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Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, double-blind, placebo-controlled trial

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Hintergrund

- Circa 16-25% der Patienten nach auto-HSZT entwickeln Herpes Zoster innerhalb von 2 Jahren
- Die meisten Patienten nach HSZT haben eine T-Zell Depletion. Die Erkennung von VZV durch T-Zellen funktioniert häufig erst nach Monaten, resp. nach einer Reaktivierung der Infektion
- Zostavax (lebende Zoster Impfung) kontraindiziert bei Immunsupprimierten
- In kleinen proof-of-concept Studien zeigten sich inaktivierte Impfstoffe nach HSCT immunogen und sicher

Methoden

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- **Phase 3 Studie von Merck**
- **Patienten:** Erwachsene mit geplanter auto-HSZT mit anamn. oder serologisch St.n. VZV
- **Intervention:** Gamma Strahlen inaktiviertes VZV
- **Kontrolle:** Plazebo
- **Outcome:** Inzidenz von bestätigtem Herpes Zoster

Methoden

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Patients/Intervention/Control/Outcome

- 135 verschiedene Zentren in Nord- und Südamerika, Europa und Asien
- Einschlusskriterien
  - >18 Jahre alt, geplante auto-HSZT innerhalb 60 Tage
  - Anamnestisch oder/und seroloigsch St.n. VZV
- Ausschlusskriterien
  - >2 Rezidive der malignen Erkrankung
  - Geplante Tandemtransplantation
  - St.n. irgendeiner VZV Impfung
  - Zoster innerhalb des letzten Jahres
  - Geplante Acyclovir/Valacyclovir Prophylaxe für mehr als 6 Monate

Methoden

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Patients/**Intervention**/Control/Outcome

- 5:1:5 Randomisierung für inaktiviertes Virus Vakzin, high-antigen inaktiviertes Virus Vakzin, Placebo
- Stratifizierte Randomisierung für Alter (>50; =< 50) und geplante Dauer der antiviralen Prophylaxe (<=3Monate, 3-6 Monate)
- Doppelt verblindet

Methoden

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Patients/**Intervention**/Control/Outcome

- Vakzin: mit Gamma Strahlen inaktiviertes Virus
- In der Hochdosisgruppe (safety Analyse) Antigen Dosis ca. 6x höher
- Zeitpunkte der Impfung: circa 60 Tage vor auto-HSZT, sowie nach 30, 60 und 90 Tagen nach auto HSZT

Methoden

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Patients/Intervention/**Control**/Outcome

- Placebo: Vakzin Stabilisator ohne Virus Antigene

Methoden

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Patients/Intervention/Control/**Outcome**

- Primary efficacy endpoint: Inzidenz von Herpes Zoster
- Primary safety endpoint: Inzidenz von serious adverse events bis zu 28 Tagen nach 4. Impfung
- Sekundäre Endpunkte: Prävention von Neuralgie, von Komplikationen, sonstigen VZV Manifestationen

