

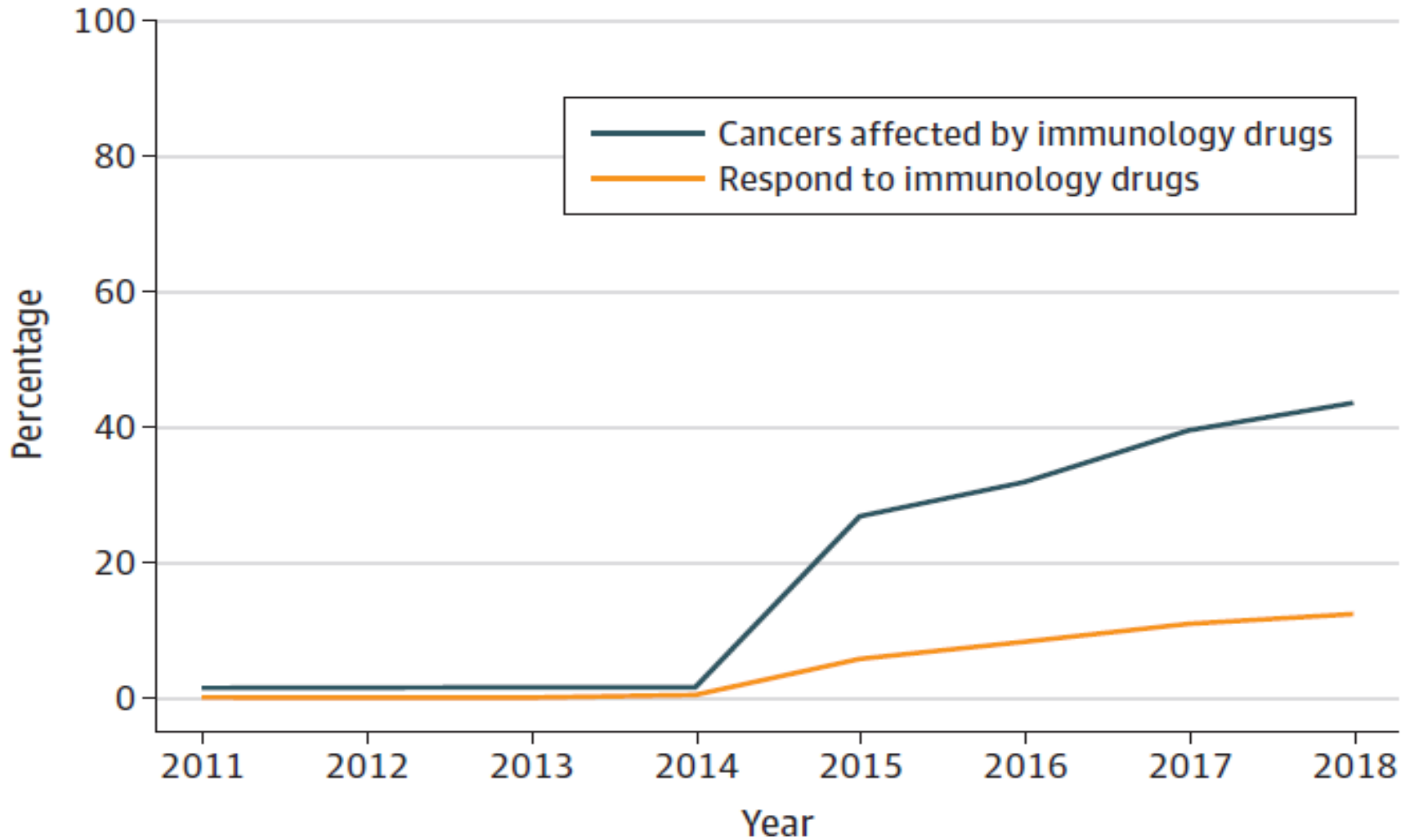
KH Pharmazie

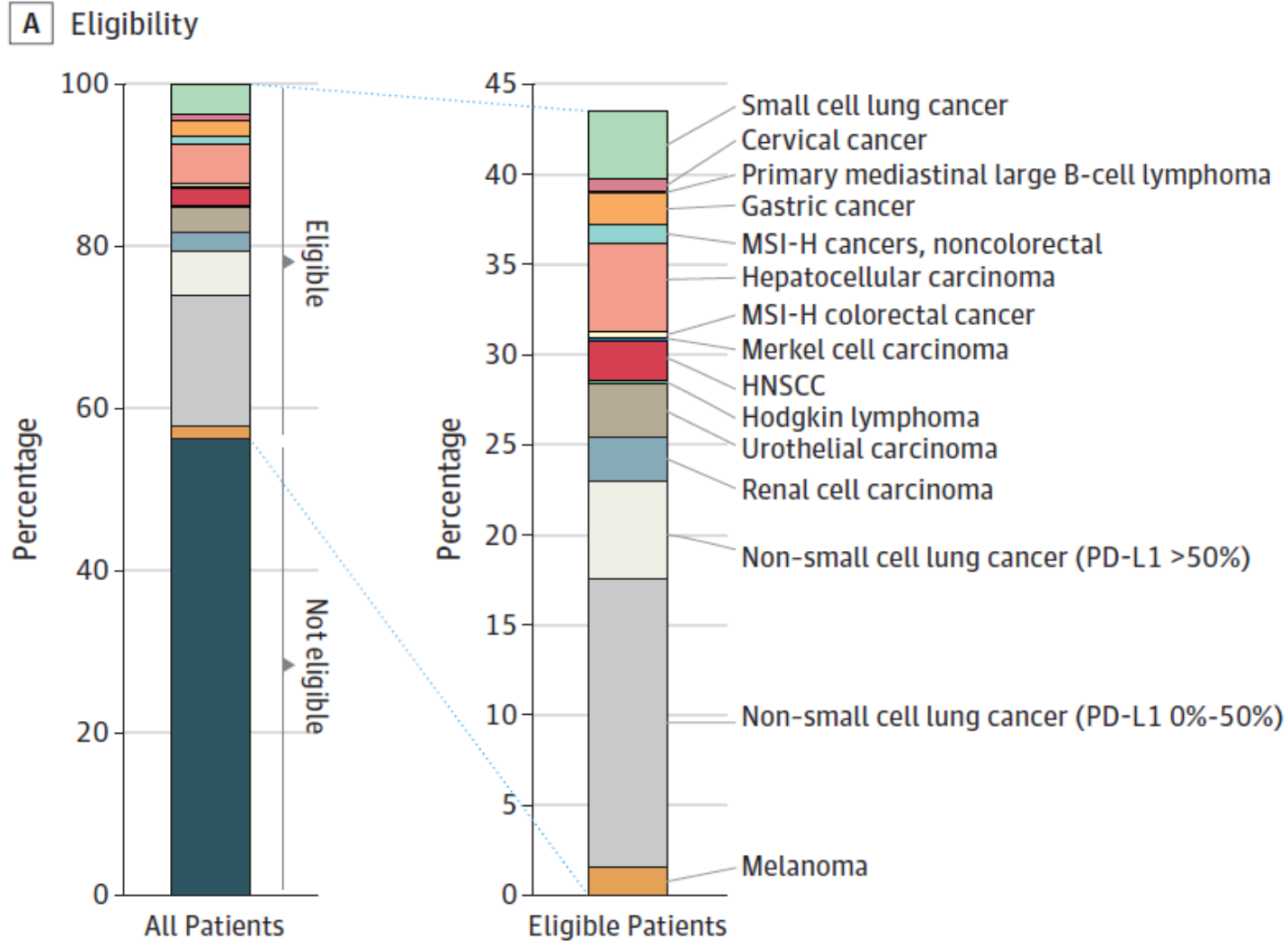
2019

Assoc.Prof.PD.Dr.Thorsten Füreder
Univ.Klinik für Innere Medizin I &CCC, MUW

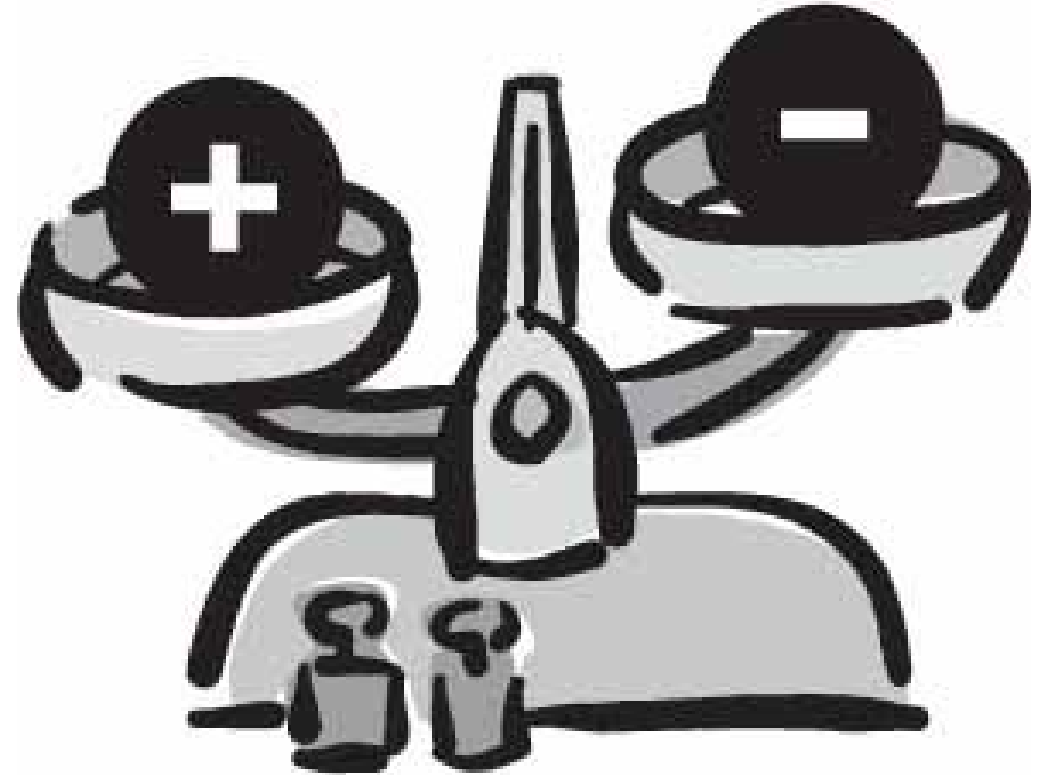


Immuntherapie





- Hohes Lebensalter
- HIV/Hepatitis Patienten
- Hirnmetastasen
- Autoimmunerkrankungen
- Nach Immuntherapie Nebenwirkungen
- Organtransplantation





