

Nowe możliwości leczenia pWZW C – co się zmieniło w ciągu roku

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Forum Wirusologiczne 2018

Łódź

- Wykład powstał przy wsparciu firmy Gilead Sciences Poland Sp. z o.o., ul. Postępu 17A, 02-676 Warszawa.
- Zawarte w wykładzie wytyczne mogą zawierać wskazania do terapii i schematy leczenia wykraczające poza zapisy rejestracyjne poszczególnych leków.

Disclosures

Krzysztof Tomasiewicz: Consultancy/Advisory Board/Speaker: AbbVie, Alfa Wasserman, BMS, Gilead, Janssen, MSD, Roche; Grant/Research: AbbVie, BMS, Gilead, Janssen, MSD, Roche

Co się wydarzyło w 2017 roku

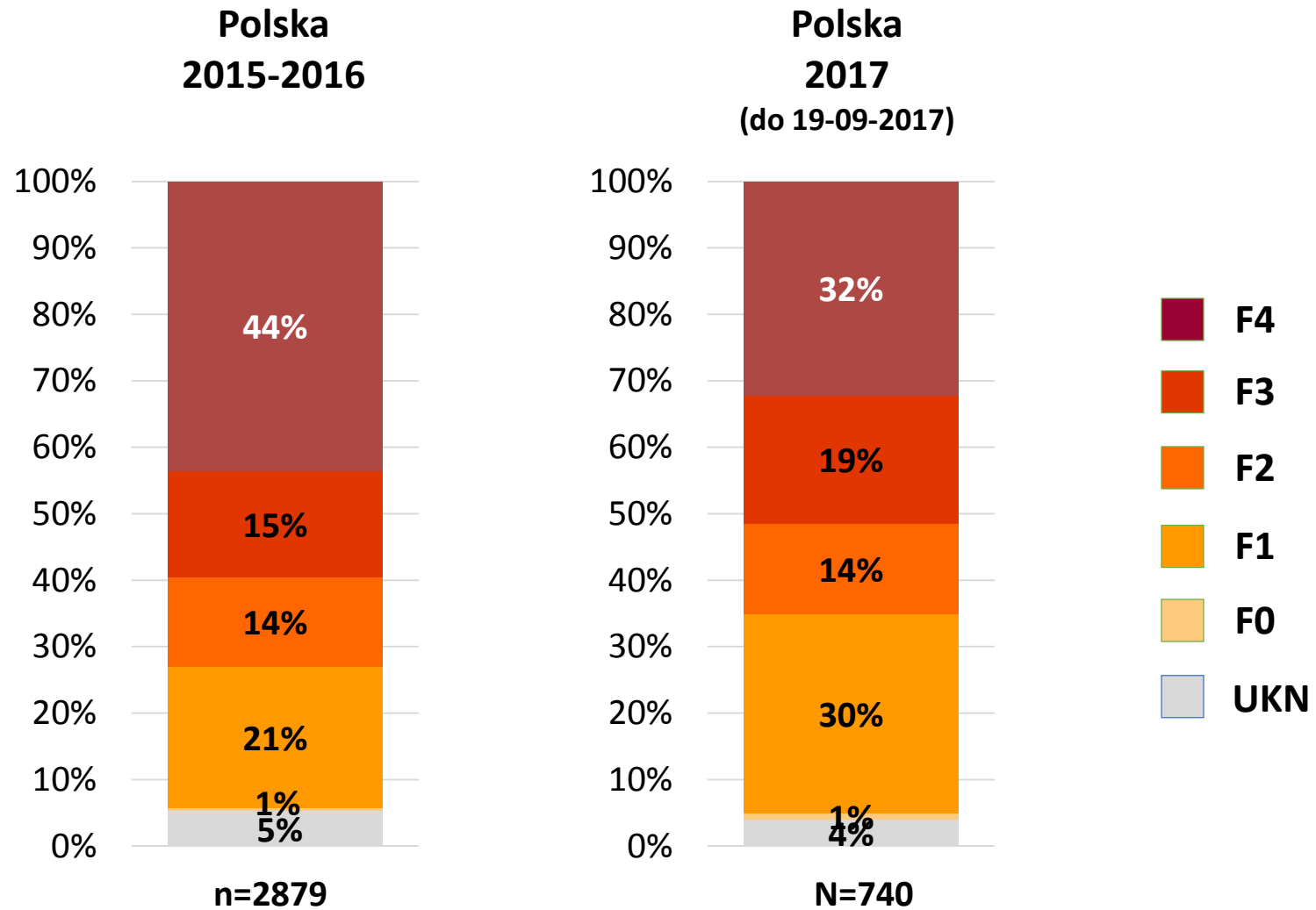
Liczba leczonych w programach terapeutycznych przekroczyła 12 000

Kwalifikacja pacjentów bez względu na stopień zaawansowania włóknienia i inne czynniki (mniejsze znaczenie priorytetów leczenia)

Dostępność wszystkich terapii, z wyjątkiem pangenuotypowych (Maviret, Epclusa i Vosevi).

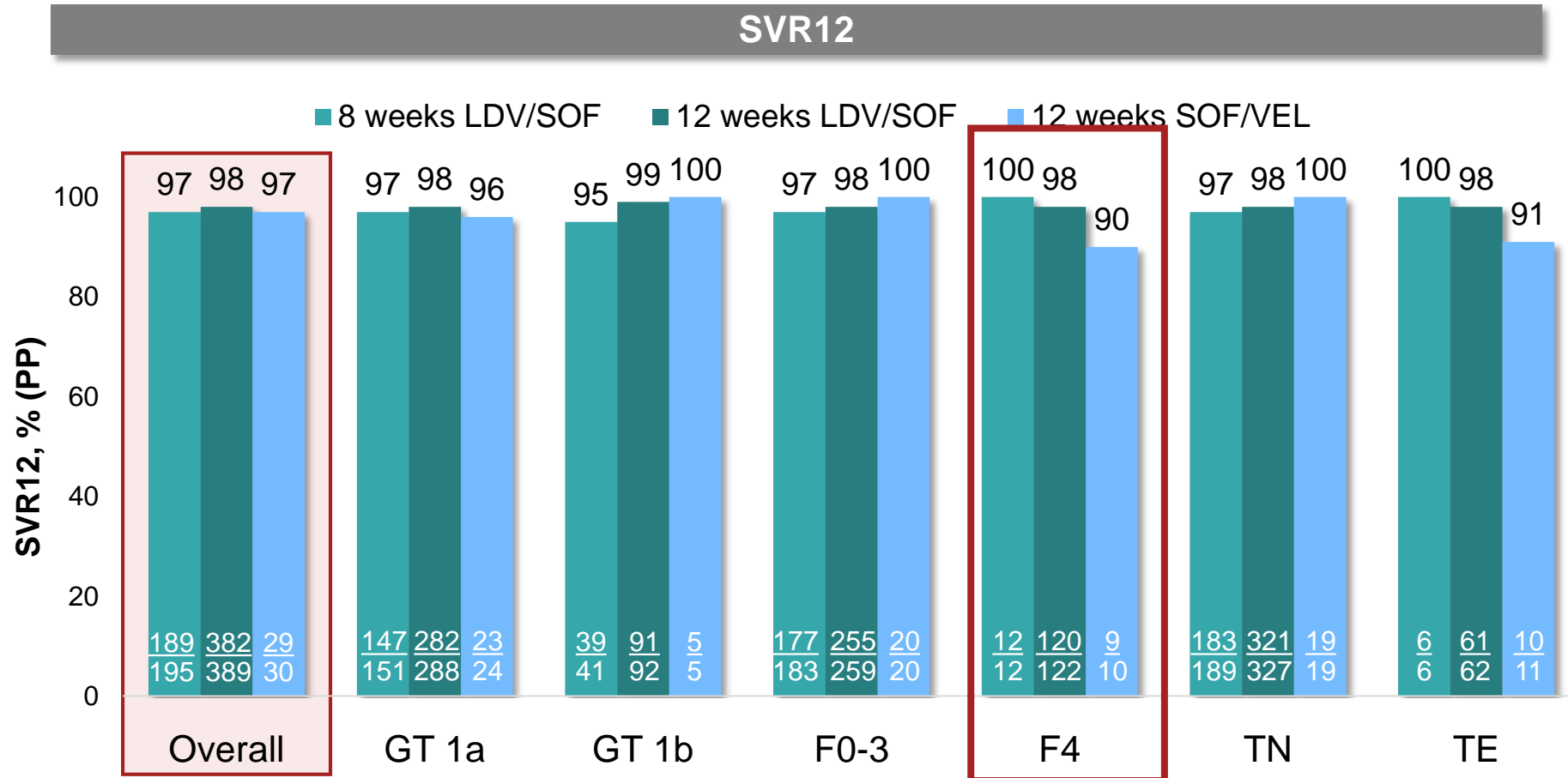
EpiTer-2

Zaawansowanie włóknienia u pacjentów leczonych





Real-World Experience LDV/SOF i SOF/VEL u pacjentów GT1



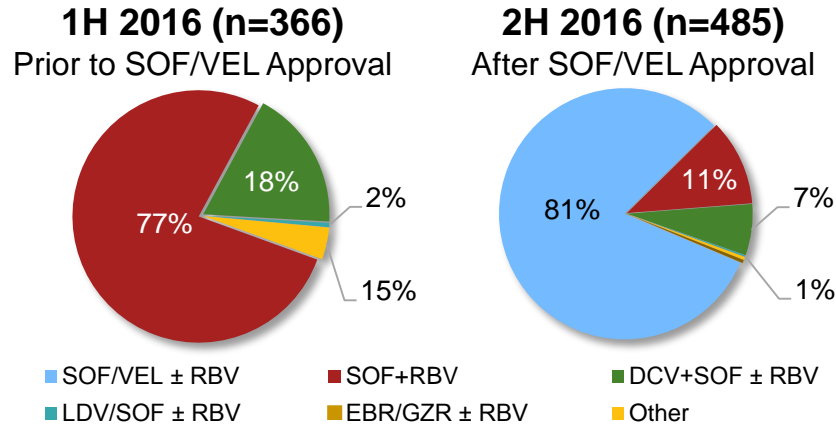
Wysoki SVR12 w schemacie 8 i 12 tyg LDV/SOF oraz 12 tyg SOF/VEL, niezależnie od genotypu/subtypu, zaawansowania włóknienia lub historii leczenia