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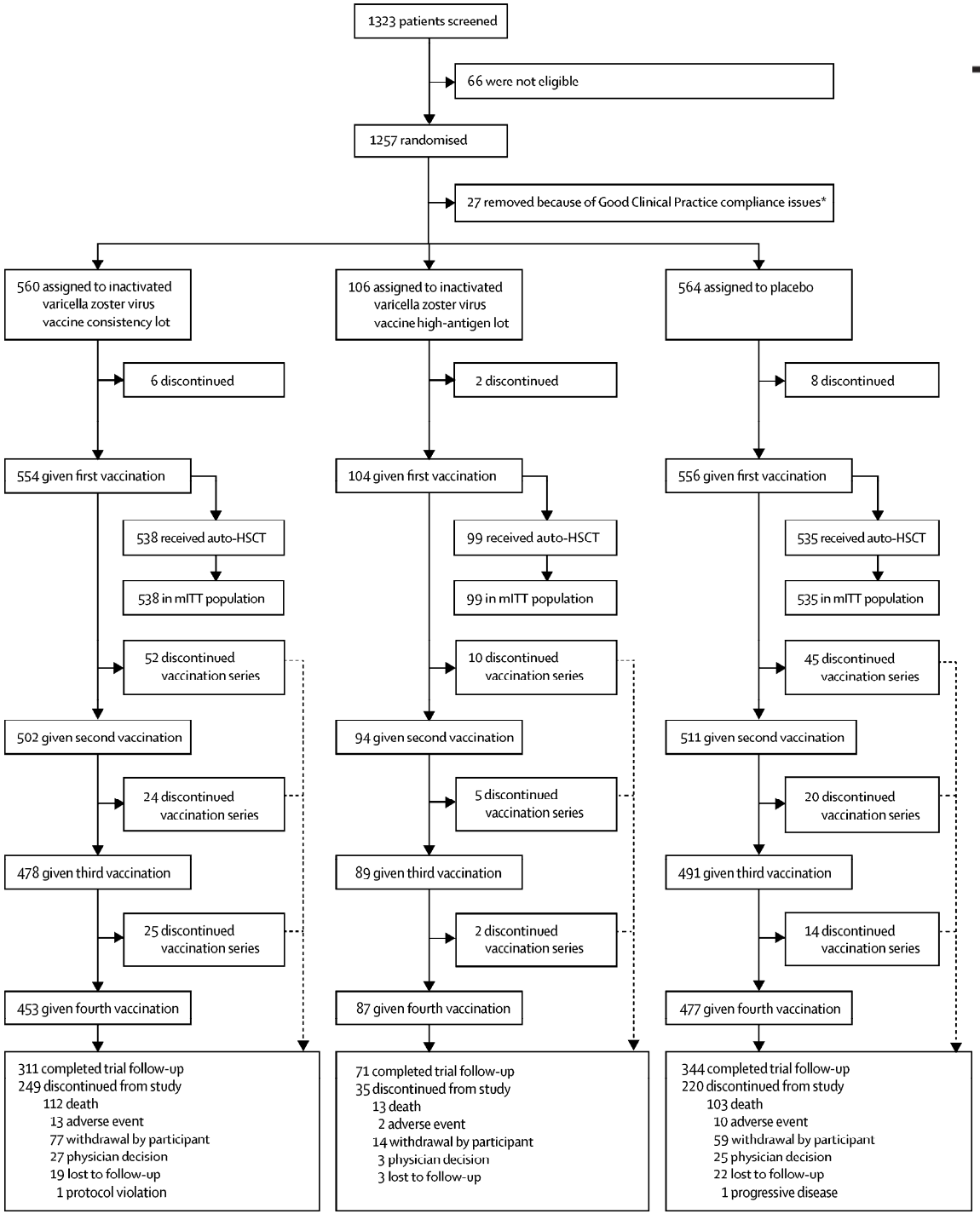
Statistik

- Annahmen
  - 170 Zoster pro 1000 Patienten Jahre, 30% lost to follow-up
- Ziel
  - Solange einschliessen bis 252 bestätigte Zoster Fälle, resp. per Protokoll Abbruch nach insgesamt 5 Jahren
- Vakzin Efficacy
  - Relative Reduktion der Hazard ratio von bestätigten Zoster Fällen in der Verum Gruppe (ohne Hochdosis) zur Placebogruppe


1323 patients screened
66 were not eligible
1257 randomised
27 removed because of Good Clinical Practice compliance issues*
560 assigned to inactivated varicella zoster virus vaccine consistency lot
106 assigned to inactivated varicella zoster virus vaccine high-antigen lot
564 assigned to placebo
6 discontinued
2 discontinued
8 discontinued
554 given first vaccination
104 given first vaccination
556 given first vaccination
538 received auto-HSCT
99 received auto-HSCT
535 received auto-HSCT
538 in mITT population
99 in mITT population
535 in mITT population
52 discontinued vaccination series
10 discontinued vaccination series
45 discontinued vaccination series
502 given second vaccination
94 given second vaccination
511 given second vaccination
24 discontinued vaccination series
5 discontinued vaccination series
20 discontinued vaccination series
478 given third vaccination
89 given third vaccination
491 given third vaccination
25 discontinued vaccination series
2 discontinued vaccination series
14 discontinued vaccination series
453 given fourth vaccination
87 given fourth vaccination
477 given fourth vaccination
311 completed trial follow-up
249 discontinued from study
112 death
13 adverse event
77 withdrawal by participant
27 physician decision
19 lost to follow-up
1 protocol violation
71 completed trial follow-up
35 discontinued from study
13 death
2 adverse event
14 withdrawal by participant
3 physician decision
3 lost to follow-up
344 completed trial follow-up
220 discontinued from study
103 death
10 adverse event
59 withdrawal by participant
25 physician decision
22 lost to follow-up
1 progressive disease