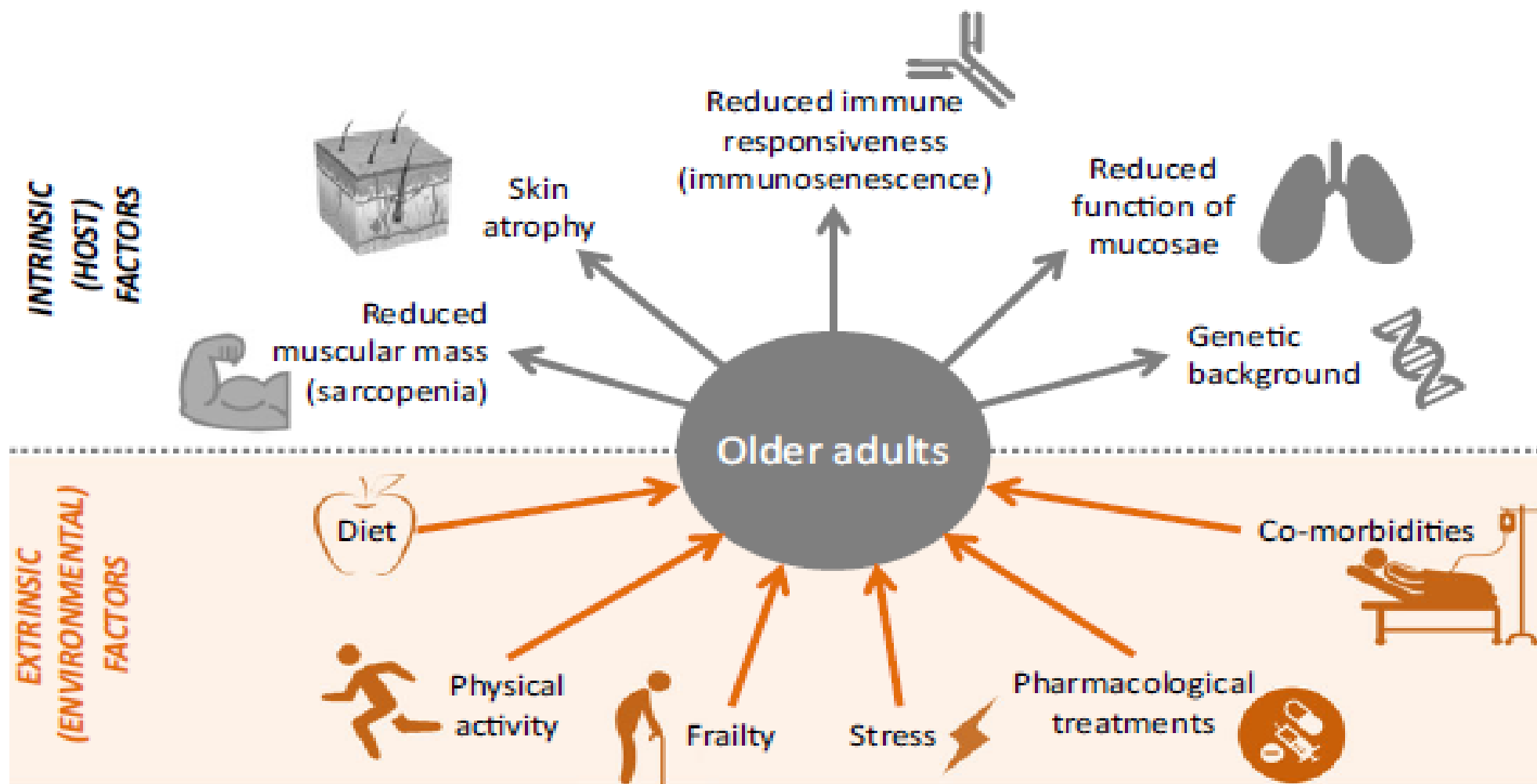
**Männlicher 90 jähriger Pat.
NSCLC met.; Plattenepithelca.
St.p. Nikotinabusus
PDL-1: 0%**

Immuntherapie?





Spezialfall: Elderly

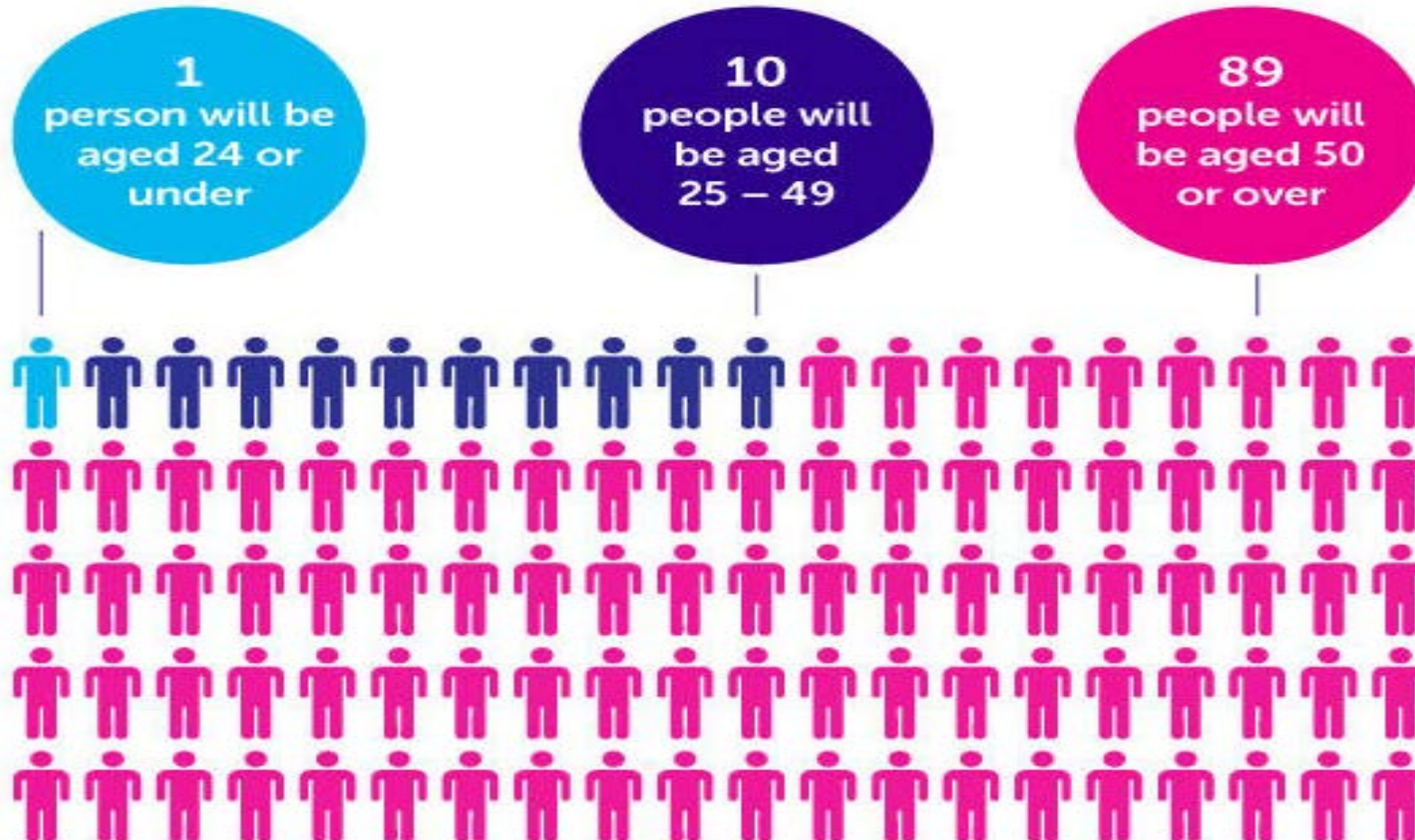




Spezialfall: Elderly

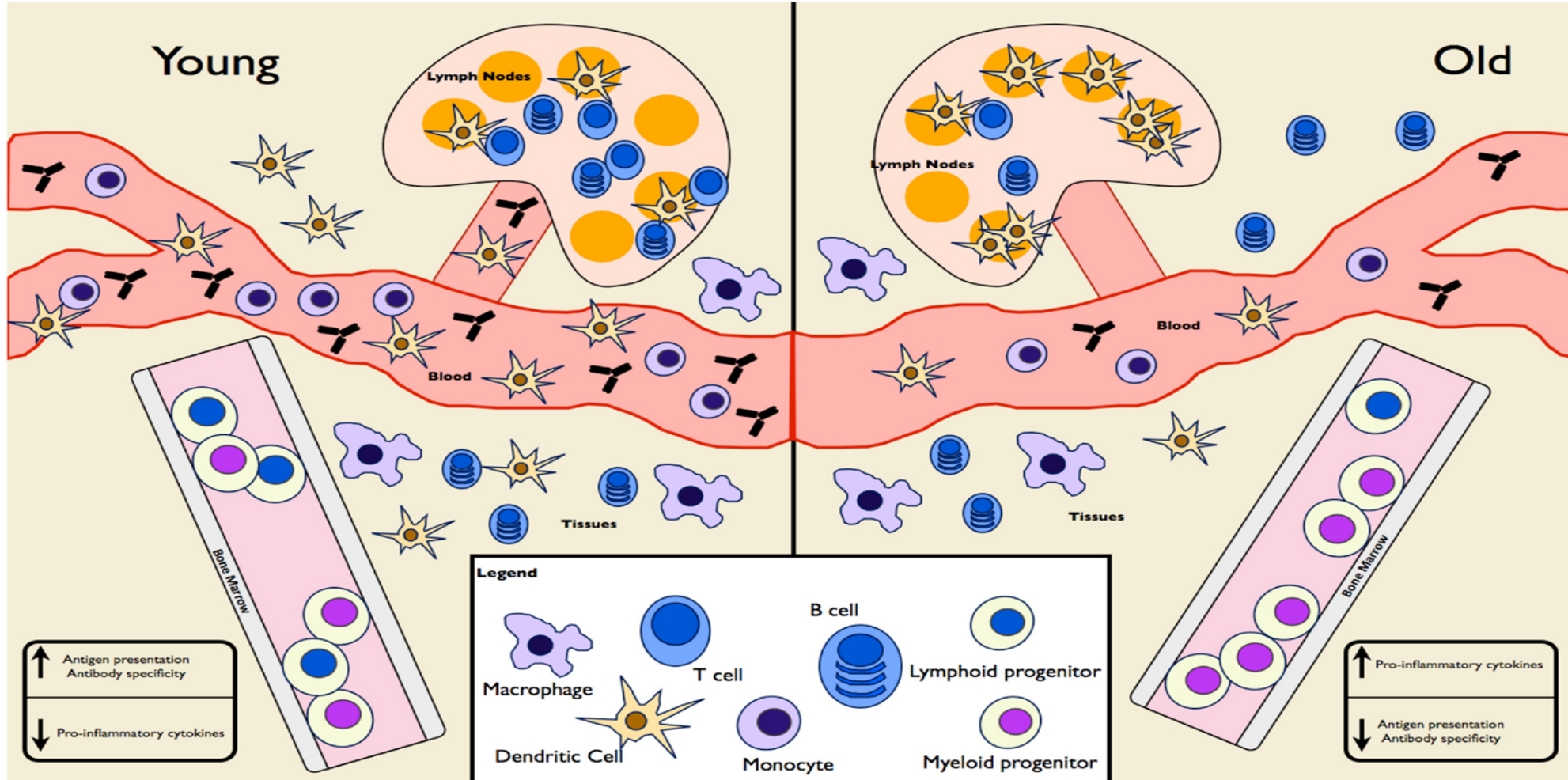


For every 100 people diagnosed with cancer:



Spezialfall: Elderly

Immunseneszenz



Spezialfall: Elderly und Mikrobiom



Chronic
Disease



Immune
System

■ Bifidobacteria
■ Other

~ 60 - 70%



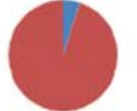
~ 30 - 40%



~ 10 %



~ 0 - 5%



Level of
bifidobacteria

Early life

Adulthood

Old age

Impacts



NEC



IBS

Obesity/
Diabetes

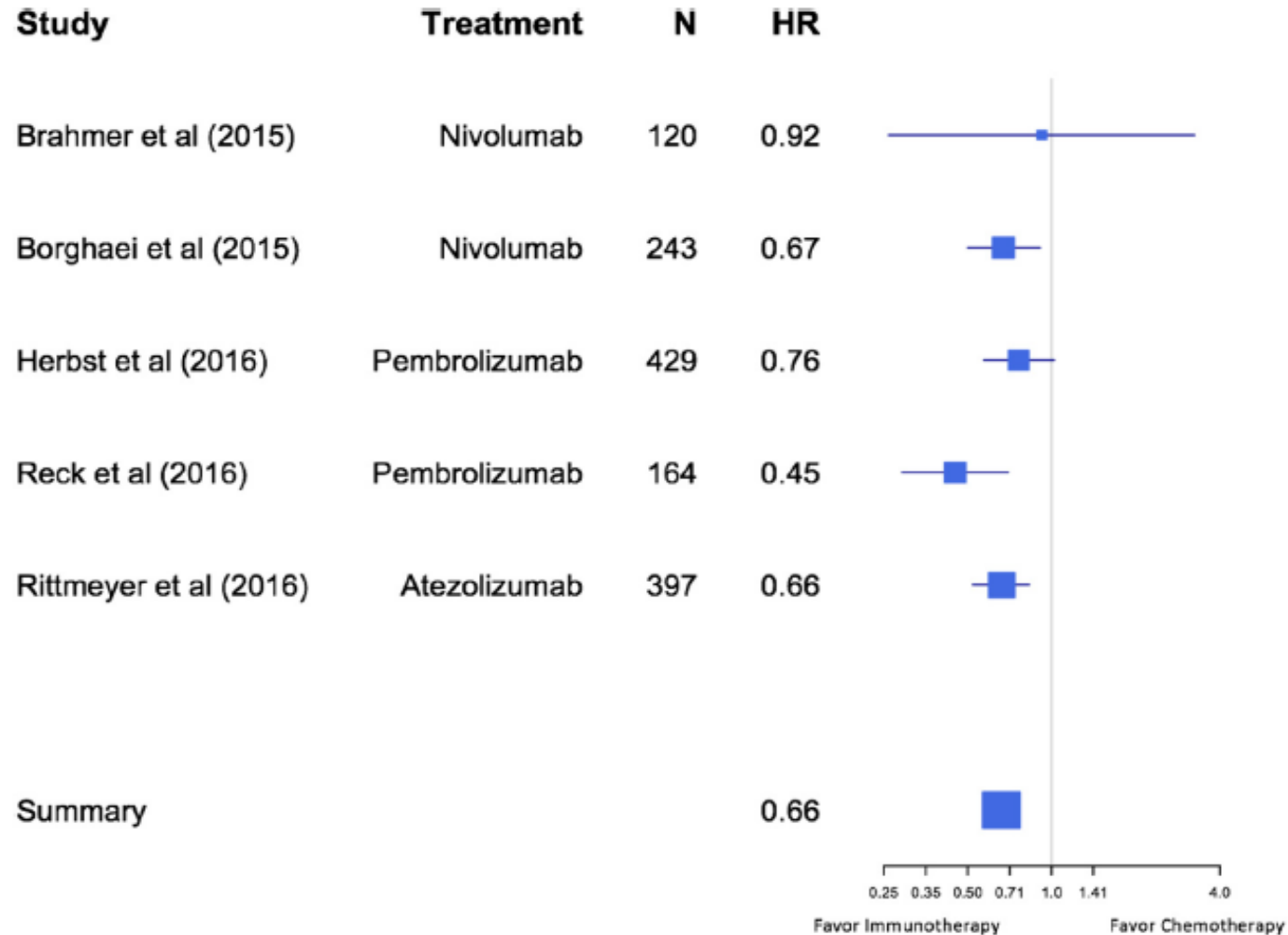


Cancer





Elderly und Immuntherapie





Spezialfall: Elderly und OS



Table 1

Assessment of risk of death in favour of immuno-oncology (IO) versus standard of care according to population subgroups.