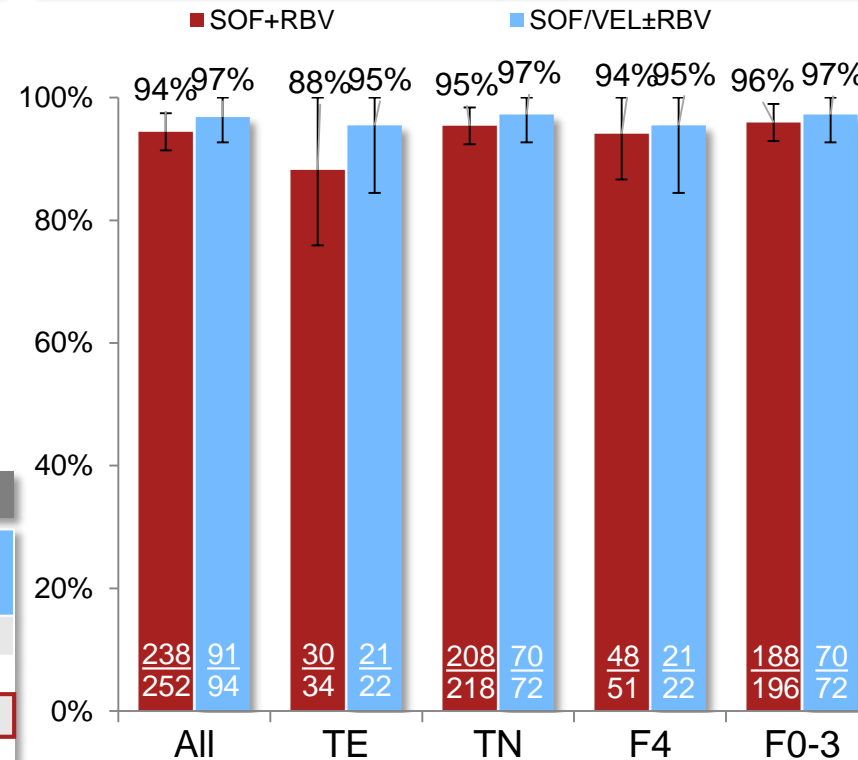


Real-World Experience SOF/VEL ± RBV w HCV GT 2

Treatment uptake



SVR12 (PP)



Baseline Demographics

	SOF + RBV (n=337)	SOF/VEL ± RBV (n=394)
12 week schedule, n (%)	280 (83)	386 (98)
Other schedule, n (%)*	53 (16)	7 (2)
+ RBV, n (%)	337 (100)	22 (6)
Age - mean (range)	59 (24-85)	61 (21-86)
Male, n (%)	195 (58)	226 (58)
TE, n (%)	45 (13)	82 (21)
F4, n (%)	68 (21)	85 (22)
CKD, n (%)	104 (32)	156 (41)
Diabetes, n (%)	41 (13)	56 (15)

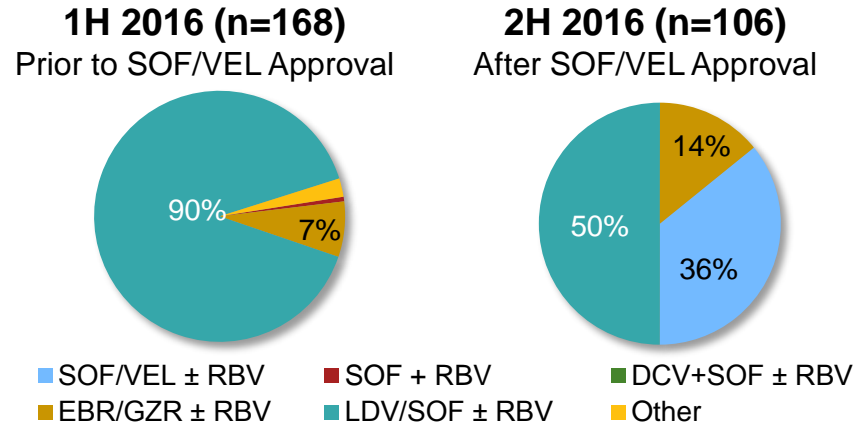
Potwierdzenie wysokiego odsetka SVR12 u pts z GT2 leczonych SOF/VEL

*A small fraction of patients were indicated for schedules other than those shown

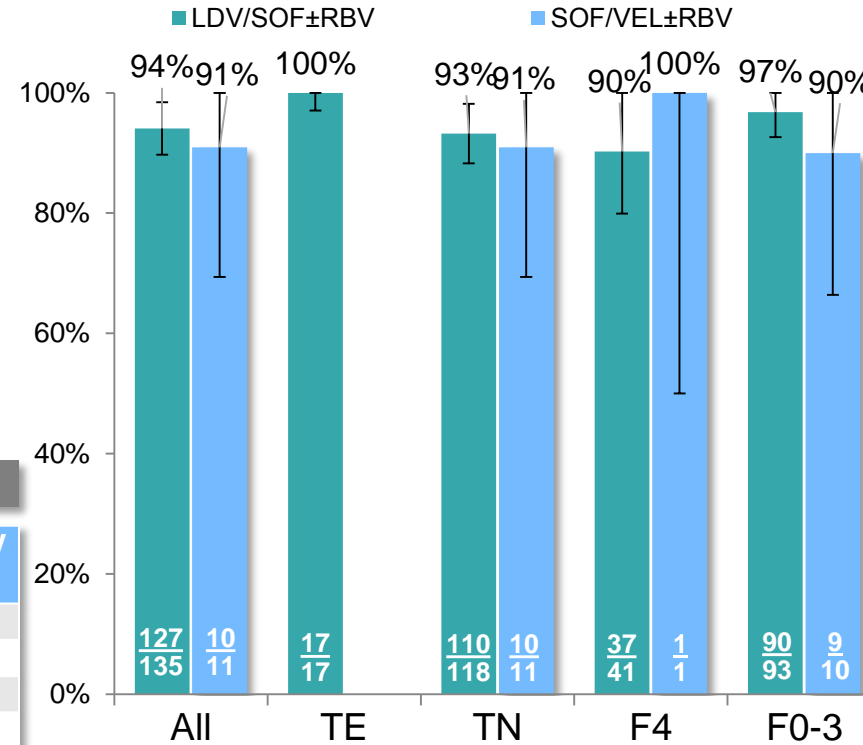


Real-World Experience SOF/VEL ± RBV w HCV GT 4-6

Treatment uptake



SVR12 (PP)



Potwierdzenie wysokiego odsetka SVR12 u pts z GT4-6 leczonych SOF/VEL

Baseline Demographics

	LDV/SOF ± RBV (n=204)	SOF/VEL ± RBV (n=38)
12 week schedule, n(%)	191 (94)	38 (100)
Other schedule, n(%)*	4 (2)	0
+ RBV, n(%)	5 (2)	2 (5)
Age - mean (range)	63 (21-87) n=182	62 (24-82) n=37
Male - no. (%)	109 (53)	23 (61)
HIV coinfection, n(%)	3 (2)	0
TE, n(%)	37 (18)	6 (16)
F4, n(%)	64 (32)	6 (16)
CKD, n(%)	70 (35)	12 (32)
Diabetes, n(%)	30 (15)	8 (21)

*A small fraction of patients were indicated for schedules other than those shown



Genotyp 3

Skuteczność i tolerancja dotychczasowych schematów

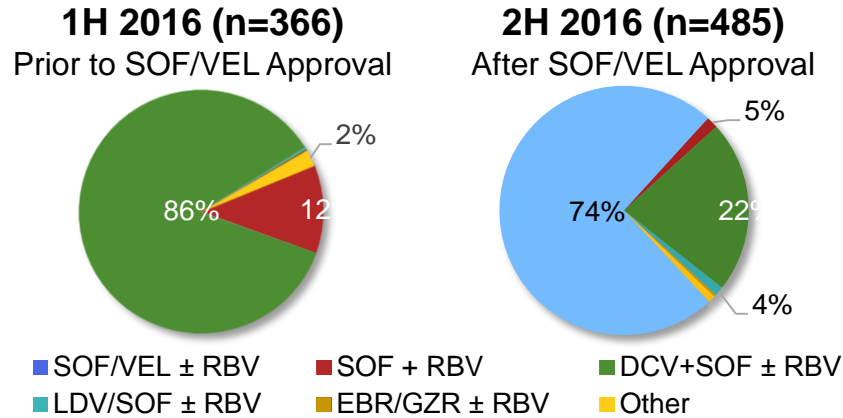
Terapia	No cirrhosis (F0-F3)			cirrhosis (F4)		
	N	SVR (%), ITT*	SVR (%), mITT**	N	SVR (%), ITT*	SVR (%), mITT**
All patients	84	91	94	114	80	83
SOF+PegIFN+RBV, 12 wks	43	98	98	56	91	91
SOF+RBV, 24 wks	24	79	86	47	68	73
PegIFN+RBV, 24 wks	16	88	88	2	0	0
SOF+DCV+RBV, 24 wks	1	100	100	9	89	100