	Inactivated varicella zoster virus vaccine consistency lot (n=560)	Inactivated varicella zoster virus vaccine high antigen lot (n=106)	Placebo (n=564)
Age, years			
Mean	54·1 (12·6)	54·3 (12·2)	54·1 (12·2)
Median	57·0 (19–76)	56·0 (21–75)	56·0 (19–79)
<50 years	158 (28%)	29 (27%)	159 (28%)
≥50 years	402 (72%)	77 (73%)	405 (72%)
Sex			
Male	357 (64%)	58 (55%)	360 (64%)
Female	203 (36%)	48 (45%)	204 (36%)
Underlying disease			
Non-Hodgkin lymphoma	234 (42%)	42 (40%)	250 (44%)
Hodgkin's lymphoma	56 (10%)	10 (9%)	53 (9%)
Multiple myeloma	244 (44%)	50 (47%)	229 (41%)
Acute leukaemia	12 (2%)	1 (1%)	11 (2%)
Others	14 (3%)	3 (3%)	21 (4%)
Conditioning regimen*			
Chemotherapy	496 (89%)	94 (89%)	499 (88%)
Pre-trial varicella zoster virus gpELISA IgG seropositivity†	533/537 (99%)	95/95 (100%)	537/537 (100%)
Intended duration of antiviral prophylaxis after auto-HSCT			
≤3 months	239 (43%)	43 (41%)	255 (45%)
>3 to ≤6 months	320 (57%)	63 (59%)	308 (55%)
Not reported	1 (0%)	0	1 (0%)
Auto-HSCT not done or not vaccinated	22 (4%)	6 (6%)	29 (5%)
mITT population‡	538	99	535
Source of stem cells§			
Peripheral blood	504 (94%)	95 (96%)	508 (95%)
Bone marrow	31 (6%)	4 (4%)	24 (5%)
Cord blood	0	0	1 (0%)
Peripheral blood plus bone marrow or cord blood	2 (0%)	0	2 (0%)
CD34 cells in graft§			
<2 x 10^6 cells per kg	22 (4·1%)	4 (4%)	19 (3·6%)
≥2 x 10^6 cells per kg	514 (95·5%)	93 (94%)	512 (95·7%)
No data	2 (0·4%)	2 (2%)	4 (0·7%)
Maintenance therapy after auto-HSCT§¶			
Rituximab	40 (7%)	9 (9%)	41 (8%)
Brentuximab vedotin	12 (2%)	1 (1%)	7 (1%)
Lenalidomide	83 (15%)	13 (13%)	83 (16%)
Bortezomib	61 (11%)	14 (14%)	71 (13%)
Relapse after auto-HSCT§¶	160 (30%)	32 (32%)	175 (33%)
Actual duration of antiviral drug use after auto-HSCT§¶‖			
None	56 (10·4%)	5 (5·1%)	43 (8·0%)
≤3 months	169 (31·4%)	32 (32·3%)	153 (28·6%)
>3 to ≤6 months	102 (19·0%)	23 (23·2%)	106 (19·8%)
>6 months	211 (39·2%)	39 (39·4%)	233 (43·6%)
Mean, days	157·9 (171·2)	161·0 (176·5)	179·0 (186·5)
Median, days	123·0 (0–1104)	126·0 (0–892)	162·0 (0–1497)

Data are n (%), mean (SD), median (range), or n/N (%). auto-HSCT=autologous haemopoietic stem-cell transplantation. gpELISA=glycoprotein ELISA. *Within 90 days before auto-HSCT. †Number of positive participants out of number with a baseline result. ‡Modified intention-to-treat (mITT) population included all participants who received one dose of vaccine and underwent auto-HSCT. §Data are from the mITT population; proportions have been calculated using the mITT population as the denominator. ¶After auto-HSCT through to the end of the study period. ‖All antiviral drugs with activity against varicella zoster virus were included. Descriptive analysis of actual duration of antiviral agents is the number of total days the patient was on antiviral agents for prophylaxis or treatment, or both, throughout the study period.