| Type of tumours | Treatment | Entire cohort (n, %) | Patients <65 years (n, %) | Patient ≥65 years (n, %) | Patients >75 years (n, %) |
|--|---|-------------------------------------|------------------------------------|---|-----------------------------------|
| Head and neck [76] | Nivolumab 3 mg/kg every 2 weeks | 0.69 (0.53–0.91) (n = 361, 100%) | 0.64 (0.45–0.89) (n = 248, 69%) | 0.93 ^a (0.56–1.54) (n = 95, 26%) | N/S (n = 18, 5%) |
| Renal cell carcinoma [78] | Nivolumab 3 mg/kg every 2 weeks | 0.76 (0.62–0.92) (n = 821, 100%) | 0.78 (0.60–1.01) (n = 497, 61%) | 0.64 ^a (0.45–0.91) (n = 250, 30%) | 1.23 (0.66–2.31) (n = 74, 9%) |
| Bladder cancer [83] | Pembrolizumab 200 mg every 3 weeks | 0.73 (0.59–0.91) (n = 542, 100%) | 0.75 (0.53–1.05) (n = 230, 42%) | 0.73 (0.56–0.94) (n = 312, 58%) | N/S |
| Melanoma [84] | Ipilimumab 3 mg/kg every 3 weeks | 0.64 (0.49–0.84) (n = 273, 100%) | 0.65 (0.47–0.90) (n = 189, 69%) | 0.61 (0.38–0.99) (n = 84, 31%) | N/S |
| Melanoma [87] | Nivolumab 3 mg/kg every 2 weeks | 0.42 (0.25–0.73) (n = 418, 100%) | 0.52 (0.10–0.61) (n = 200, 48%) | 0.44 ^a (0.24–0.81) (n = 151, 36%) | 0.25 (0.10–0.61) (n = 67, 16%) |
| Melanoma [89] | Pembrolizumab 10 mg/kg every 2 weeks | 0.63 (0.47–0.83) (n = 557, 100%) | 0.65 (0.44–0.95) (n = 319, 57%) | 0.56 (0.36–0.87) (n = 238, 43%) | N/S |
| Melanoma [89] | Pembrolizumab 10 mg/kg every 3 weeks | 0.69 (0.52–0.90) (n = 555, 100%) | 0.77 (0.53–1.12) (n = 318, 57%) | 0.66 (0.44–1.01) (n = 237, 43%) | N/S |
| Non-squamous cell non-small lung cancer [96] | Nivolumab 3 mg/kg every 2 weeks | 0.75 (0.62–0.91) (n = 582, 100%) | 0.81 (0.62–1.04) (n = 339, 58%) | 0.63 ^a (0.45–0.89) (n = 200, 34%) | 0.90 (0.43–1.87) (n = 43, 7%) |
| Squamous cell non-small-cell lung cancer [97] | Nivolumab 3 mg/kg every 2 weeks | 0.59 (0.44–0.79) (n = 272, 100%) | 0.52 (0.35–0.75) (n = 152, 56%) | 0.56 ^a (0.34–0.91) (n = 91, 33%) | 1.85 (0.76–4.51) (n = 29, 11%) |
| Non-small-cell lung cancer PD-L1 positive [94] | Pembrolizumab 200 mg every 3 weeks | 0.50 (0.37–0.68) (n = 305, 100%) | 0.61 (0.40–0.92) (n = 141, 46%) | 0.45 (0.29–0.70) (n = 164, 54%) | N/S |

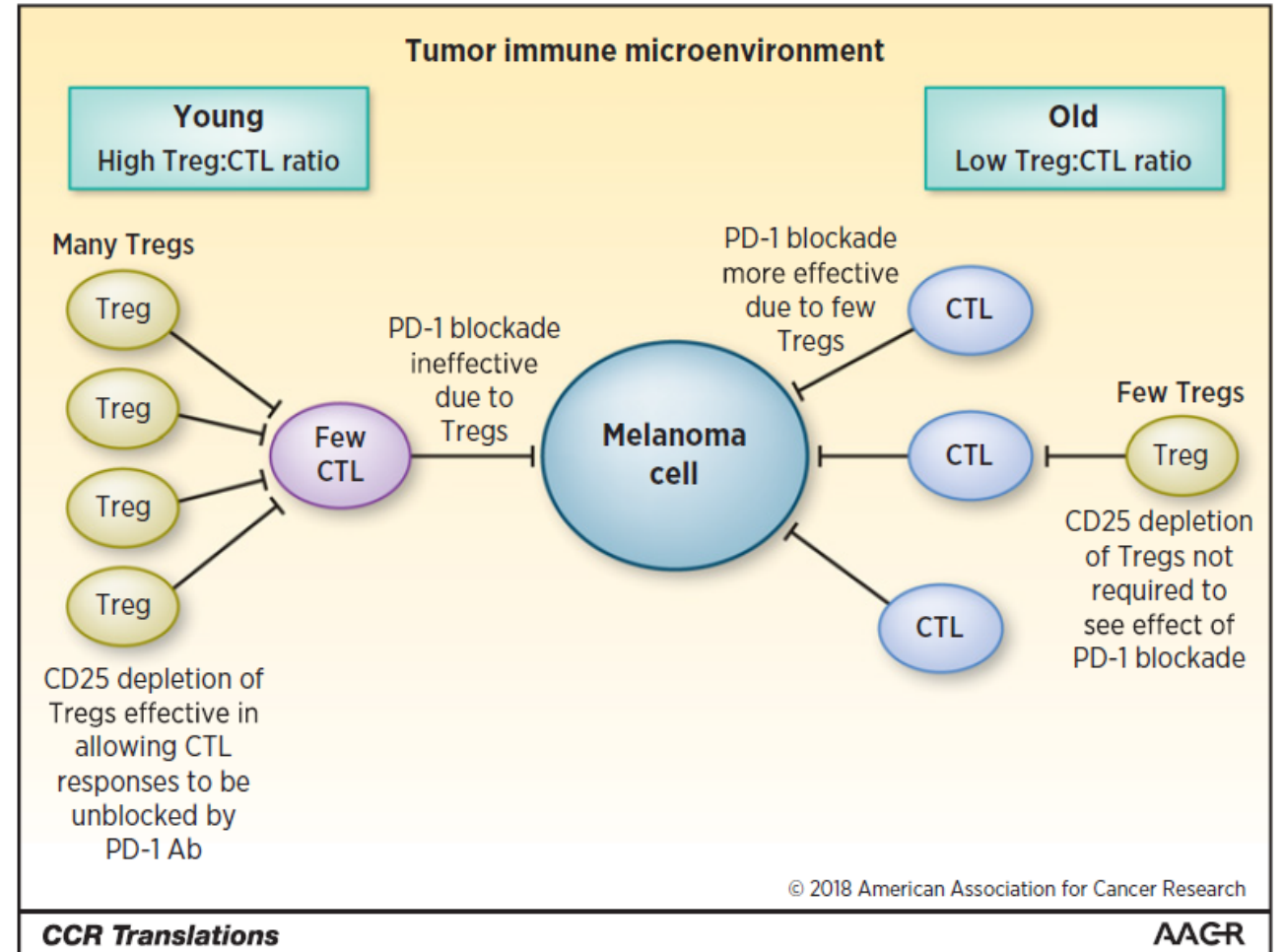
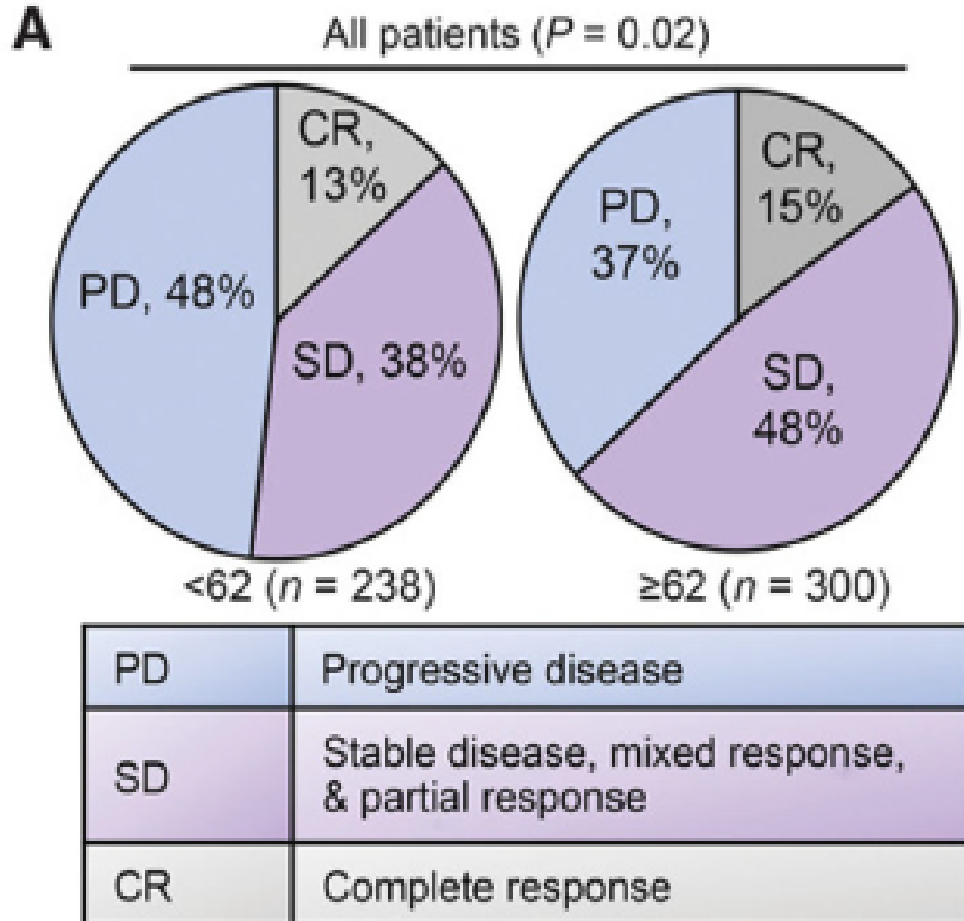