	No cirrhosis (F0-F3)			cirrhosis (F4)		
	N	Modyfikacja	Przerwanie	N	Modyfikacja a	Przerwa
All patients	84	8 (9.5%)	3 (3.6%)	114	16 (14%)	4 (3.5%)
SOF+PegIFN+RBV,12 wks	43	2 (4.6%)	1 (2.3%)	56	7 (12.5%)	0
SOF+RBV, 24 wks	24	3 (12.5%)	2 (8.3%)	47	7 (14.9%)	2 (4.2%)
PegIFN+RBV, 24 wks	16	3 (18.7%)	0	2	0	0
SOF+DCV+RBV, 24 wks	1	0	0	9	2 (22.2%)	2 (22.2%)

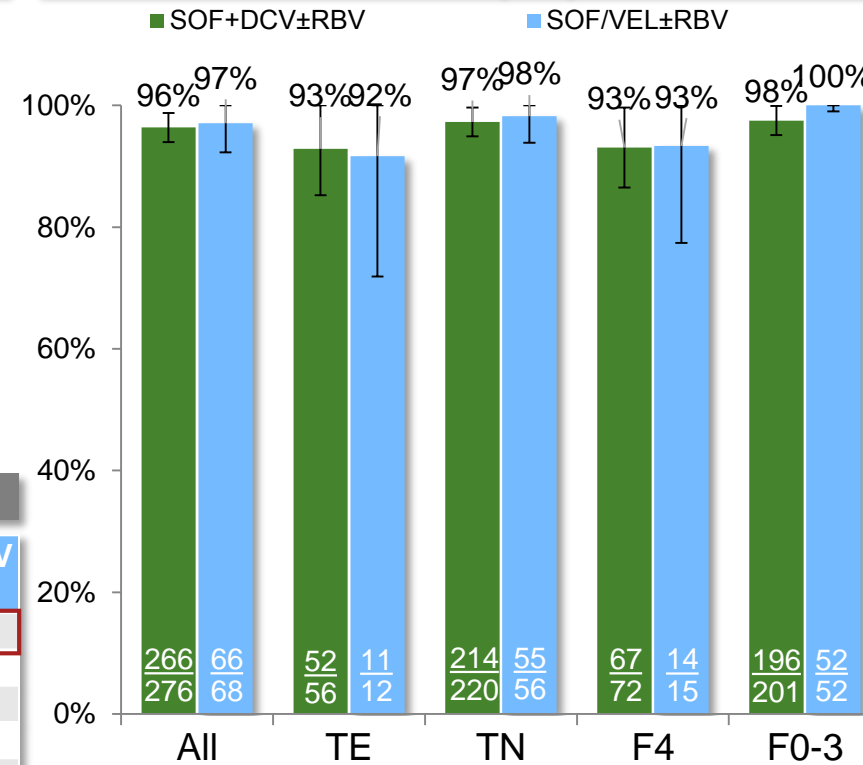


Real-World Experience of SOF/VEL ± RBV w HCV GT 3

Treatment uptake



SVR12 (PP)



Baseline Demographics

	SOF+DCV ± RBV (n=392)	SOF/VEL ± RBV (n=244)
12 week schedule, n (%)	307 (78)	238 (98)
Other schedule, n (%)*	82 (21)	6 (2)
+ RBV, n (%)	78 (20)	35 (14)
Age - mean (range)	54 (22-81)	52 (21-83)
Male, n (%)	224 (57)	140 (57)
HIV coinfection, n (%)	7 (2)	5 (4)
TE, n (%)	82 (21)	54 (22)
F4, n (%)	110 (29)	69 (29)
CKD, n (%)	99 (26)	64 (27)
Diabetes, n (%)	46 (13)	33 (14)

Wysokie odsetki SVR12 u pts z GT3 leczonych SOF/VEL

*A small fraction of patients were indicated for schedules other than those shown

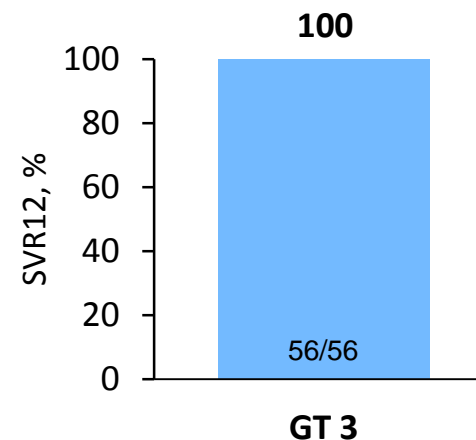
SOF/VEL±RBV: Niemieckie doświadczenia Real-World u pacjentów z GT 3

Safety and efficacy of patients receiving SOF/VEL±RBV in clinical practice

Baseline Demographics

	GT 3 N=122
Median age (range), years	47 (26–73)
Males, n (%)	97 (80)
White, n (%)	113 (93)
Metavir score, % F0 / F1 / F2 / F3 / F4	23 / 12 / 12 / 11 / 41
TN, n (%)	104 (85)
TE, n (%)	18 (15)
Prior DAA therapy, n (%)	4 (22)
Prior NS5A and/or SOF, n (%)	4 (100)
No prior DAA therapy	14 (78)
HIV coinfection, n (%)	4 (3)

SVR12 (PP)



- 1 (0.8%) AE led to D/C
- No grade 3/4 AEs and no deaths

Wszyscy pacjenci z GT3, którzy skończyli leczenie osiągnęli SVR12

Efficacy and Safety of Glecaprevir / Pibrentasvir in Patients Infected with HCV GT1 – 3 by Renal Impairment Status: A Pooled Analysis of Two Phase 3 Japanese Trials

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	CKD 1 (n=31)	CKD 2 (n=220)	CKD 3 (n=69)	CKD 4 (n=7)	CKD 5 (n=5)	Total N=332
Male	16 (52)	82 (37)	34 (49)	2 (29)	4 (80)	194 (58)
Age < 65	24 (77)	113 (51)	23 (33)	2 (29)	2 (40)	164 (49)
Age ≥65 and <75 years	6 (19)	67 (30)	24 (35)	3 (43)	3 (60)	103 (31)
Age ≥75	1 (3)	40 (18)	22 (32)	2 (29)	0	65 (20)
BMI, median (range), kg/m ²	23.7 (14.2–33.6)	22.8 (16.0–33.4)	23.3 (15.2–38.0)	20.5 (18.9–23.3)	23.9 (20.6–30.9)	23.0 (14.2–38.0)
HCV genotype, n (%) [*]						
GT1	12 (39)	143 (65)	44 (64)	1 (14)	2 (40)	202 (61)
GT2	16 (52)	9 (4)	2 (3)	0	0	27 (8)
GT3	3 (10)	8 (4)	1 (1)	0	0	12 (4)
Treatment-naïve	20 (65)	148 (67)	45 (65)	6 (86)	3 (60)	222 (67)
Treatment Experienced						
IFN-experienced	10 (32)	46 (21)	18 (26)	1 (14)	2 (40)	77 (23)
DAA-experienced	1 (3)	26 (12)	6 (9)	0	0	33 (10)
Cirrhotic status						
Yes	2 (6)	36 (16)	24 (35)	0	2 (40)	64 (19)
No	29 (94)	184 (84)	45 (65)	7 (100)	3 (60)	268 (81)
Baseline HCV RNA level, log ₁₀ IU/mL, median (range)	6.2 (4.4–6.9)	6.2 (2.7–7.4)	6.2 (4.0–7.0)	6.1 (2.9–7.4)	5.7 (5.2–6.5)	6.2 (2.7–7.4)
Baseline FIB-4, median (range)	1.3 (0.4–7.7)	2.2 (0.6–17.0)	2.8 (1.0–12.4)	2.4 (1.2–4.6)	5.5 (0.4–6.2)	2.2 (0.4–17.0)

^{*}No Japanese patients with GT4-6 were enrolled in the CERTAIN studies despite being eligible

Table 2. Summary of Treatment Emergent Adverse Events

	CKD 1 (n=31)	CKD 2 (n=220)	CKD 3 (n=69)	CKD 4 (n=7)	CKD 5 (n=5)	Total N=332
Any AE	16 (52)	125 (57)	42 (61)	5 (71)	5 (100)	193 (58)
AE occurring in ≥10% patients [*]						
Nasopharyngitis	1 (3)	30 (13)	7 (10)	1 (14)	0	39 (12)
Pruritus	1 (3)	14 (6)	7 (10)	0	2 (40)	24 (7)
Blood creatinine increased	0	0	0	2 (29)	0	2 (0.6)
Any SAE	0	2 (0.9)	0	0	1 (20)	3 (0.9)
DAA-related SAE	0	0	0	0	0	0
AE leading to discontinuation [†]	0	2 (0.9)	1 (1)	0	0	3 (0.9)
Any Fatal AE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

^{*}AEs occurring in > 1 patient for CKD stage 4 or 5 due to small numbers.

[†]SAEs by patient were as follows: unstable angina at Day 86, spontaneous pneumothorax at Day 63, and fluid overload at Day 42.

