Metavir, n (%)	F0	23 (29)	20 (23)	43 (26)
	F1	17 (21)	17 (20)	34 (20)
	F2	10 (13)	12 (14)	22 (13)
	F3	12 (15)	22 (26)	34 (20)
	F4	16 (20)	14 (16)	30 (18)
	Not reported	2 (2)	1 (1)	3 (2)

Metavir categorization was converted from FibroTest score

Efficacy Through SVR_{12} (Observed)



Missing Data at Posttreatment Week 12

DCV + ASV + '325 75 mg	DCV + ASV + '325 150 mg
3 patients, mITT SVR_{12} = 88.8%	2 patients, mITT SVR_{12} = 89.5%

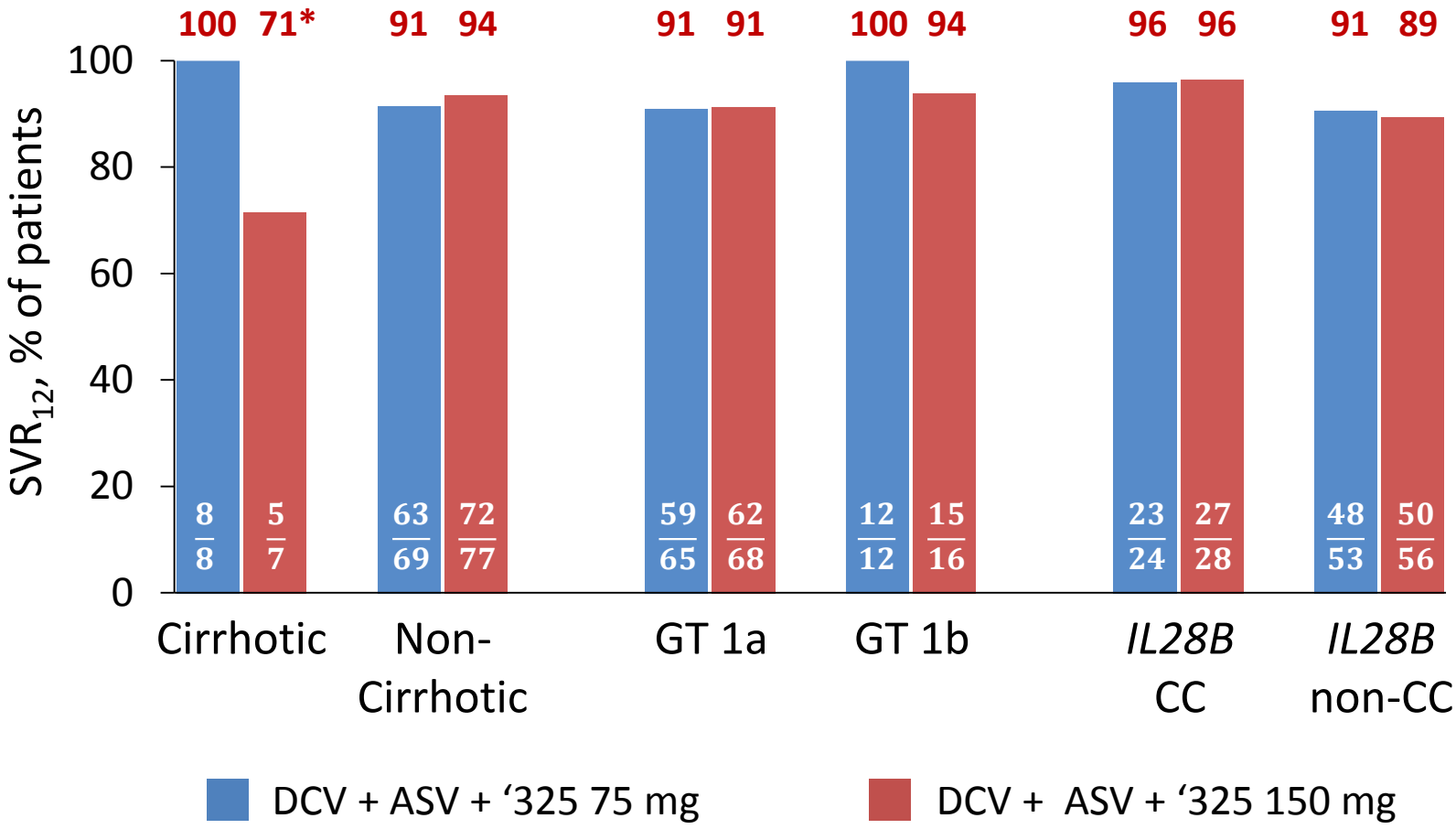
Patients Without SVR_{12}

Failure Category	DCV + ASV + ‘325 75 mg N = 80	DCV + ASV + ‘325 150 mg N = 86
Virologic failure	6	5
Viral breakthrough	2	3
*Relapse **prior** to post-treatment Week 4*	4	2
*Relapse **after** post-treatment Week 4*	0	0
Other[a]	0	2