Spezialfall: Elderly und irAEs



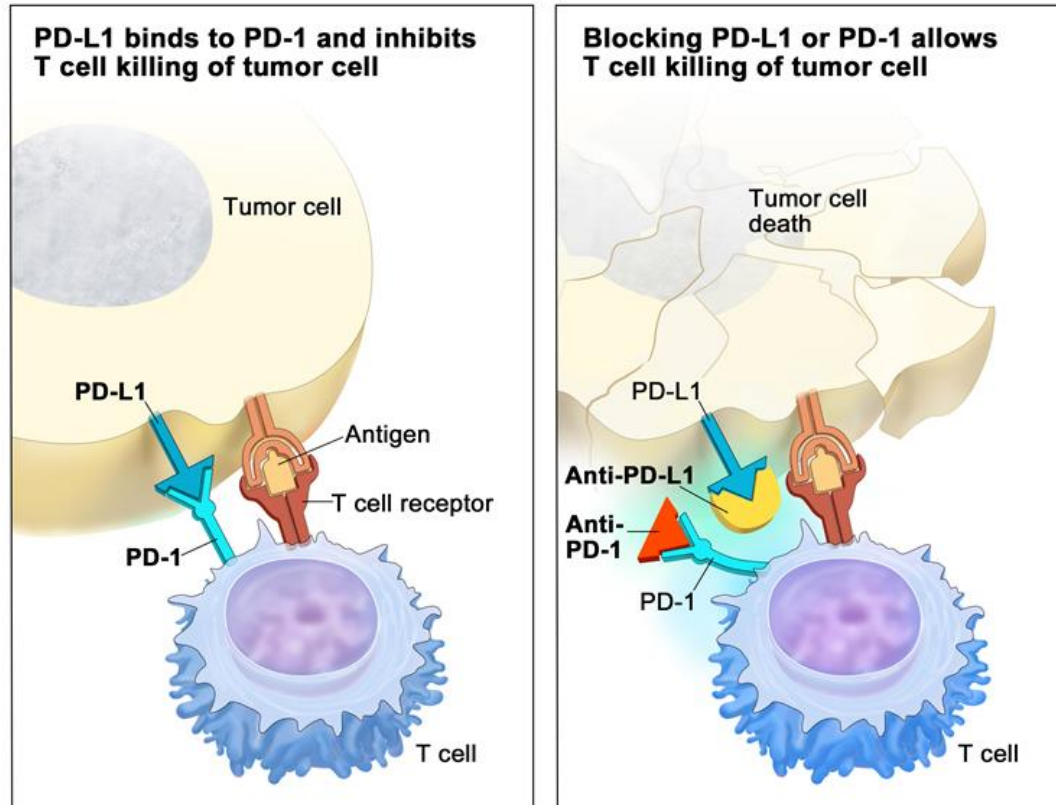
| | Patients < 65 yrs (N=616) n% | Patients ≥ 65 yrs (N=414) n% | Patients ≥ 70 yrs (N=212) n% |
|--|--|---|---|
| Grade 1-2 Adverse Events | 584 (94.8) | 394 (95.2) | 202 (95.3) |
| Grade 3-5 Adverse Events | 360 (58.4) | 259 (62.6) | 152 (71.7) |
| Serious Adverse Events | 313 (50.8) | 242 (58.5) | 123 (58.0) |
| All Adverse Events leading to Discontinuation | 89 (14.4) | 71 (17.1) | 42 (19.8) |
| AEs Requiring Treatment with Immune Modulating Medication | 256 (41.5) | 196 (47.3) | 110 (51.9) |
| Select irAE's where immune modulating medication was initiated | | | |
| Diarrhea/colitis | 15 (2.4) | 17 (4.1) | 11 (5.2) |
| Pneumonitis | 23 (3.7) | 8 (1.9) | 5 (2.4) |
| Hepatitis | 8 (1.3) | 3 (0.7) | 1 (0.5) |
| Nephritis and renal dysfunction | 6 (1.0) | 8 (1.9) | 7 (3.3) |
| Rash | 47 (7.6) | 34 (8.2) | 22 (10.4) |

Spezialfall: Elderly und ORR





Elderly und Immuntherapie



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**Weibliche 46 jährige Pat.
NSCLC met.; Adenoca.
St.p. Nikotinabusus
Keine aktivierenden Mut.
PDL-1: 50%**

| Serum | | | |
|---|--------------------|--------------|---------------------------|
| Hepatitis: virale Antigene und virusspezifische Antikörper | | | |
| CMIA Hepatitis-A-Virus IgG | negativ | | negativ |
| CMIA Hepatitis-A-Virus IgM | negativ | | negativ |
| CMIA Hepatitis-B-Virus HBs Ag | negativ | | negativ |
| CMIA Hepatitis-B-Virus HBs Ag quant.(IU/mL) | n.d. | | |
| CMIA Hepatitis-B-Virus HBs Ak | negativ | | negativ |
| CMIA Hepatitis-B-Virus HBc Ak | schwach positiv | | schwach positiv |
| CMIA Hepatitis-B-Virus HBe Ag | n.d. | | |
| CMIA Hepatitis-B-Virus HBe Ak | n.d. | | |
| CMIA Hepatitis-C-Virus Ak | schwach positiv | | schwach positiv |
| ELISA Hepatitis-E-Virus IgG | negativ | | |
| ELISA Hepatitis-E-Virus IgM | negativ | | |
| Hepatitis: Virusnukleinsäure und Resistenz | | | |
| PCR Hepatitis-C-Virus RNS quant. (IU/mL) | | negativ | negativ |
| HIV: virales Antigen und virusspezifische Antikörper | | | |
| CMIA HIV-1/2 Ag/Ak | | | positiv |
| IBL HIV Westernblot | | | n.d. |
| EDTA Plasma | | | |
| HIV: Virusnukleinsäure und Resistenz | | | |
| PCR HIV-1 RNS quant. (c/mL) | | nicht nachw. | nicht nachw. nicht nachw. |

Immuntherapie?