[‡]AEs leading to discontinuation were as follows listed by patient: GT1-infected patient with grade 2 drug eruption on Day 16, GT2-infected patient with grade 2 exanthematic drug eruption on Day 12, and GT2-infected patient with grade 2 nausea and vomiting on Day 18.

Rozwiązanie w terapii pacjentów z Genotypem 3 i niewydolnością nerek ?

Overall ITT SVR = 98%

Pacjenci z (zaawansowaną) marskością/dekompensacją

Real world data

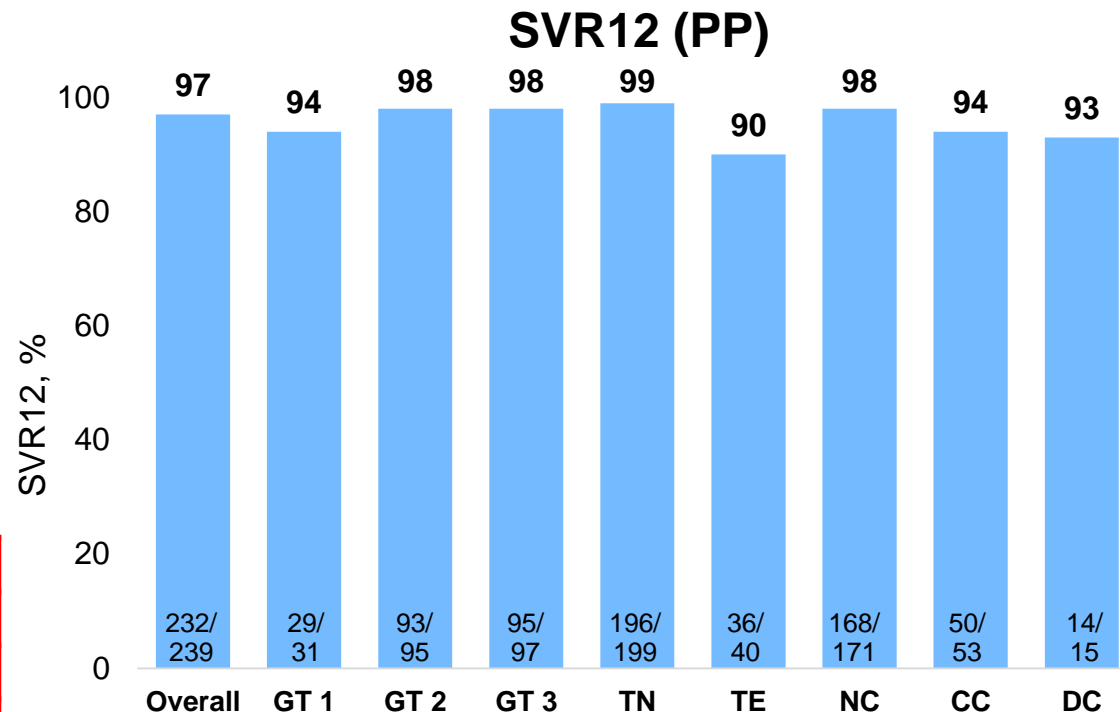
Real-World Experience SOF/VEL (bez RBV) u pts z HCV GT 1–6

407 pacjentów leczonych SOF/VEL w ramach HCV-TARGET
początek Lipiec 2016 – Luty 2017)

Baseline Demographics

	SOF/VEL n=407
Male, n (%)	228 (56)
Age ≥60, n (%)	164 (40)
HCV GT, % 1 / 2 / 3 / Other	17 / 39 / 38 / 6
Treatment duration	
12 weeks, n (%)	330 (81)
Other, n (%)	39 (10)
Ongoing	38 (9)
Cirrhosis, n (%)	113 (28)
History of DC, n (%)	30 (7)
TE*, n (%)	67 (17)
Liver transplant, n (%)	8 (2)

* 21 (5%) were DAA treatment failures (per abstract only).



TN=treatment-naïve
TE=treatment-experienced
NC=non-cirrhotic
CC=compensated cirrhotic
DC=decompensated cirrhotic

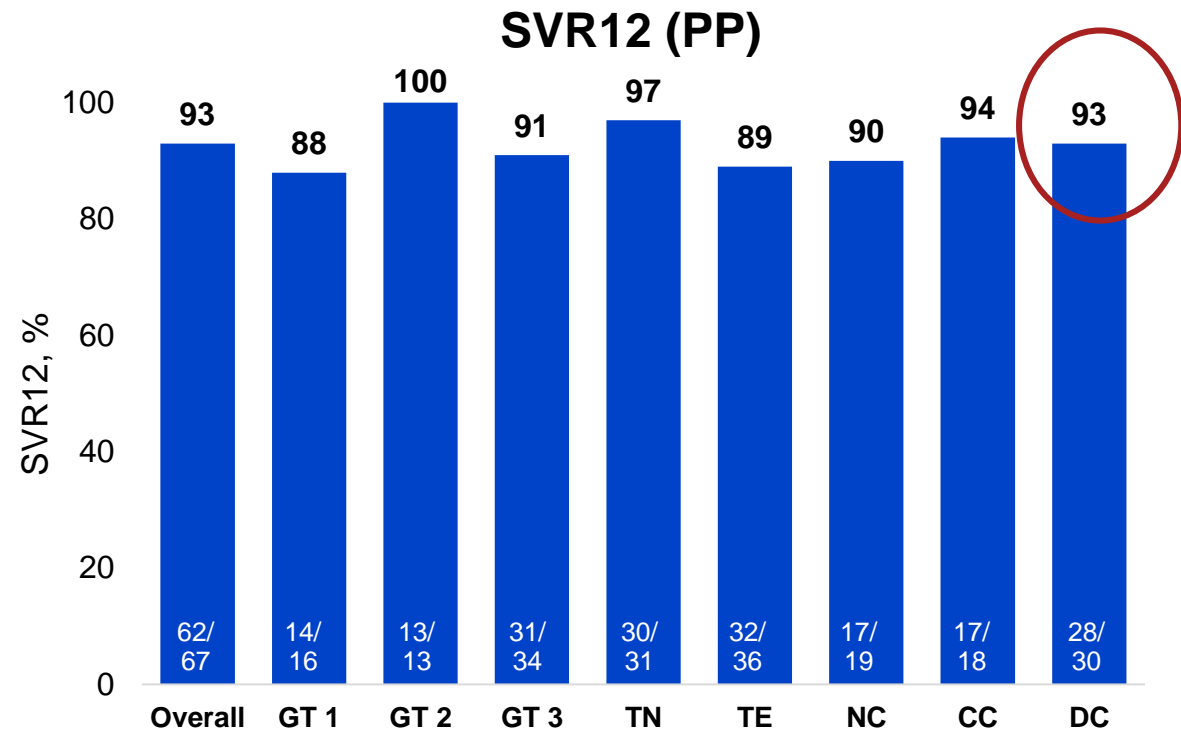
Real-World Experience of SOF/VEL+RBV u pacjentów z HCV GT 1–6

113 pacjentów leczonych SOF/VEL+RBV w ramach HCV-TARGET
początek Lipiec 2016 – Luty 2017)

Baseline Demographics

	SOF/VEL+RBV n=113
Male, n (%)	83 (74)
Age ≥60, n (%)	49 (43)
HCV GT, % 1 / 2 / 3 / Other	34 / 14 / 46 / 6
Treatment duration	
12 weeks, n (%)	85 (75)
Other, n (%)	22 (20)
Ongoing	6 (5)
Cirrhosis, n (%)	81 (72)
History of DC, n (%)	57 (50)
TE*, n (%)	66 (58)
Liver transplant, n (%)	14 (12)

* 54 (45%) were DAA treatment failures (per abstract only)



TN=treatment-naïve
TE=treatment-experienced
NC=non-cirrhotic
CC=compensated cirrhotic
DC=decompensated cirrhotic

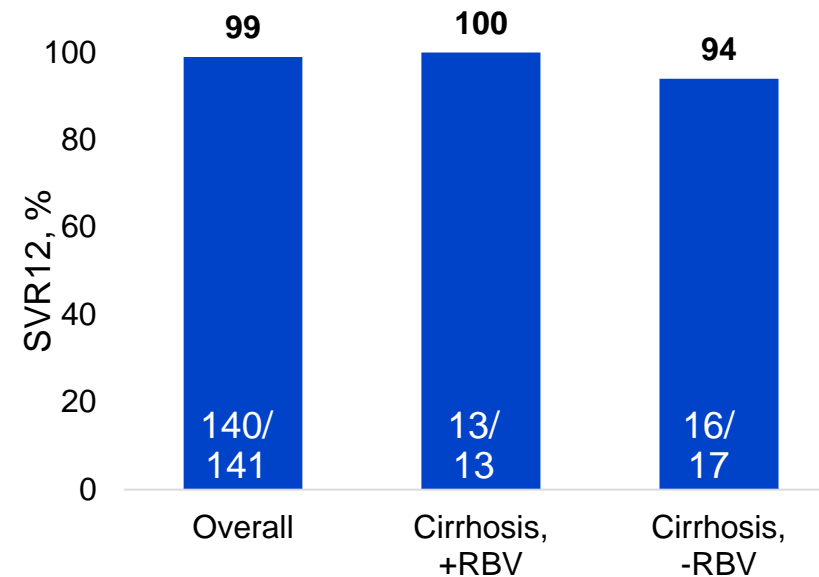
Impact of RAS or RBV Use on Treatment Success of SOF/VEL±RBV for 12 Weeks in HCV GT3 Patients