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	Inactivated varicella zoster virus vaccine consistency lot group (n=538)			Placebo group (n=535)			Estimated vaccine efficacy (%; 95% CI)*
	Confirmed participants	Follow-up (person-years)	Incidence (per 1000 person-years)	Confirmed participants	Follow-up (person-years)	Incidence (per 1000 person-years)	
Herpes zoster disease	42 (8%)	1277	32·9	113 (21%)	1230	91·9	63·8% (48·4–74·6)
Moderated-to-severe herpes zoster-associated pain†	19 (4%)	1277	14·9	61 (11%)	1230	49·6	69·5% (49·0–81·8)
Herpes zoster-related complications†	12 (2%)	1277	9·4	44 (8%)	1230	35·8	73·5% (49·8–86·0)
Post-herpetic neuralgia‡	3 (1%)	1277	2·3	18 (3%)	1230	14·6	83·7% (44·6–95·2)

n=number of participants in the mITT (modified intention-to-treat) population. *Point estimate and 95% CI of vaccine efficacy obtained from Cox proportional hazards regression model adjusted for age (<50 years *vs* ≥50 years) and intended duration of antiviral prophylaxis (≤3 months *vs* >3 to ≤6 months after transplantation). Vaccine efficacy was calculated as 1 minus the hazard ratio of herpes zoster in the inactivated varicella zoster virus vaccine consistency lot group *vs* placebo group. Moderate-to-severe herpes zoster-associated pain is defined as two or more occurrences of a score of 3 or more on the Zoster Brief Pain Inventory[24] (ZBPI; 0–10 point scale) at any time from the onset of herpes zoster to the end of the 6-month follow-up. †Herpes zoster-related complications, including admission to hospital or an extended stay in hospital due to herpes zoster, dissemination of herpes zoster manifested by disseminated rash or varicella zoster viraemia, visceral herpes zoster, ophthalmic herpes zoster, neurological impairment due to herpes zoster, or the need for intravenous aciclovir for treatment of herpes zoster. ‡Post-herpetic neuralgia is defined as pain in the area of a herpes zoster rash with a worst pain in the past 24 h score of 3 or greater on the ZBPI that persists or recurs beyond 90 days after onset of the rash.

Table 2: **Incidence of confirmed cases of herpes zoster, moderate-to-severe pain, complications related to herpes zoster, and post-herpetic neuralgia, in the mITT population**

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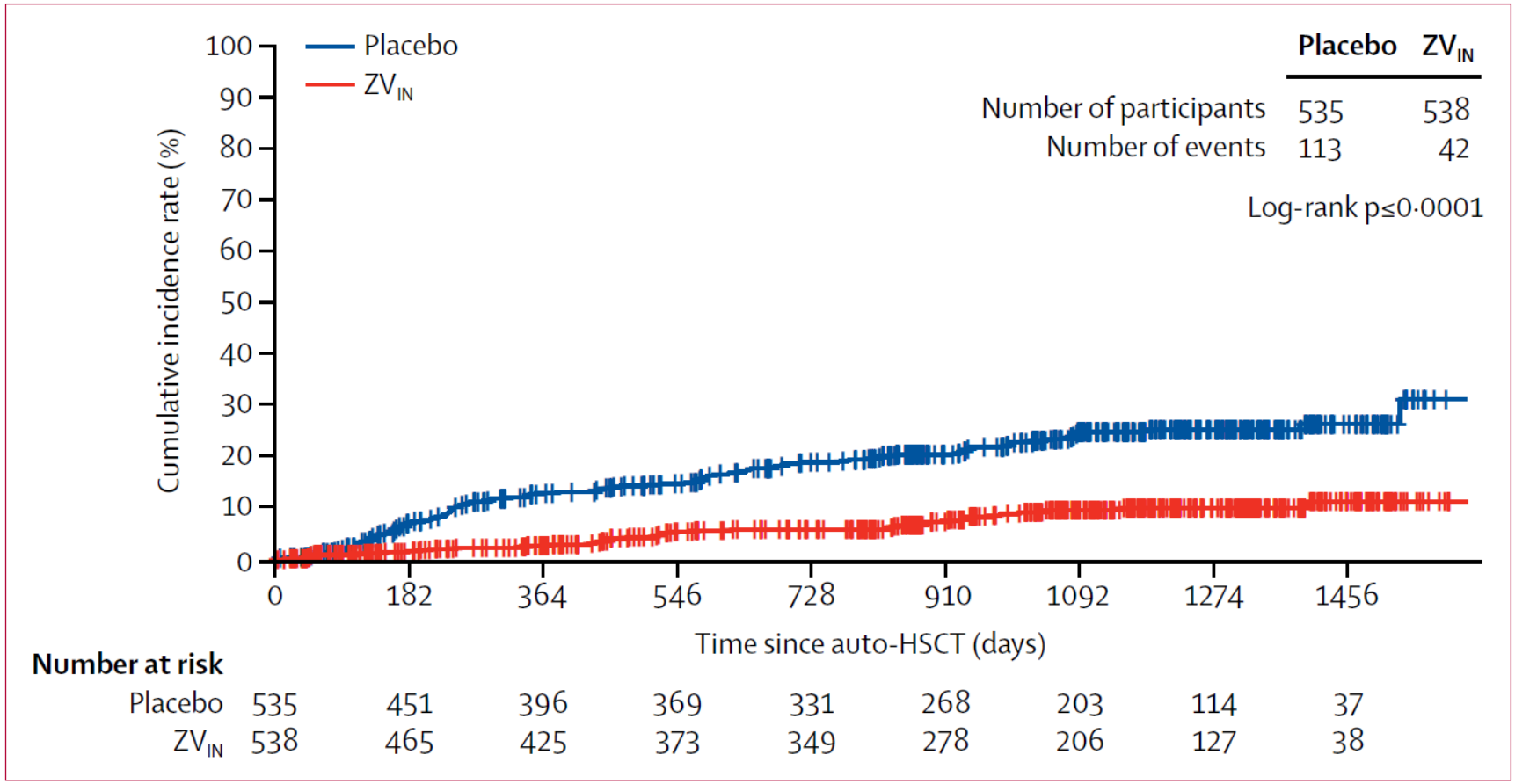
Follow-up