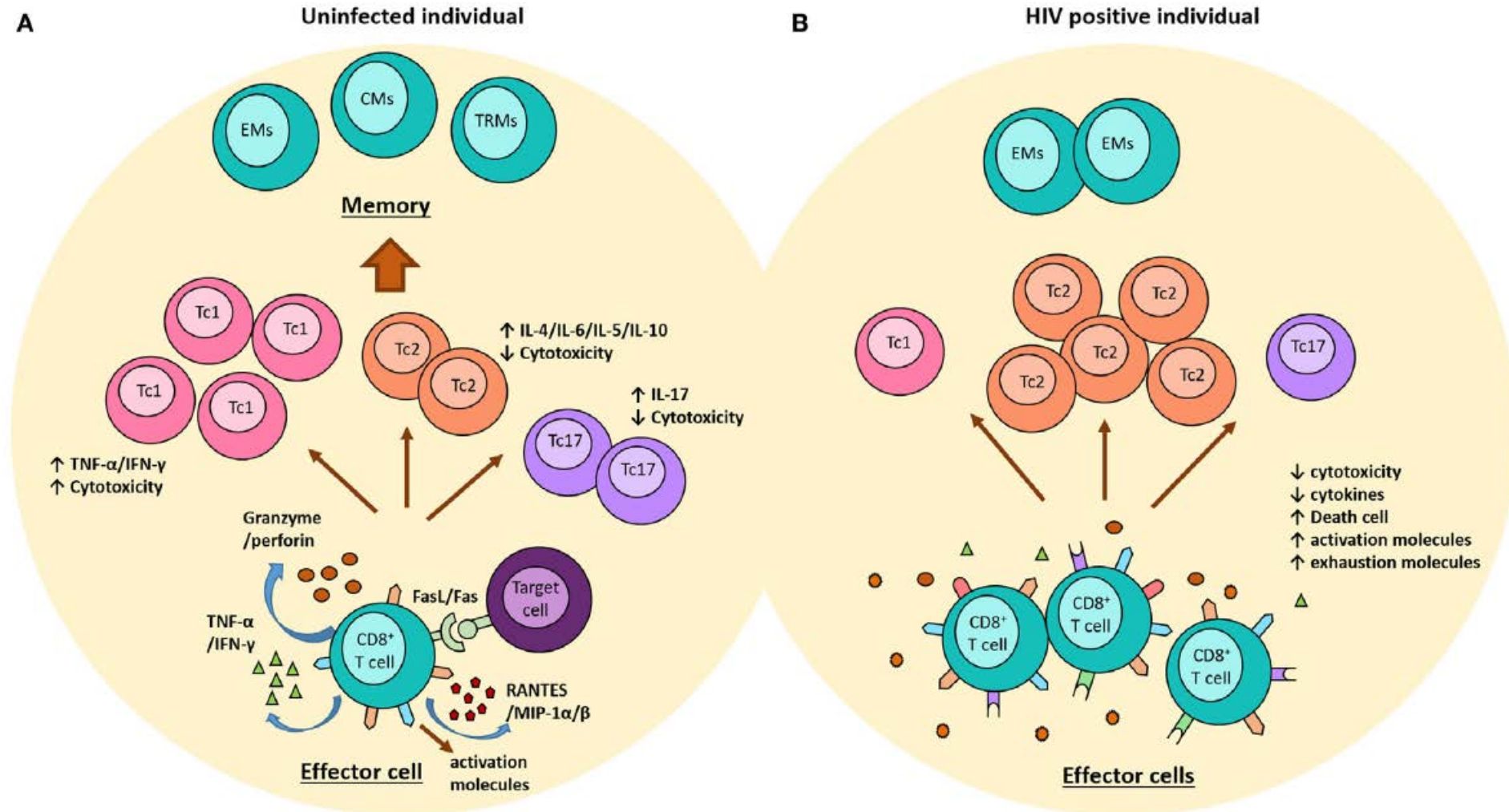


Spezialfall: HIV und Hepatitis

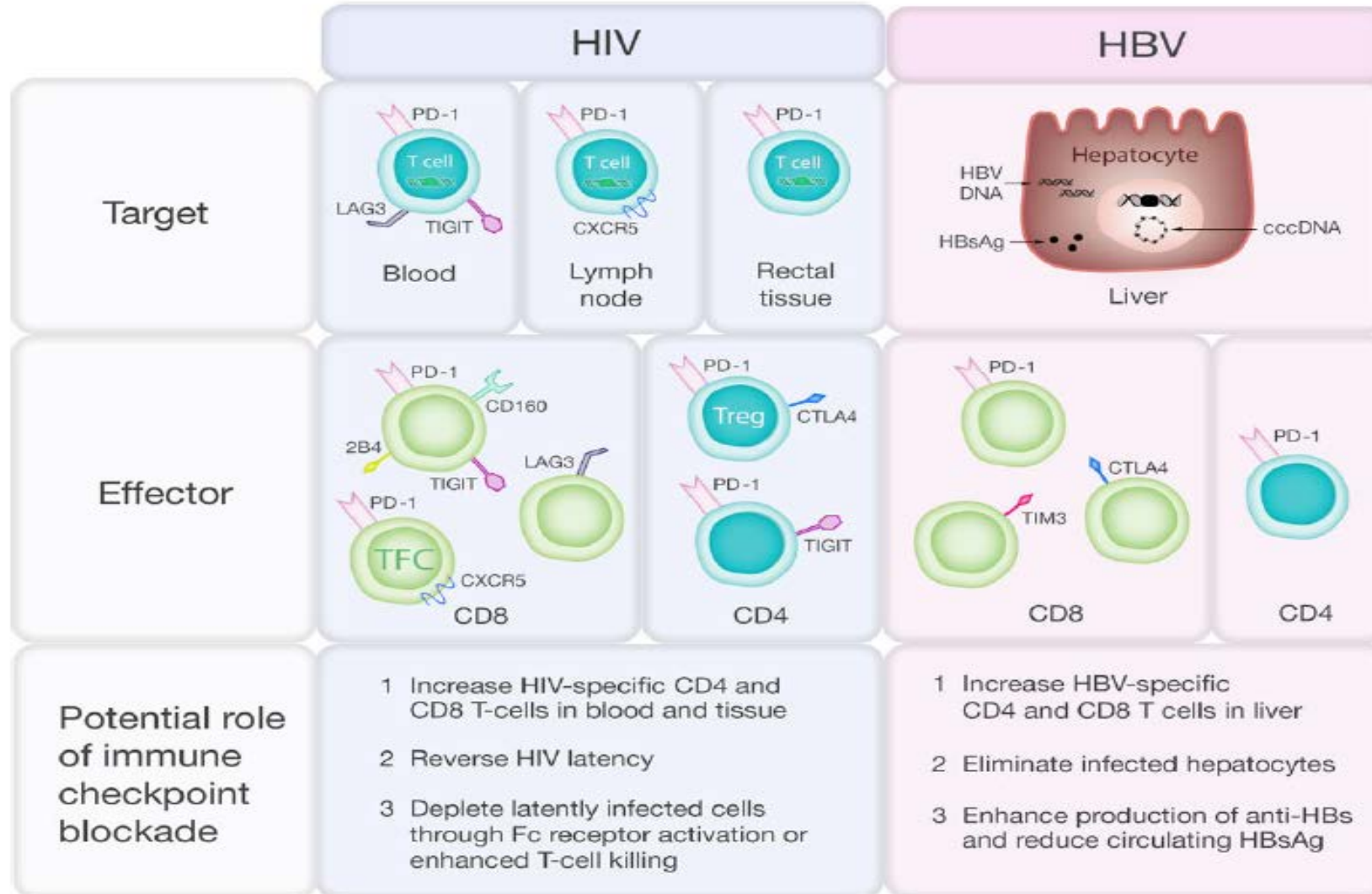


| Non-AIDS-defining cancers | | | | | | | |
|-----------------------------|---------------------|---------------------|---------------------|--------------------|----------------------|---------------------|---------------------|
| Lip | 3.10 (1.89-4.79) | 2.26 (1.08-4.16) | .. | .. | .. | .. | .. |
| Oral cavity and pharynx† | 2.93 (2.54-3.38) | 2.45 (0.90-5.33) | .. | .. | .. | 1.10 (0.40-2.37) | 2.10 (1.43-2.98) |
| Oesophagus | 1.60 (1.10-2.25) | 2.11 (0.44-6.17) | .. | .. | .. | 0.50 (0.06-1.81) | 1.90 (0.91-3.50) |
| Stomach | 2.00 (1.53-2.57) | 0.61 (0.07-2.22) | 2.25 (0.97-4.43) | 2.94 (0.07-16.39) | 1.82 (0.22-6.57) | 0.40 (0.05-1.44) | 1.80 (0.98-3.02) |
| Small intestine | 1.30 (0.62-2.39) | 2.7 (0.07-15.06) | .. | .. | .. | 3.39 (0.40-12.04) | 1.90 (0.39-5.55) |
| Colon | .. | 0.33 (0.07-0.95) | 0.95 (0.26-2.43) | .. | .. | .. | .. |
| Rectum | .. | 0.64 (0.18-1.65) | 2.29 (0.74-5.35) | .. | .. | .. | .. |
| Colon and rectum | 0.90 (0.77-1.05) | 0.45 (0.18-0.93) | 1.41 (0.64-2.67) | .. | .. | 0.90 (0.49-1.51) | 1.00 (0.70-1.38) |
| Anus | 33.79 (29.48-38.55) | 37.04 (17.76-68.11) | 33.33 (12.23-72.55) | .. | 50.00 (16.23-116.68) | 23.08 (13.33-35.56) | 19.63 (14.21-26.45) |
| Liver | 7.70 (6.17-9.50) | 2.73 (0.56-7.97) | 1.90 (0.39-5.55) | 22.22 (2.69-80.27) | 7.14 (2.32-16.67) | 5.60 (3.01-9.67) | 3.30 (2.02-5.10) |
| Pancreas | 2.39 (1.75-3.20) | 1.55 (0.32-4.54) | 1.57 (0.19-5.69) | .. | 2.86 (0.35-10.32) | 0.80 (0.16-2.31) | 0.70 (0.23-1.63) |
| Larynx | 2.80 (2.32-3.35) | 0.60 (0.02-3.32) | 1.03 (0.12-3.70) | .. | .. | 2.00 (0.65-4.67) | 2.70 (1.54-4.38) |
| Trachea, bronchus, and lung | 4.50 (4.19-4.82) | 1.44 (0.84-2.31) | 2.44 (1.53-3.69) | 4.10 (1.33-9.56) | 3.18 (1.74-5.34) | 2.20 (1.57-3.01) | 2.60 (2.14-3.13) |
| Melanoma | 1.30 (1.10-1.53) | 1.34 (0.93-1.88) | 0.81 (0.17-2.36) | .. | 1.05 (0.29-2.70) | 0.20 (0.02-0.72) | 1.00 (0.52-1.75) |
| Non-melanoma skin‡ | .. | .. | 1.51 (0.82-2.53) | 2.80 (1.03-6.10) | 3.20 (2.17-4.54) | 19.61 (15.16-24.57) | .. |
| Breast | 1.10 (0.93-1.30) | 1.13 (0.23-3.31) | 0.68 (0.14-1.98) | .. | 1.43 (0.46-3.33) | 0.80 (0.41-1.40) | 0.80 (0.53-1.16) |
| Vulva and vagina | 6.79 (4.03-10.74) | .. | .. | .. | .. | .. | 4.41 (0.91-12.89) |
| Uterus | 0.90 (0.47-1.58) | .. | .. | .. | .. | .. | 0.50 (0.06-1.81) |
| Ovary | 1.50 (0.95-2.26) | 3.23 (0.08-17.97) | 4.41 (0.91-12.89) | .. | .. | 1.00 (0.12-3.61) | 0.30 (0.01-1.67) |
| Penis | 3.90 (2.13-6.54) | .. | .. | .. | .. | 3.90 (0.77-10.96) | 8.00 (2.18-20.48) |
| Prostate | 0.70 (0.59-0.82) | 1.06 (0.53-1.89) | 1.16 (0.14-4.20) | .. | 1.43 (0.29-4.17) | 0.90 (0.29-2.08) | 0.50 (0.35-0.69) |
| Testis | 1.76 (1.51-2.05) | 1.46 (0.70-2.69) | 1.07 (0.29-2.75) | 0.70 (0.02-3.90) | 1.58 (0.58-3.44) | 1.10 (0.66-1.72) | 0.74 (0.34-1.41) |
| Kidney | 1.50 (1.19-1.87) | 0.79 (0.16-2.31) | 1.09 (0.22-3.19) | .. | 2.00 (0.24-7.22) | 1.10 (0.40-2.37) | 1.90 (1.06-3.14) |
| Bladder | 0.60 (0.43-0.81) | 1.06 (0.29-2.70) | 0.42 (0.05-1.51) | 4.17 (0.50-15.05) | .. | 0.50 (0.10-1.46) | .. |
| Eye | 2.00 (0.96-3.68) | 1.72 (0.04-9.61) | .. | .. | .. | .. | .. |
| Brain | 3.50 (2.97-4.09) | 1.81 (0.73-3.74) | 4.44 (2.21-7.94) | 3.28 (0.40-11.84) | 2.86 (0.78-7.32) | 1.00 (0.46-1.90) | 0.50 (0.10-1.46) |
| Thyroid | 0.80 (0.55-1.12) | 0.56 (0.01-3.10) | .. | .. | 3.00 (0.62-8.77) | 0.40 (0.01-2.23) | 0.50 (0.14-1.28) |
| Hodgkin's lymphoma | 11.50 (10.61-12.45) | 7.85 (4.40-12.95) | 16.25 (11.85-21.74) | 3.57 (0.43-12.9) | 18 (10.67-28.45) | 5.60 (3.95-7.67) | 13.61 (10.65-17.14) |
| Multiple myeloma | 2.60 (1.92-3.44) | 4.17 (1.35-9.72) | 4.84 (1.00-14.14) | .. | 5.00 (0.61-18.06) | 2.70 (1.00-5.94) | 2.20 (1.10-3.94) |
| Leukaemia | 3.60 (3.09-4.17) | 3.38 (1.80-5.77) | 5.33 (2.84-9.11) | 2.22 (0.06-12.38) | 1.82 (0.22-6.57) | 2.50 (1.51-3.90) | 1.87 (0.97-3.27) |
| All cancers | 2.70 (2.62-2.78) | 1.63 (1.41-1.87) | 2.28 (1.95-2.65) | 1.80 (1.15-2.68) | 2.79 (2.33-3.31) | 2.50 (2.27-2.74) | 1.70 (1.56-1.85) |

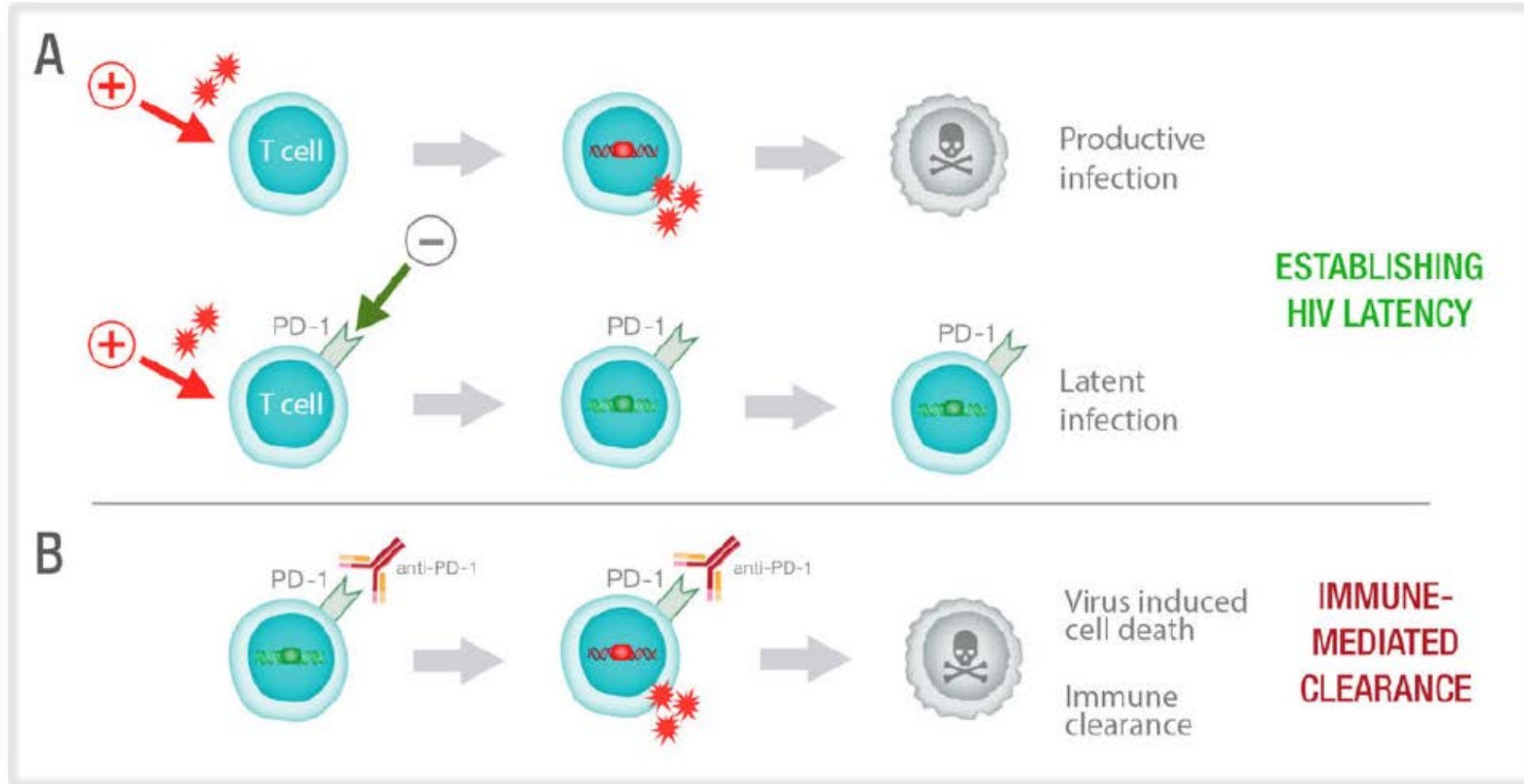
Spezialfall: HIV und Hepatitis



Spezialfall: HIV und Hepatitis



Spezialfall: HIV und Hepatitis



Spezialfall: HIV und Hepatitis

Table 2. Select Studies of Immune Checkpoint Inhibitor Therapy in Patients With Advanced-Stage Cancer