Prospective multicenter cohort from Germany

Baseline Demographics

	N=232
Male, n (%)	161 (69)
Age, years	47 (38–54)
HIV/HCV, %	11
TE, %	26
Cirrhosis (%)	22
Child Pugh A / B / C, %	90 / 10 / 0
Baseline NS5A RAS available, n (%)	177 (76)
Baseline NS5A RAS positive (A30K/Y93H/A30T)	16 (9%) (8/7/1)
+RBV, n (%)	32 (14)

SVR12 (PP)



- 100% SVR in patients with baseline RASs
 - A30K (n=5)
 - Y93H (n=5)
- One relapser

SVR12 for SOF/VEL ± RBV in this real-world cohort of GT 3 patients with and without baseline RASs was similar to registrational Phase 3 studies

Leczenie po przeszczepie wątroby

- Patients with post-transplant HCV recurrence without cirrhosis, with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis can be treated with the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), or with the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes) (**A1**).
- Patients with post-transplant recurrence of HCV genotype 1, 4, 5 or 6 infection, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and ledipasvir or the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, without the need for pre-treatment immunosuppressant drug dose adjustments (**A1**).
- Patients with post-transplant recurrence of HCV genotype 2 or 3, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks, without the need for pre-treatment immunosuppressant drug dose adjustments (**A1**).
- Patients with post-transplant recurrence of all HCV genotypes, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, with an eGFR <30 ml/min/1.73 m² can be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 12 weeks. Immunosuppressant drug levels need to be monitored and adjusted as needed during and after the end of treatment (**B1**).
- Patients with post-transplant HCV recurrence with decompensated (Child-Pugh B or C) cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), or with the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), for 12 weeks with daily weight-based ribavirin (1,000 or 1,200 mg in patients <75 kg or ≥ 75 kg, respectively). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**B1**).

SOF/VEL przez 12 Tyg po przeszczepie wątroby HCV GT 1-4

Single-arm, open-label phase 2 study conducted in Europe

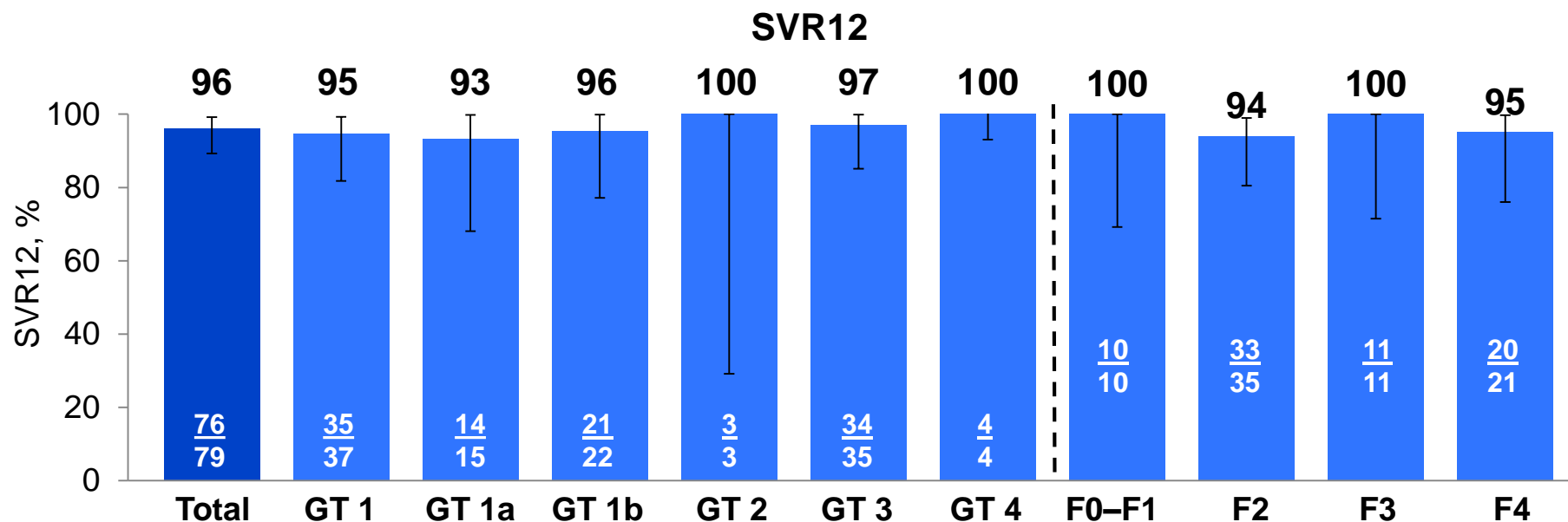
Baseline Demographics

	N=79
Mean age, y (range)	62 (45–81)
Male, n (%)	64 (81)
Mean time since transplant, y (range)	8.7 (0.3–23.9)
HCV GT, % 1a / 1b / 2 / 3 / 4	19 / 28 / 4 / 44 / 5
Protocol-defined Cirrhosis, n (%)	7 (9)
TE, n (%)	47 (60)
DAA ± PEG + RBV*	4 (5)
IFN/PEG ± RBV	43 (54)
Immunosuppression use, n (%)	
Tacrolimus	56 (71)
Cyclosporine	11 (14)
Sirolimus	8 (10)
Everolimus	5 (6)
Mycophenolate	19 (24)
Azathioprine	9 (11)
Prednisolone	1 (1)



* DAA regimens: SOF + RBV, boceprevir + PegIFN + RBV, and telaprevir + PegIFN + RBV

SOF/VEL przez 12 Tyg po przeszczepie wątroby HCV GT 1-4



- 3 patients did not achieve SVR: one early D/C and 2 relapses
- 4/4 patients with baseline Y93H RASs (3 GT 3 and 1 GT 1b) achieved SVR12
- No changes in immunosuppression were needed for rejection or suspected drug-drug interactions

Safety

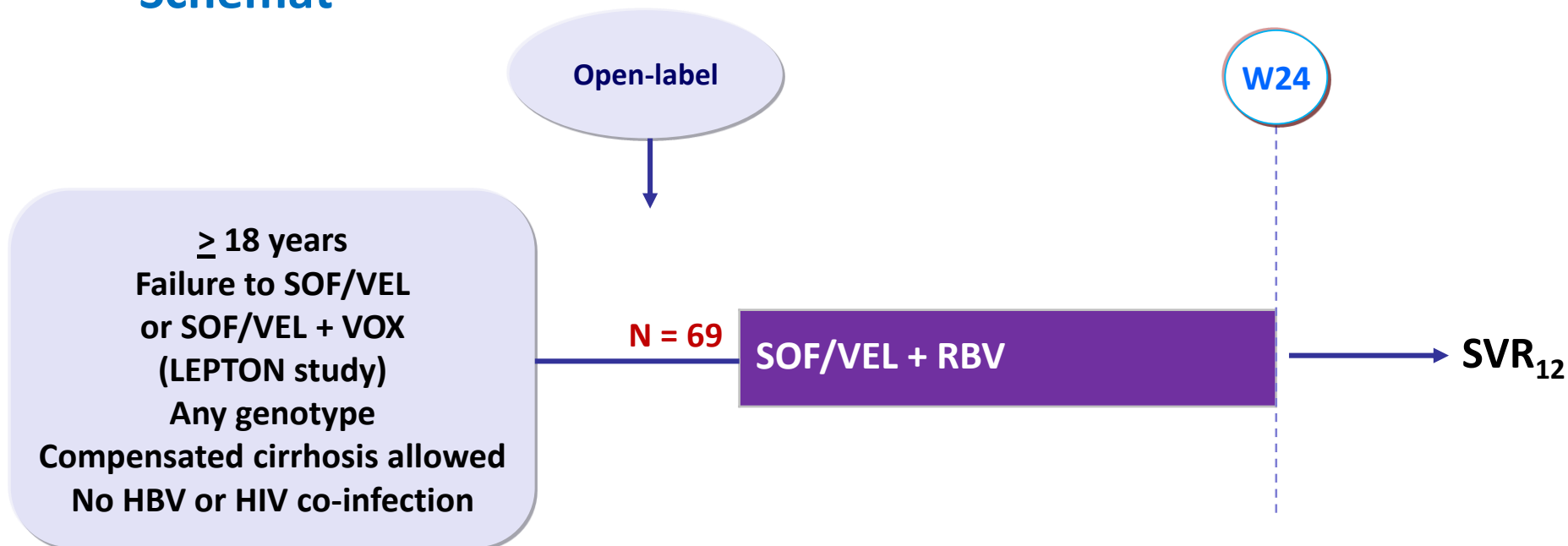
Patients, n (%)	n=79
AEs	62 (78)
Grade 3–4 AE	3 (4)
Serious AE	3 (4)
Treatment D/C due to AE	1 (1)

Wysoka skuteczność SOF/VEL przez 12 tygodni u pacjentów po przeszczepie wątroby

Pacjenci po nieskutecznym leczeniu DAA

Retreatment study: SOF/VEL + RBV in prior NS5A failure - Phase II

■ Schemat



SOF/VEL: 400/100 mg FDC QD ; RBV: weight based in twice daily dose (1000 mg/day if < 75 kg, 1200 mg/day if ≥ 75 kg)