- Medianes efficacy Follow up 2.56 Jahre (1 Tag -4.5 Jahre)


Placebo
ZVIN
Cumulative incidence rate (%)
100
90
80
70
60
50
40
30
20
10
0
0
182
364
546
728
910
1092
1274
1456
Time since auto-HSCT (days)
Placebo ZVIN
Number of participants 535 538
Number of events 113 42
Log-rank p≤0·0001
Number at risk
Placebo 535 451 396 369 331 268 203 114 37
ZVIN 538 465 425 373 349 278 206 127 38

	Inactivated varicella zoster virus vaccine* (n=657)	Placebo (n=554)	Risk difference (95% CI)	p value
Participants with one or more adverse event	644 (98%)	537 (97%)	1·1% (–0·7 to 3·0)	0·249
Vaccine-related adverse event†	214 (33%)	70 (13%)	20·0% (15·5 to 24·5)	<0·0001
Vaccine-related injection site adverse event‡	191 (29%)	36 (7%)	22·6% (18·5 to 26·6)	<0·0001
Vaccine-related non-injection site adverse event	42 (6%)	38 (7%)	–0·4% (–3·3 to 2·4)	0·804
Serious adverse event	216 (33%)	181 (33%)	0·2% (–5·1 to 5·5)	0·942
Serious vaccine-related adverse event	5 (1%)	5 (1%)	–0·1% (–1·4 to 1·1)	0·834
Discontinued because of adverse event	20 (3%)	17 (3%)	0·0% (–2·1 to 2·0)	0·994
Death	41 (6%)	35 (6%)	–0·1% (–2·9 to 2·7)	0·965

Data are n (%) unless otherwise specified. All adverse events observed from the time of first dose of vaccine through to 28 days after the fourth dose were recorded. *All participants who were in the consistency lot group and the high-antigen lot group. †Determined by an investigator to be related to the vaccine. ‡Pain, erythema, swelling, or induration at injection site.

Table 4: Summary of adverse events

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Diskussion

- Studie bestätigt Proof-of-concept Studien, Impfeffizienz 63.8% (95%CI 48.4-74.6%)
- Impfung ist bis auf erhöhte Anzahl von Lokalreaktionen (mild) sicher
- Die Impfung ist früh nach auto HSZT immunogen

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Limitationen

- Nicht alle Zoster PCR bestätigt (83% Verum, 75% Placebo), Rest duch ein Expertenkommitee
- Viele Abbrecher/Loss to follow up
- Knapp 40% mit Prophylaxe mehr als 6 Monate
- Von Merck gesponsert, viele Mitarbeiter beteiligt

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Offene Fragen

- Würde es auch mit dem rekombinanten verfügbaren Impfstoff (Shingrix, GSK) funktionieren?
- Allo HSZT?
- 4fach Impfung wirklich notwendig?

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- Fragen
- Kommentare?