| Source | Sample Size | Study Type | Tumor Type (No.) | ICI Therapy (No.) | Adverse Events (No.) | HIV Load | CD4 Cell Count | Best Response |
|---|-------------|----------------------------|---|---|---|---|--|------------------------------------|
| Ostios-Garcia et al, ²⁰ 2018 | 7 | Retrospective case series | NSCLC (7) | Pembrolizumab (5), nivolumab (2) | Grade 1 arthralgia (1), grade 1 fatigue (1), grade 1 headache (1), grade 1 chest pain (1), grade 2 arthralgia (2) | Remained suppressed ^a | Stable ^b | Stable disease (2), PR (3), PD (2) |
| Samri et al ²⁸ 2017 | 12 | Retrospective case series | NSCLC (12) | Nivolumab (12) | Grade 1 hepatitis (1), hypereosinophilia (1) | Remained suppressed ^c | Stable | Stable disease (4), PR (3), PD (5) |
| Heppt et al, ¹⁷ 2017 | 10 | Retrospective case series | Melanoma (9), Merkel cell carcinoma (1) | Nivolumab (1), pembrolizumab (3), ipilimumab (3), ipilimumab plus nivolumab (3) | Grade 1 pneumonitis (1), grade 1 fatigue (1) | Remained suppressed | Stable ^d | PR (1), CR (2), PD (6), NR (1) |
| Park et al, ²⁷ 2018 | 8 | Retrospective case series | HNSCC (3), melanoma (2), cutaneous SCC (2), SCC (1) | Anti-PD-1 (7), ipilimumab plus nivolumab (1) | Anti-PD-1, grade 1 fatigue (4), grade 1 rash (2); ipilimumab plus nivolumab, grade 3 hepatitis (1) | Remained suppressed | Upward trend ^e | PR (4), CR (1), PD (2), NR (1) |
| Galanina et al, ²⁶ 2018 | 8 | Retrospective case series | Kaposi sarcoma (8) | Nivolumab (8) | No grade ≥ 2 toxic effects reported ^f | Pretreatment median (range): 20.5 /mL (0-116 706 mL); posttreatment median (range): 64 /mL (0-1 390 000 mL) | Upward trend (mean increase by 80.5 / μ L) | PR (4), CR (1), stable disease (3) |
| Uldrick, ²⁹ 2017 | 21 | Prospective clinical trial | Primary effusion lymphoma (2), Kaposi sarcoma (1), diffuse large B-cell lymphoma (1), anal cancer (5), head and neck (5), SCC (1), NSCLC (2), HCC (1), transitional cell carcinoma (1), pancreatic cancer (1), cholangiocarcinoma (1) | Pembrolizumab (21) | Most treatment-emergent AEs were grades 1-2 (93%), ^g immune-related AEs, grade 1 hypothyroidism (2), grade 1 ALT increase (1), grade 1 joint stiffness (1), grade 1 pneumonitis (1), grade 2 pneumonitis (2), grade 2 hypothyroidism (4), grade 3 ALT increase (1) | Remained suppressed | Upward trend | NR |

Spezialfall: HIV und Hepatitis

Table 3. Objective Response Rates per Disease Type

| Disease Type | No. of Patients With Known Response | Patients With Previous Systemic Treatment, No. (%) | Response (No. of Patients) | ORR, % ^a |
|--------------------------|-------------------------------------|--|--|---------------------|
| NSCLC | 23 | 19 (83) | CR (1), PR (6), stable disease (8), PD (8) | 30 |
| Melanoma | 11 | 5 (45) | CR (1), PR (2), PD (8) | 27 |
| Kaposi sarcoma | 8 | Unknown ^b | CR (1), PR (4), PD (3) | 63 |
| Classic Hodgkin lymphoma | 2 | 2 (100) | CR (1), PR (1) | NA |
| Merkel cell carcinoma | 1 | 1 (100) | CR (1) | NA |

Spezialfall: HIV und Hepatitis

| | Uninfected untreated/intolerant (n=56) | | Uninfected progressor (n=57) | | HCV infected (n=50) | | HBV infected (n=51) | | All patients (n=214) | |
|---|--|-----------|------------------------------|-----------|---------------------|-----------|---------------------|-----------|----------------------|-----------|
| | Any grade | Grade 3/4 | Any grade | Grade 3/4 | Any grade | Grade 3/4 | Any grade | Grade 3/4 | Any grade | Grade 3/4 |
| Patients, n (%) | | | | | | | | | | |
| Treatment-related serious AEs | 4 (7) | 2 (4) | 5 (9) | 2 (4) | 5 (10) | 4 (8) | 2 (4) | 1 (2) | 16 (7) | 9 (4) |
| AEs leading to discontinuation | 5 (9) | 1 (2) | 7 (12) | 3 (5) | 9 (18) | 8 (16) | 3 (6)* | 2 (4) | 24 (11)* | 14 (7) |
| Treatment-related deaths | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Patients with a treatment-related AE | 44 (79) | 15 (27) | 40 (70) | 7 (12) | 40 (80) | 15 (30) | 35 (69) | 3 (6) | 159 (74) | 40 (19) |
| Treatment-related AEs [†] | | | | | | | | | | |
| Rash | 6 (11) | 1 (2) | 10 (18) | 1 (2) | 9 (18) | 0 | 8 (16) | 0 | 33 (15) | 2 (1) |
| Pruritus | 11 (20) | 0 | 7 (12) | 0 | 14 (28) | 1 (2) | 13 (25) | 0 | 45 (21) | 1 (<1) |
| Diarrhoea | 10 (18) | 1 (2) | 9 (16) | 1 (2) | 5 (10) | 0 | 3 (6) | 1 (2) | 27 (13) | 3 (1) |
| Decreased appetite | 4 (7) | 0 | 2 (4) | 0 | 2 (4) | 1 (2) | 3 (6) | 0 | 11 (5) | 1 (<1) |
| Fatigue | 14 (25) | 1 (2) | 20 (35) | 1 (2) | 8 (16) | 1 (2) | 7 (14) | 0 | 49 (23) | 3 (1) |
| Nausea | 3 (5) | 0 | 7 (12) | 0 | 6 (12) | 0 | 1 (2) | 0 | 17 (8) | 0 |
| Dry mouth | 4 (7) | 0 | 5 (9) | 0 | 2 (4) | 0 | 2 (4) | 0 | 13 (6) | 0 |
| Laboratory treatment-related AEs [†] | | | | | | | | | | |
| AST increase | 6 (11) | 2 (4) | 3 (5) | 2 (4) | 6 (12) | 5 (10) | 1 (2) | 0 | 16 (7) | 9 (4) |
| ALT increase | 4 (7) | 0 | 3 (5) | 2 (4) | 7 (14) | 3 (6) | 3 (6) | 0 | 17 (8) | 5 (2) |

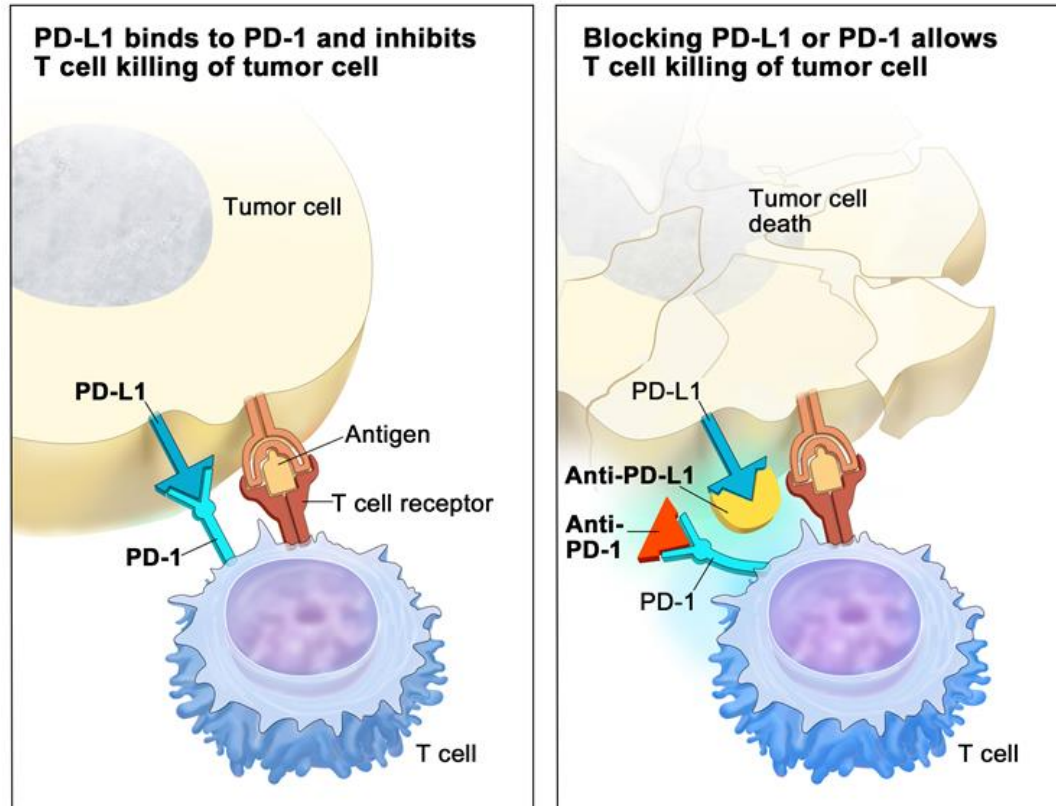
HCV, hepatitis C virus; HBV, hepatitis B virus; AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

*Includes 1 patient who discontinued due to a grade 5 malignant neoplasm progression event.

[†]Treatment-related AEs reported in $\geq 5\%$ of all patients, any grade.