■ Objective

- SVR₁₂ (HCV RNA < 15 IU/mL), by ITT

Retreatment study: SOF/VEL + RBV in prior NS5A failure - Phase II

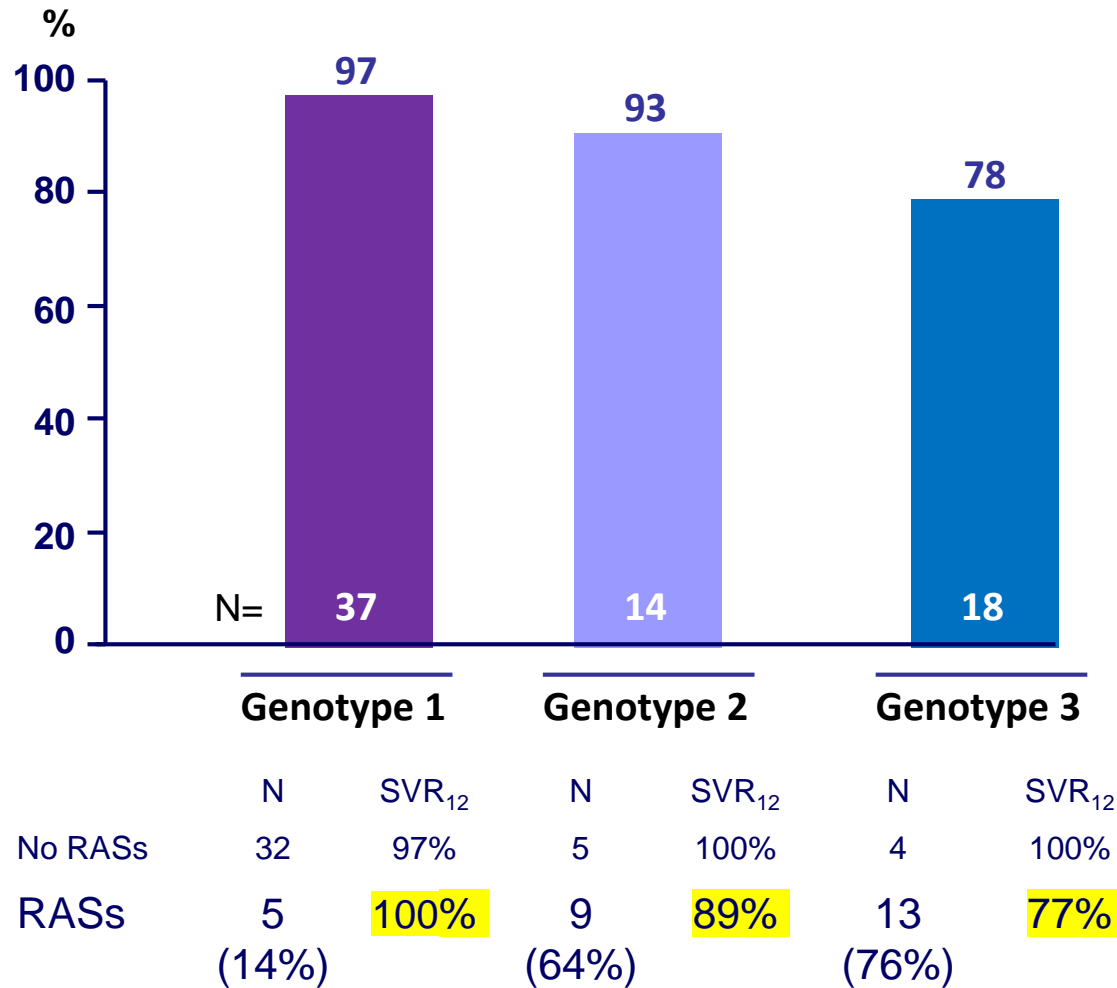
Baseline characteristics, disposition and outcome

	SOF/VEL + RBV N = 69
Age, years, mean	57
Female, %	23
White, %	88
HCV RNA, log ₁₀ IU/mL, mean	6.4
IL28B CC, %	33
Cirrhosis, %	26
Genotype 1a / 1b / 2 / 3, %	46 / 7 / 20 / 26
Prior SOF/VEL + VOX, %	41
Prior VEL dose : 25 mg / 50 mg, %	41 / 59
Prior treatment duration, 4-6W / 8W / 12W, %	36 / 39 / 25
Relapse of prior treatment, %	99
Mean time to retreatment, days	356
Discontinuation, N	3 (adverse event, incarceration, withdrew consent)
SVR ₁₂ *	63/69 (91% [95% CI : 82-97])

* 4 patients excluded from analysis (still in follow-up)

Retreatment study: SOF/VEL + RBV in prior NS5A failure - Phase II

SVR₁₂ by genotype, and by baseline RASs

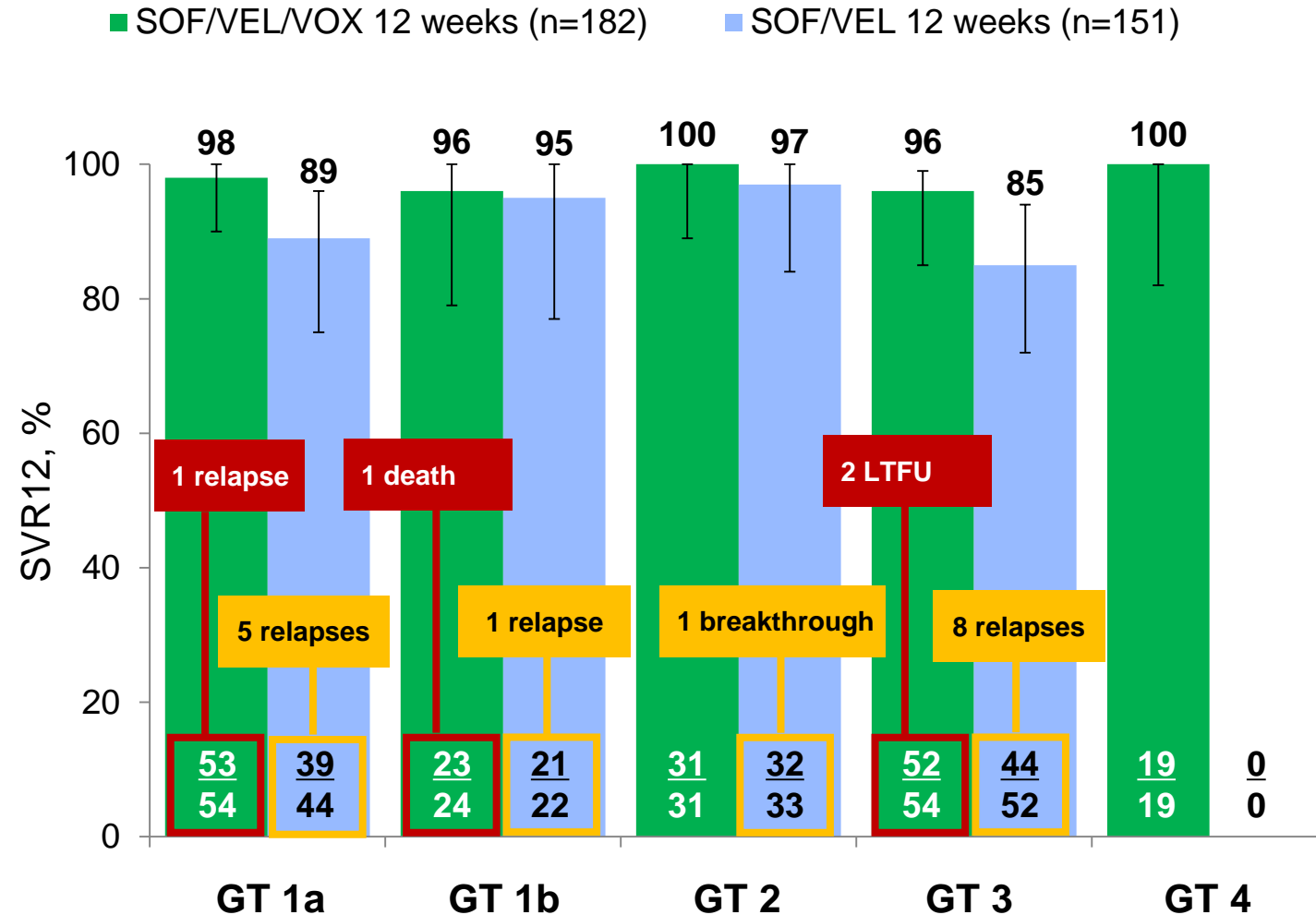


- SVR₁₂ in cirrhosis :
78% vs 96% if no cirrhosis
- Niepowodzenia**
 - Genotype 1: 1 on-treatment virological failure after discontinuation for AE
 - Genotype 2: 1 post-treatment relapse after discontinuation at W8 (pre-treatment with SOF/VEL)
 - Genotype 3: 1 non-response ((pre-treatment with SOF/VEL), 2 relapses (pre-treatment with SOF/VEL in 1, SOF/VEL + RBV in 1) , 1 withdrew consent