[a] 1 patient discontinued due to AE, 1 patient discontinued ‘325 only and added pegIFNα/RBV for 12 weeks

- Virologic failures all GT 1a, no other predictive characteristics identified
- 17 patients had NS3 or NS5A signature resistance-associated variants (RAVs) at baseline; 13/17 achieved SVR
- Signature RAVs detected at failure included:
  - NS3: V36M, T54S, and R155K
  - NS5A: M28T, Q30E/H/R, L31M, and Y93H/N
  - NS5B: P495L/S

Efficacy in Subgroups (Observed SVR_{12})



**2 cirrhotic patients added pegIFNα/RBV: 1 viral breakthrough; 1 met a protocol stopping rule for '325*

Reasons for Treatment Discontinuation

n (%)	DCV + ASV + ‘325 75 mg N = 80	DCV + ASV + ‘325 150 mg N = 86	Total N = 166
Total discontinuations	2 (2.5)	6 (7.0)	8 (4.8)
Adverse event	1 (1.3)	1 (1.2)	2 (1.2)
Lack of efficacy	0[a]	3 (3.5)	3 (1.8)
Poor/non-compliance	0	1 (1.2)	1 (0.6)
Other	1 (1.3)	1 (1.2)	2 (1.2)

[a] 2 patients had breakthrough confirmed on or after EOT visit

- *Adverse events*: Grade 2 SAE of esophageal tumor on Day 71 (‘325 75 mg group, unrelated) and Grade 2 AE of throat tightness on Day 3 (‘325 150 mg group, related)
- *Lack of efficacy*: 3 patients with virologic breakthrough; 2 added treatment intensification with pegIFNα/RBV to DCV/ASV/’325 regimen
- *Poor/non-compliance*: Protocol noncompliance after a Grade 2 SAE of abdominal wall abscess on Day 54 (unrelated)
- *Other*: One patient in each group was incarcerated

Safety Outcomes

Event, n (%)	DCV + ASV + '325 75 mg N = 80	DCV + ASV + '325 150 mg N = 86	Total N = 166
Serious AEs [a]	1 (1.3)	2 (2.3)	3 (1.6)
AEs leading to discontinuation [b]	1 (1.3)	1 (1.2)	2 (1.1)
Grade 3/4 AEs [a]	0	1 (1.2)	1 (0.5)
Most frequent on-treatment AEs (≥ 10%)			
Headache	17 (21.3)	24 (27.9)	41 (24.7)
Diarrhea	12 (15.0)	13 (15.1)	25 (15.1)
Fatigue	12 (15.0)	7 (8.1)	19 (11.4)
Nausea	10 (12.5)	7 (8.1)	17 (10.2)
Grade 3/4 lab abnormalities			
Aspartate aminotransferase (AST) [c]	1 (1.3)	0	1 (0.5)
Glucose, fasting serum (high) [d]	1 (1.3)	1 (1.2)	2 (1.2)
Phosphorus, inorganic	0	1 (1.2)	1 (0.5)
Bilirubin, total [e]	0	1 (1.2)	1 (0.5)

[a] SAEs and Grade 3/4 AEs included esophageal neoplasm; abdominal wall abscess; pleurisy/chest pain (reported as both SAEs and grade 3 AEs); all unrelated to study drugs
[b] Esophageal neoplasm; throat tightness
[c] Grade 3 AST elevation on Day 24, normalized by Day 50 on treatment; concurrent bilirubin normal, not considered an AE
[d] Both patients had history of diabetes mellitus
[e] Baseline Grade 2 elevation to Grade 3 on Day 7 in cirrhotic patient with ALT/AST improving; not considered an AE

Conclusions

- This 12-week, IFN- and RBV-free, all-oral 3 DAA regimen achieved SVR_{12} in > 90% of patients despite high prevalence of GT 1a, advanced fibrosis/cirrhosis, and *IL28B* non-CC genotypes
- Virologic failures were infrequent
- Well tolerated regimen with low rates of adverse events and treatment discontinuations, regardless of BMS-791325 dose
- These results support phase 3 trials with a twice-daily fixed-dose combination of DCV/ASV/BMS-791325 at the 75 mg dose level[1]

[1]http://www.clinicaltrials.gov/ct2/show/NCT01973049?term=bms-791325&rank=2v

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