HIV und Hepatitis Patienten

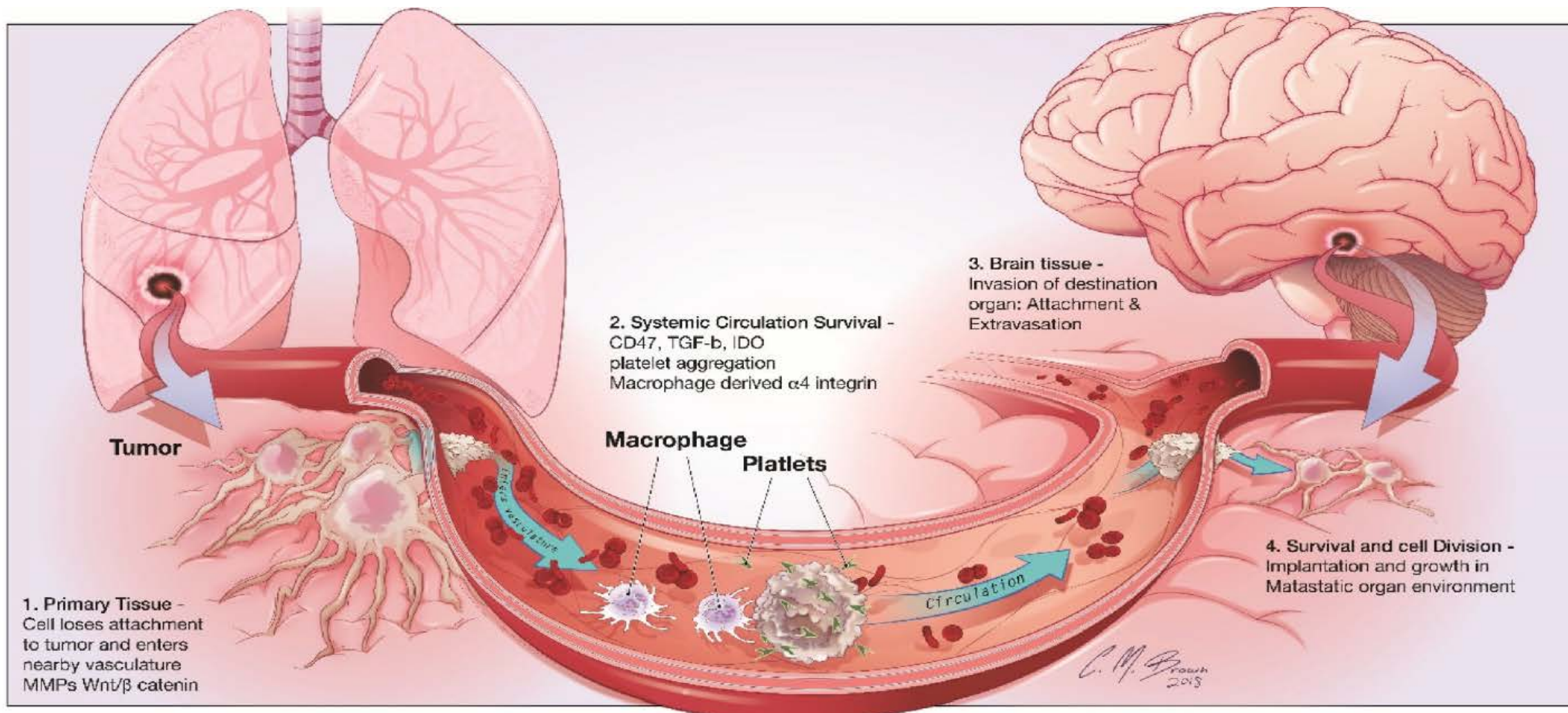


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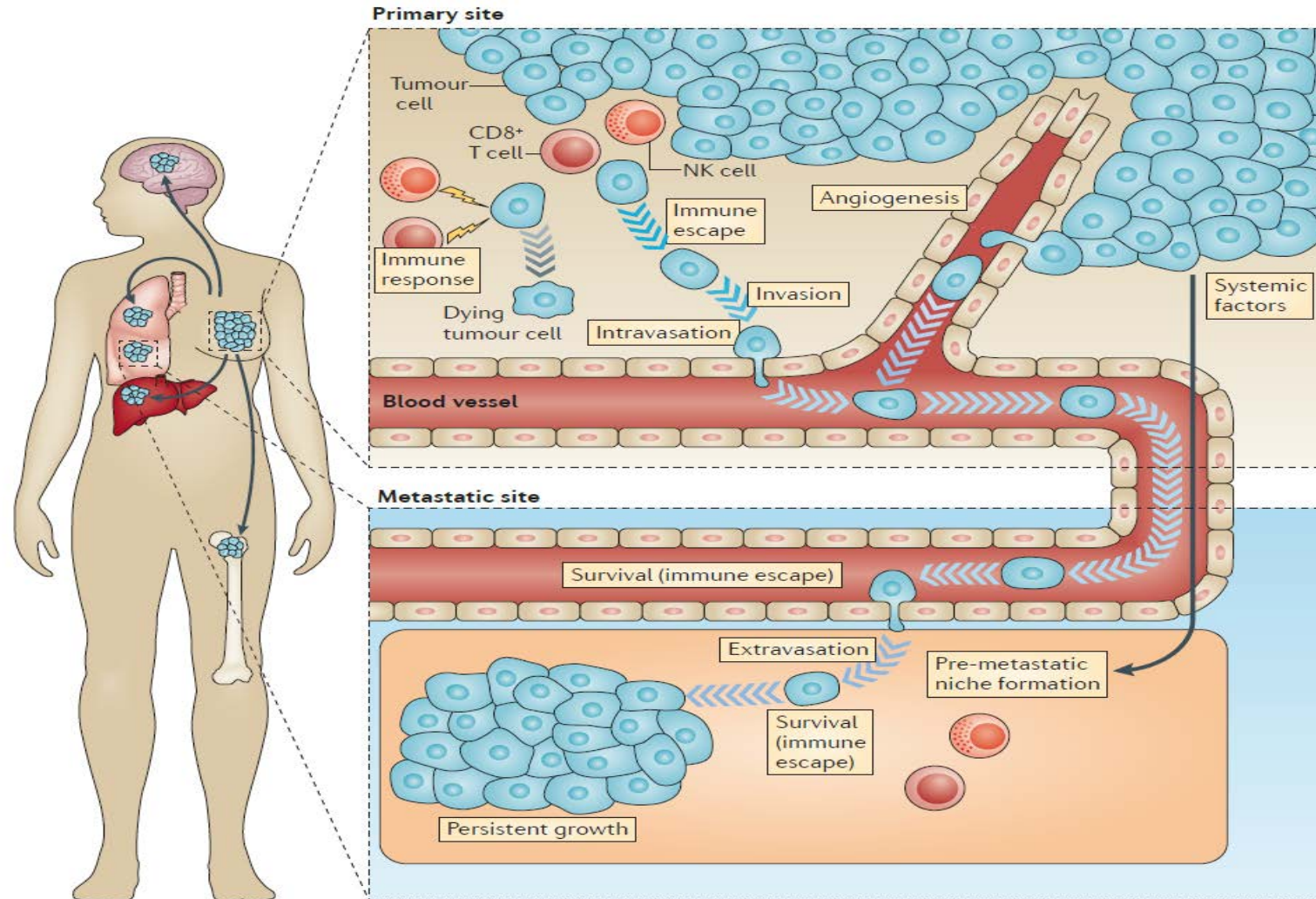


Spezialfall: Hirnmetastasen





Spezialfall: Hirnmetastasen

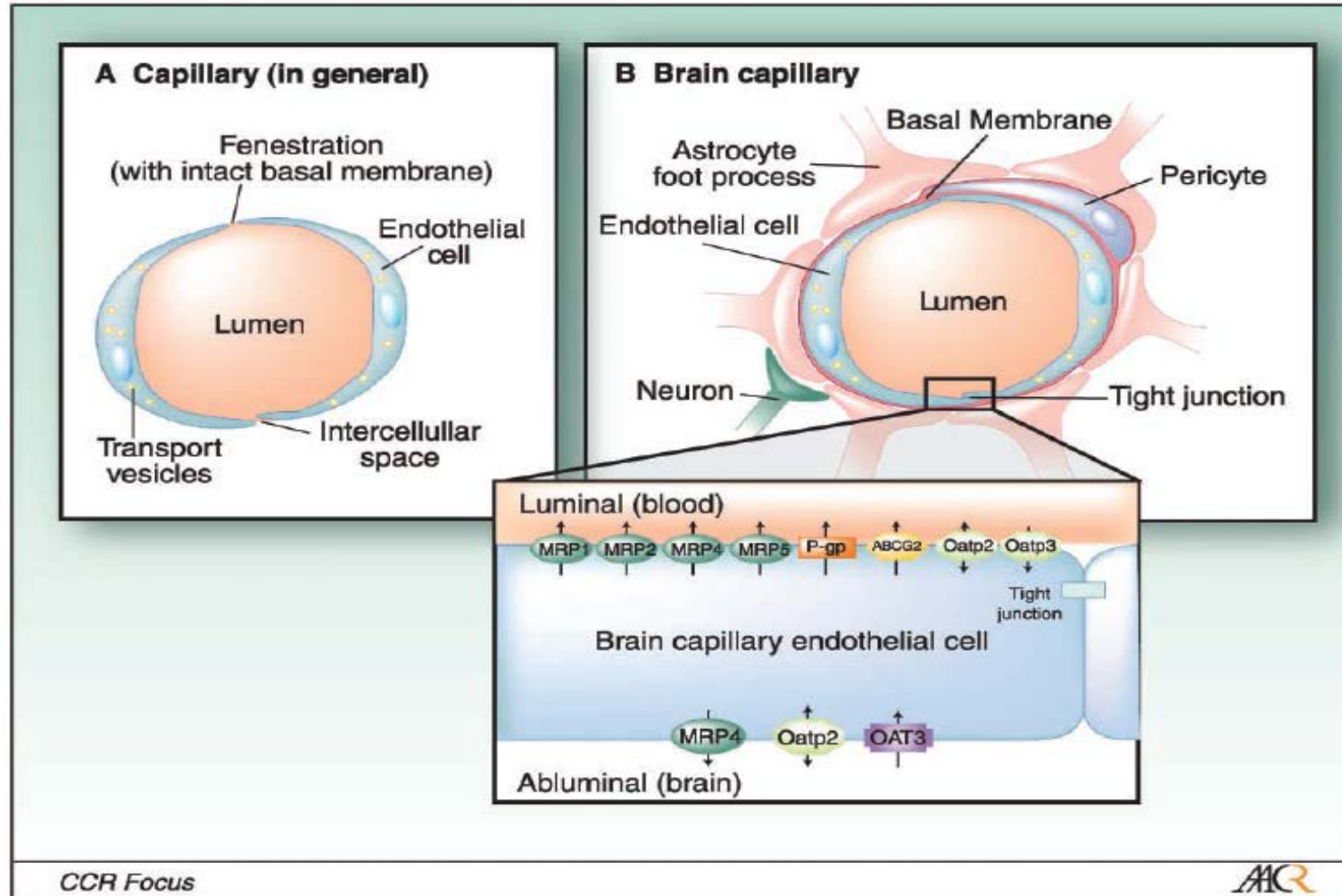


Spezialfall: Hirnmetastasen

| Type | Incidence of Brain Metastases at Initial Diagnosis (%) | Incidence of Brain Metastases Among Patients with Metastatic Disease (%) | Median Survival after Brain Metastasis Diagnosis (months) | Incidence of Leptomeningeal Disease (%) |
|--------------------------------|--|--|---|---|
| Small Cell Lung Cancer | 15.83 | 22.43 | 6.0 | 10–25 |
| Non Small Cell Lung Cancer NOS | 12.81 | 22.56 | 4.0 | 1–3.8 |
| Breast Cancer | 0.41 | 7.58 | 10 | 5 |
| Renal Cancer | 1.48 | 10.84 | 5 | 0.03 |
| Colorectal Cancer | 0.27 | 1.36 | 6 | 0.058 |
| Melanoma | 0.65 | 28.16 | 6 | 22–46 |



Spezialfall: Hirnmetastasen

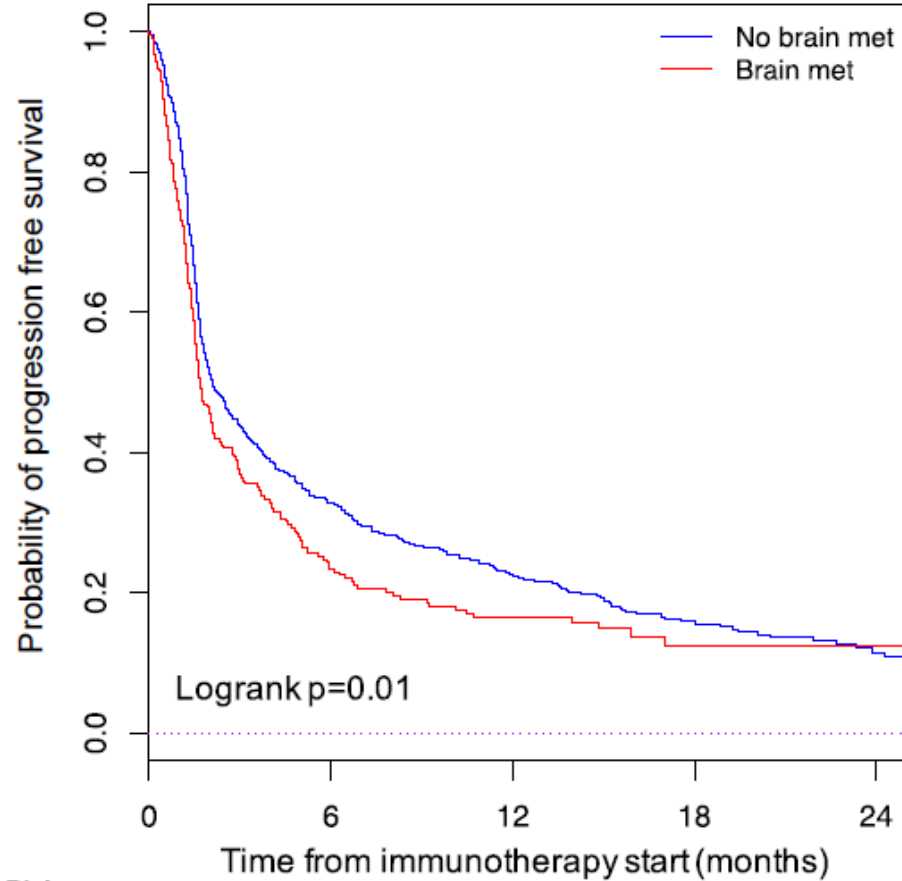




Spezialfall: Hirnmetastasen+ CPI

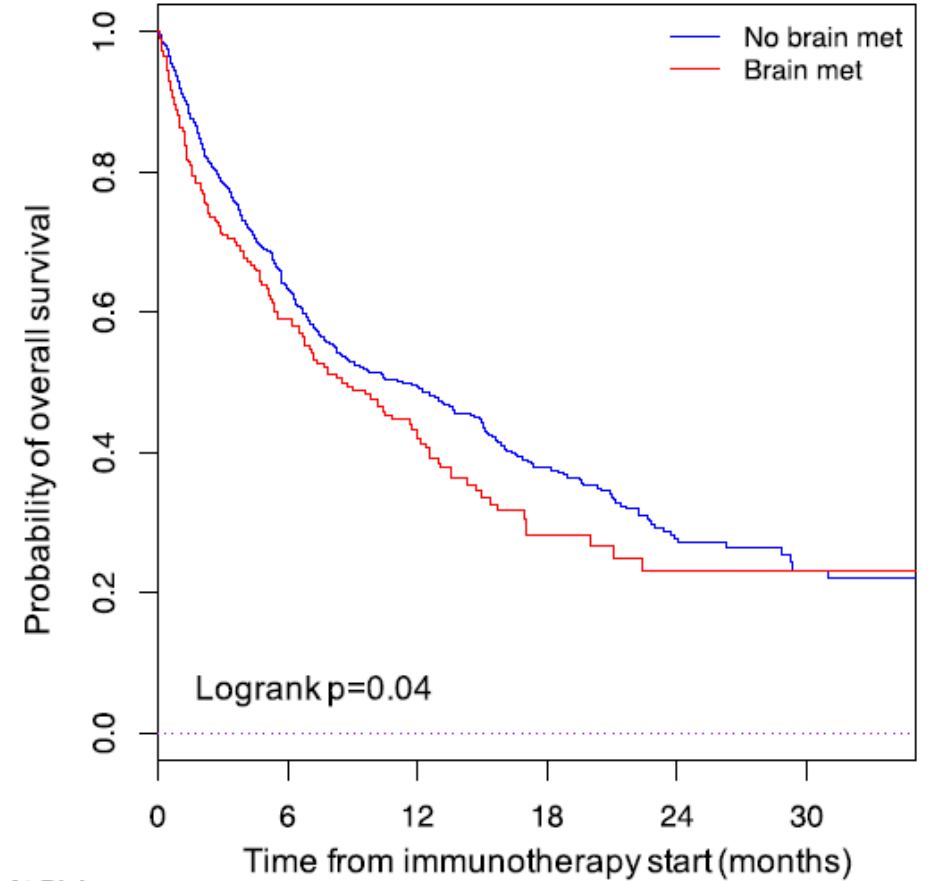


A



| No. At Risk | 0 | 6 | 12 | 18 | 24 |
|--------------|-----|-----|-----|----|----|
| No brain met | 770 | 202 | 109 | 47 | 21 |
| Brain met | 255 | 52 | 24 | 8 | 3 |