Pacjenci po nieskutecznym leczeniu DAA

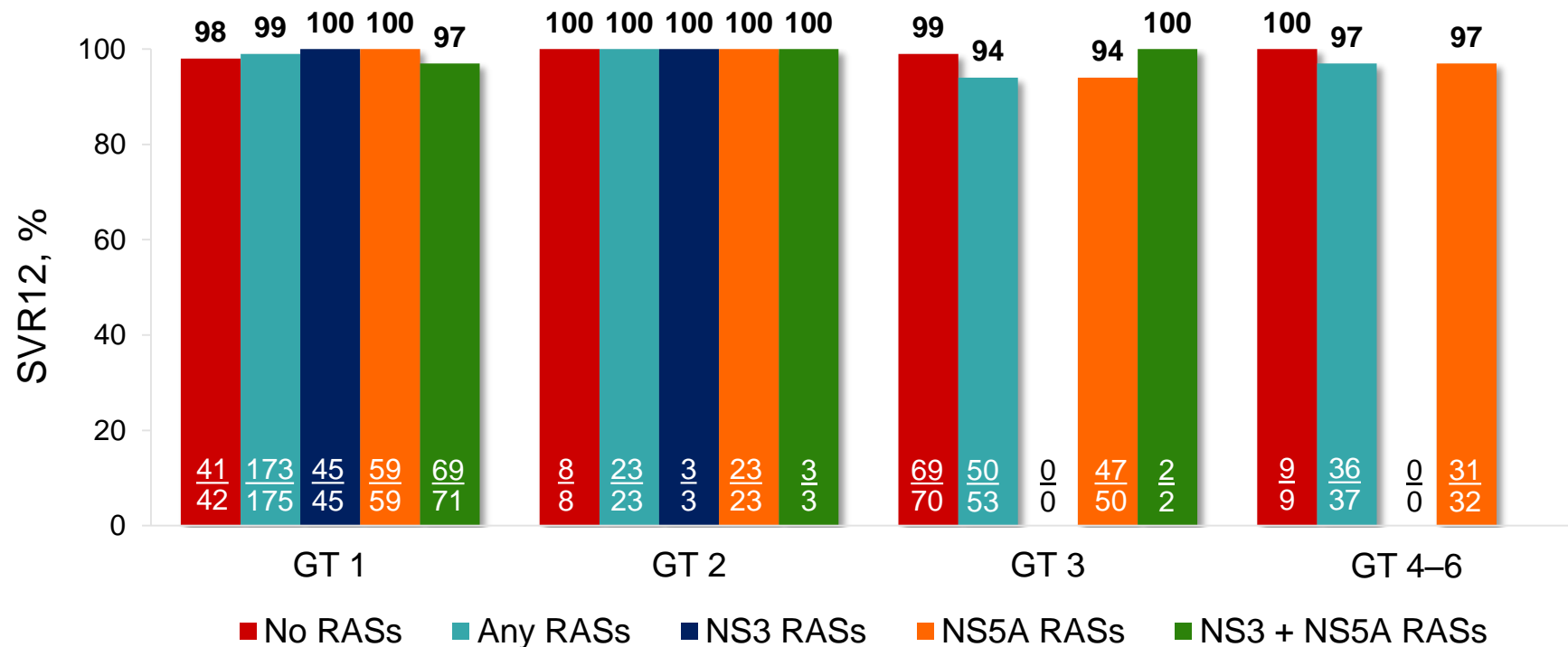
Zatem może SOF/VEL/VOX

SVR12 w zależności od genotypu



Analiza oporności dla SOF/VEL/VOX podawanego przez 12 tygodni u pacjentów leczonych wcześniej DAA

SVR12 in DAA-Experienced Patients With and Without RASs By HCV GT



No impact of RAS on the SVR12 rate in DAA-experienced patients treated with SOF/VEL/VOX for 12 weeks

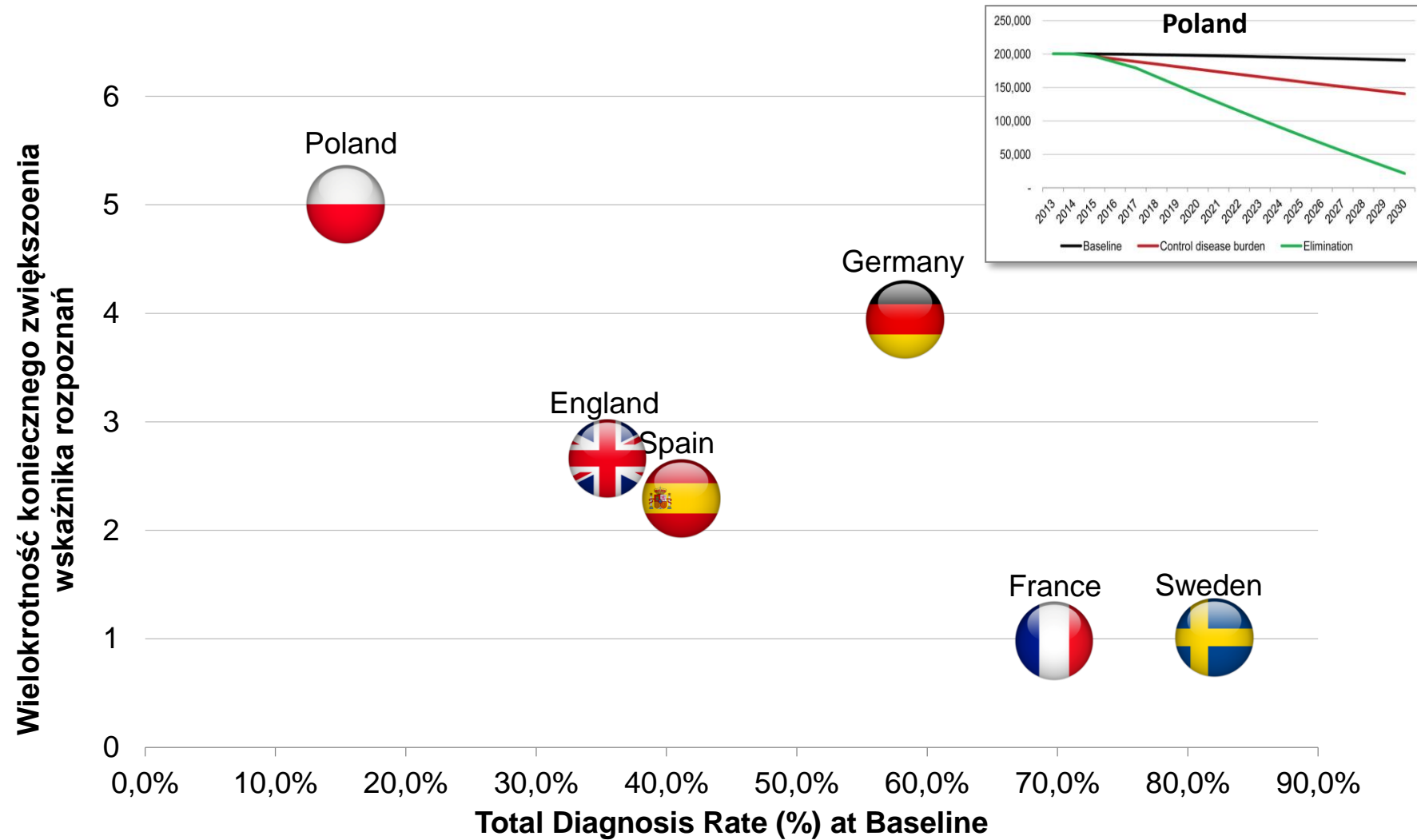
Gdzie ci pacjenci.....?

Akcje przesiewowe:

Populacja ogólna/wybrane grupy wiekowe versus screening w oparciu o czynniki ryzyka

Zadanie na 2018/2019?

A challenge – to increase a rate of new diagnosis to eliminate 90% of HCV in 2030



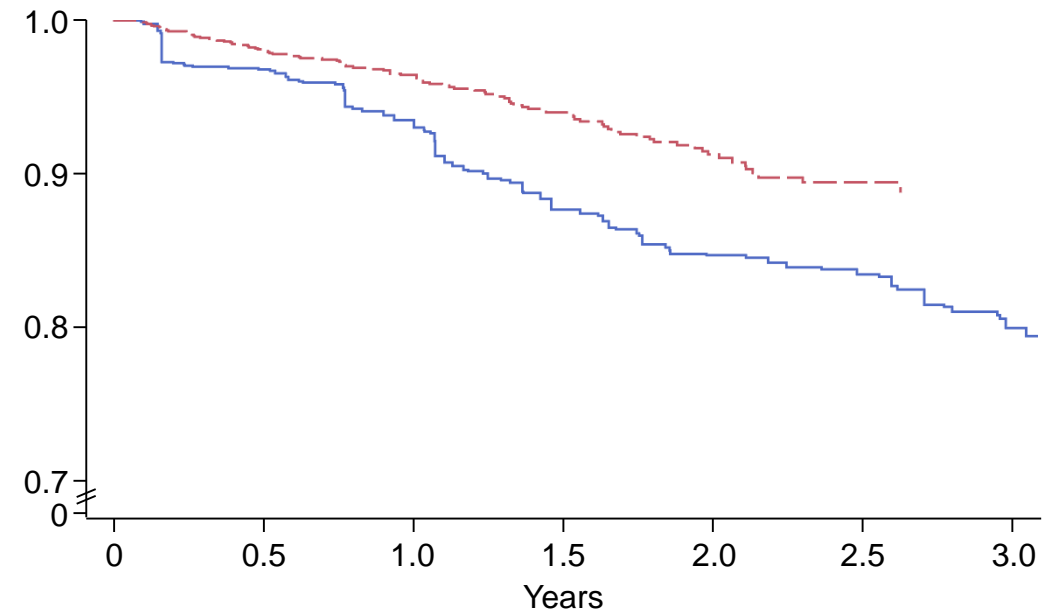
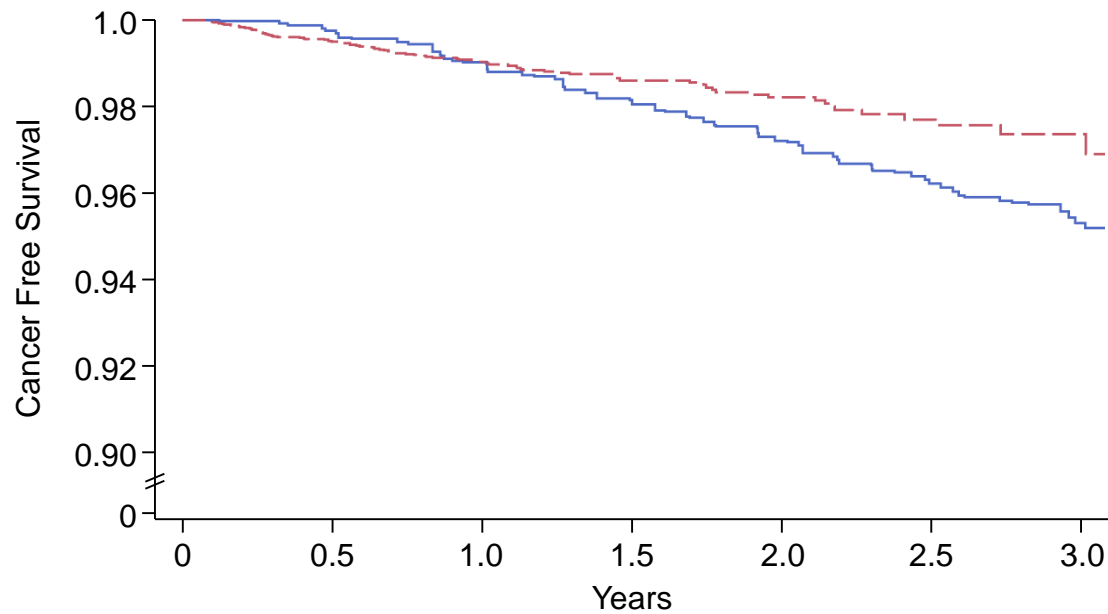
Gdzie ci pacjenci.....?

Dlaczego warto poszukiwać (oprócz choroby wątroby, manifestacji pozawątrobowych, itp....) RÓWNIEŻ

Results: Risk of Other Major Cancers

Prostate Cancer and Lung Cancer

Prostate Cancer				Lung Cancer		
Exposure	N events	Unadjusted rate /100 PY (95% CI)	Adjusted HR (95% CI)	N events	Unadjusted rate /100 PY (95% CI)	Adjusted HR (95% CI)
DAA	86	0.35 (0.28–0.43)	0.71 (0.52–0.97)	97	0.25 (0.20–0.31)	0.55 (0.40–0.74)
pre-DAA IFN	80	0.31 (0.25–0.39)	1.00 (ref)	97	0.24 (0.19–0.29)	1.00 (ref)

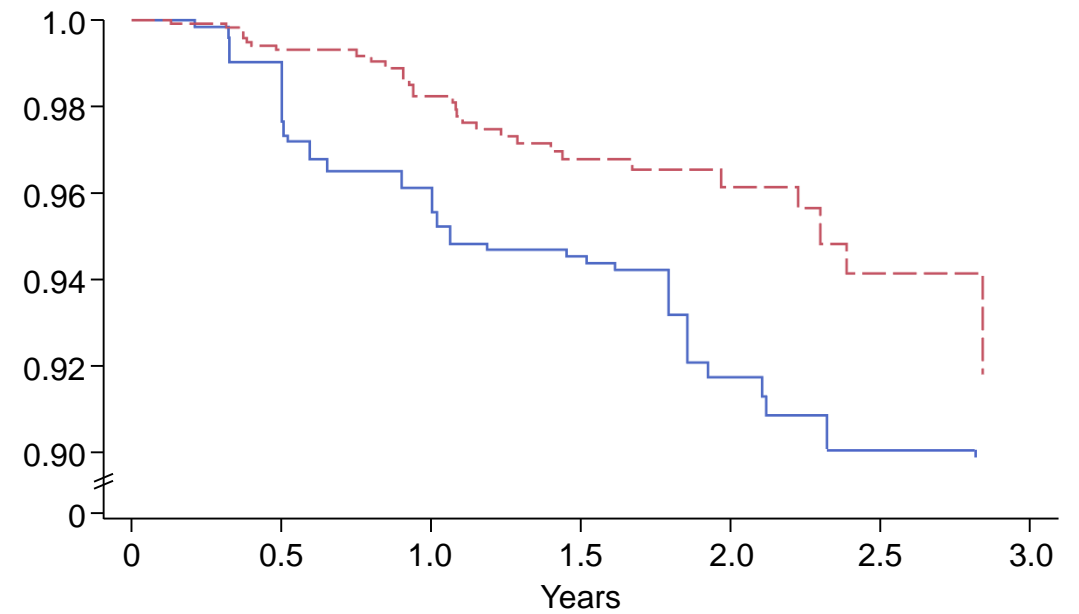
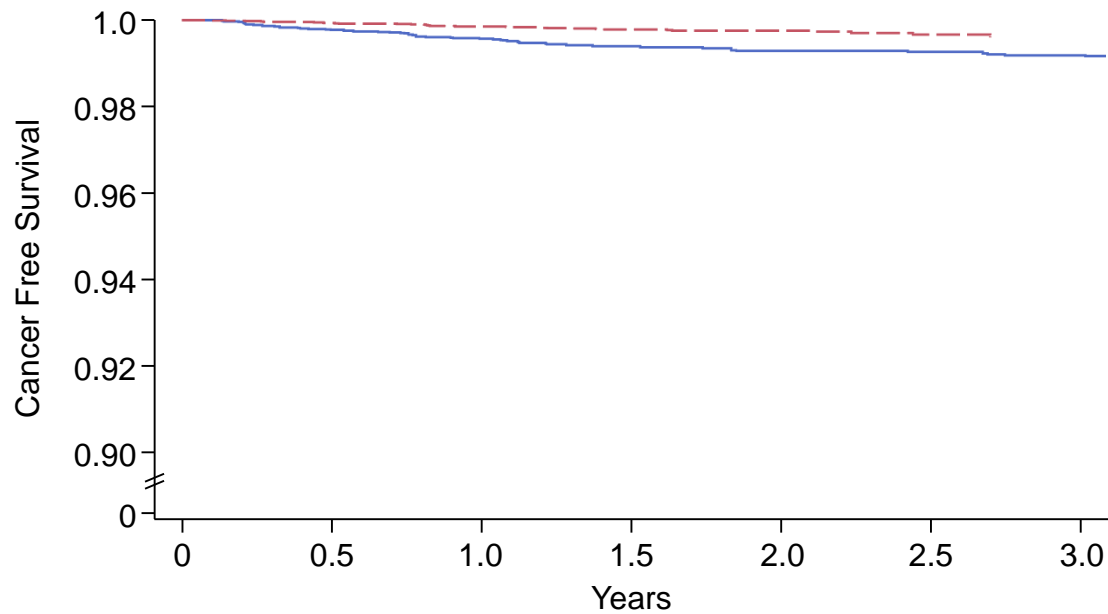


DAA	19,862	15,285	10,528	7078	4142	1756	607	31,355	24,121	16,461	11,074	6413	2703	896
Pre-DAA IFN	8383	7792	6919	6187	5485	4854	4089	13,196	12,239	10,881	9762	8685	7730	6514

Results: Risk of Other Major Cancers

Leukemia and Bladder Cancer

Exposure	Leukemia			Bladder Cancer		
	N events	Unadjusted rate /100 PY (95% CI)	Adjusted HR (95% CI)	N events	Unadjusted rate /100 PY (95% CI)	Adjusted HR (95% CI)
DAA	35	0.09 (0.06–0.13)	0.38 (0.24–0.60)	30	0.08 (0.05–0.11)	0.51 (0.31–0.86)
pre-DAA IFN	63	0.16 (0.12–0.20)	1.00 (ref)	38	0.09 (0.07–0.13)	1.00 (ref)



DAA	31,336	24,111	16,460	11,081	6,403	2688	890	31,382	24,149	16,488	11,101	6429	2706	893
Pre-DAA IFN	13,172	12,215	10,856	9744	8678	7728	6513	13,208	12,255	10,897	9783	8707	7748	6531

Results: Risk of Other Major Cancers

Colorectal, Breast, Esophageal and Pancreas Cancer

	Exposure	N events	Unadjusted rate /100 PY (95% CI)	Adjusted HR (95% CI)
Colorectal	DAA	69	0.18 (0.14–0.23)	0.95 (0.65–1.39)
	Pre-DAA IFN	55	0.14 (0.10–0.18)	1.00 (ref)
Breast (female)	DAA	58	0.44 (0.34–0.57)	0.95 (0.64–1.43)
	Pre-DAA IFN	52	0.36 (0.27–0.47)	1.00 (ref)
Esophageal	DAA	14	0.04 (0.02–0.06)	0.62 (0.28–1.43)
	Pre-DAA IFN	20	0.05 (0.03–0.08)	1.00 (ref)
Esophageal	DAA	17	0.04 (0.03-0.07)	0.62 (0.31-1.23)
	Pre-DAA IFN	22	0.05 (0.03-0.08)	1.00 (ref)

Podsumowanie

Wzrost dostępności leków i leczenia (dla różnych grup pacjentów).

2018 – ostatni rok list oczekujących na leczenie?

Skuteczna i bezpieczna terapia dla (prawie) wszystkich, także po wcześniejszych niepowodzeniach

Zadanie: zidentyfikować niezdiagnozowanych.