B



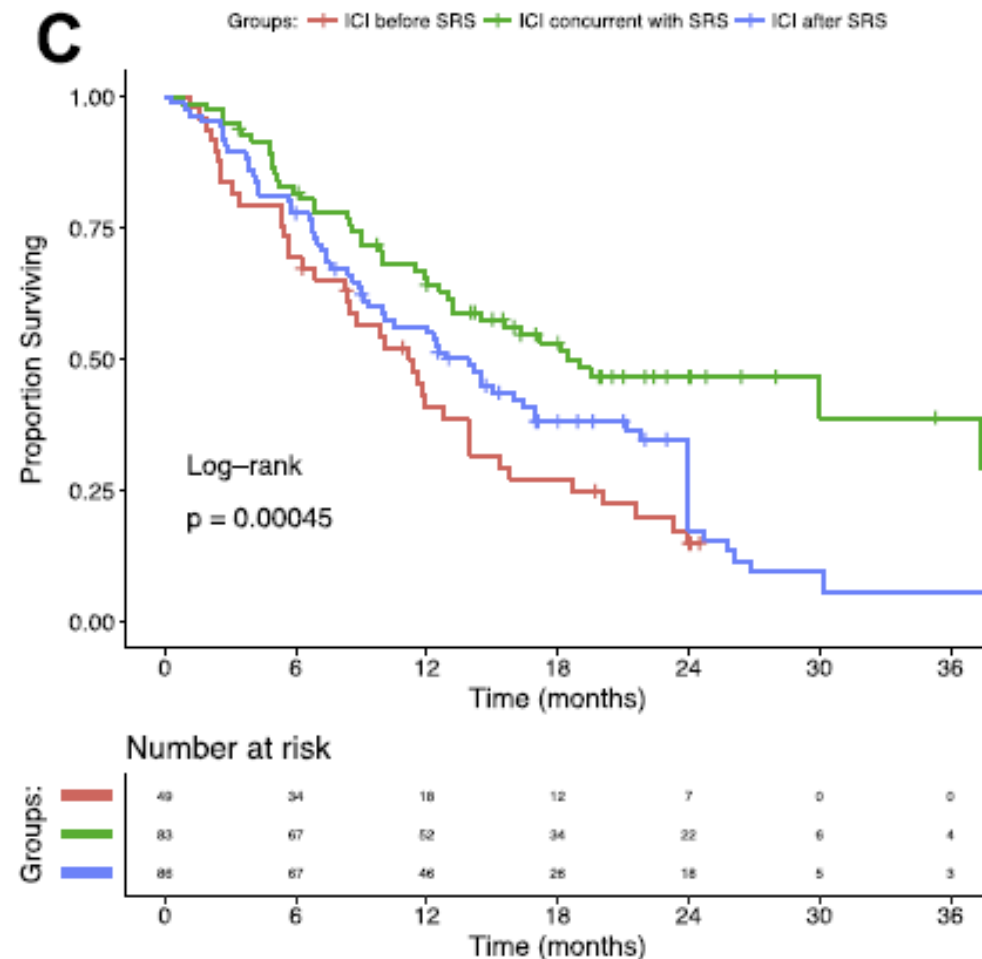
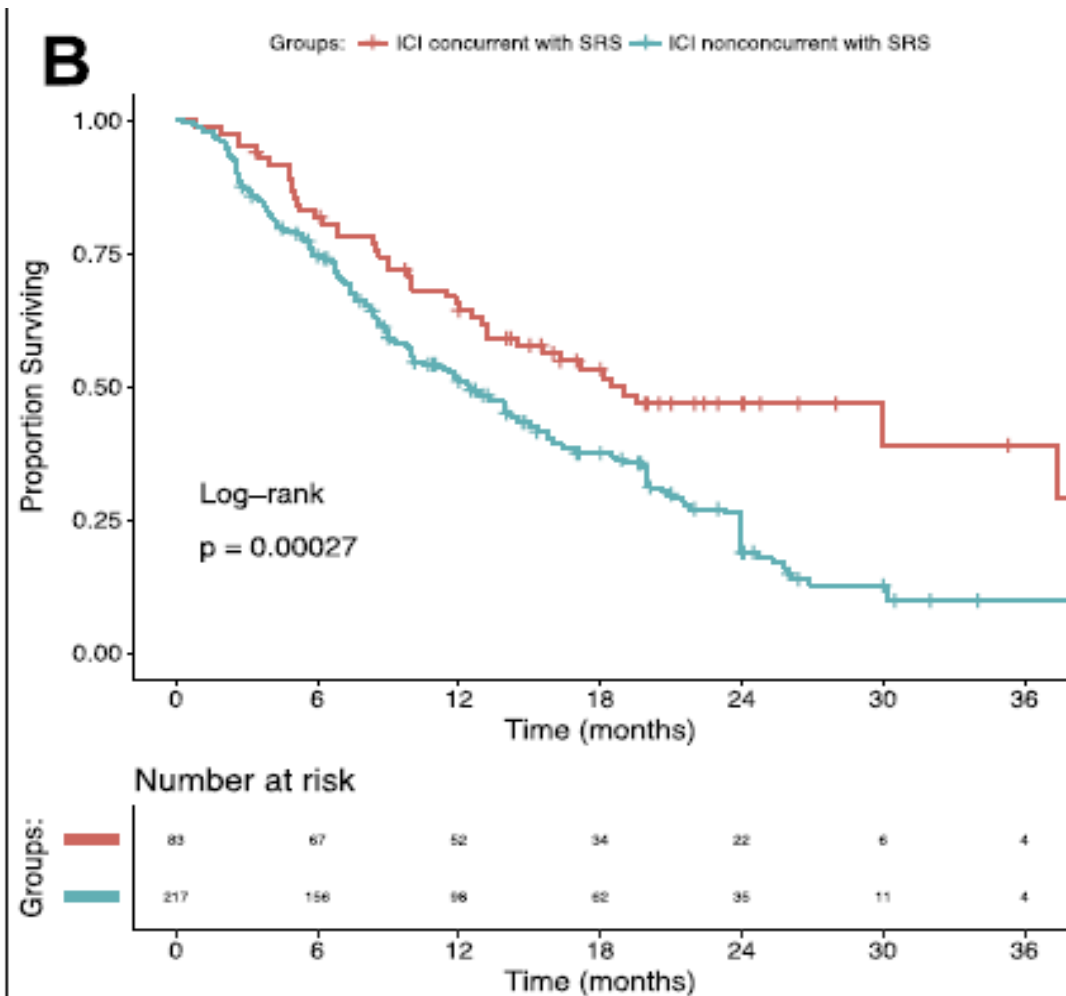
| No. At Risk | 0 | 6 | 12 | 18 | 24 | 30 |
|--------------|-----|-----|-----|-----|----|----|
| No brain met | 770 | 396 | 227 | 116 | 54 | 19 |
| Brain met | 255 | 117 | 63 | 20 | 10 | 3 |

Spezialfall: Hirnmetastasen + CPI

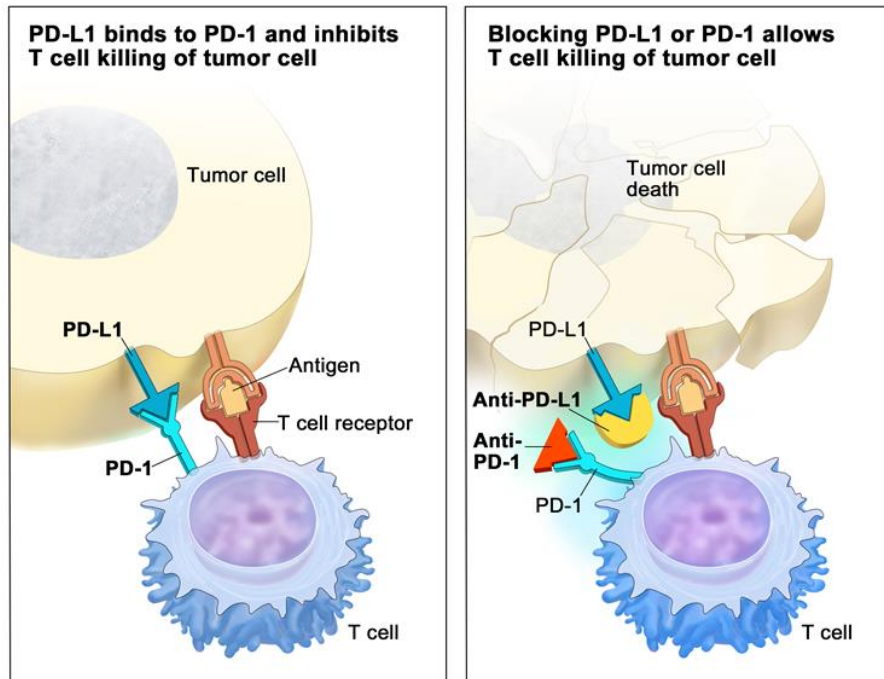
| Factor | PFS HR (95% CI) | p Value | OS HR (95% CI) | p Value |
|--|------------------|---------|------------------|---------|
| Age, >65 y vs. ≤65 y | 1.03 (0.89-1.20) | 0.667 | 1.11 (0.93-1.33) | 0.26 |
| Smoking, yes vs. no | 0.52 (0.41-0.67) | <0.0001 | 0.79 (0.59-1.06) | 0.112 |
| Histologic type | | | | |
| Squamous vs. adeno | 1.04 (0.87-1.24) | 0.86 | 1.18 (0.95-1.45) | 0.28 |
| NSCLC, other vs. adeno | 1.06 (0.80-1.42) | | 1.14 (0.81-1.60) | |
| No. of organs with metastases, >2 vs. ≤2 | 1.29 (1.10-1.50) | 0.001 | 1.42 (1.18-1.71) | <0.0001 |
| ICI line, >2 vs. ≤2 | 1.01 (0.87-1.18) | 0.881 | 1.07 (0.90-1.29) | 0.44 |
| WHO PS, ≥2 vs. 0-1 | 2.29 (1.89-2.77) | <0.0001 | 3.37 (2.72-4.16) | <0.0001 |
| Use of corticosteroids, yes vs. no | 1.31 (1.07-1.62) | 0.01 | 1.46 (1.16-1.84) | 0.001 |
| Brain metastases, yes vs. no | 1.10 (0.92-1.31) | 0.28 | 0.99 (0.81-1.23) | 0.96 |

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; adeno, adenocarcinoma; ICI, immune checkpoint inhibitor; PS, performance status.

Hirnmetastasen + CPI+Radiatio



Hirnmetastasen



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Autoimmunerkrankungen

The *CTLA4*, *PD-1* and *PD-L1* genes are linked to self-tolerance and are involved in autoimmune diseases.

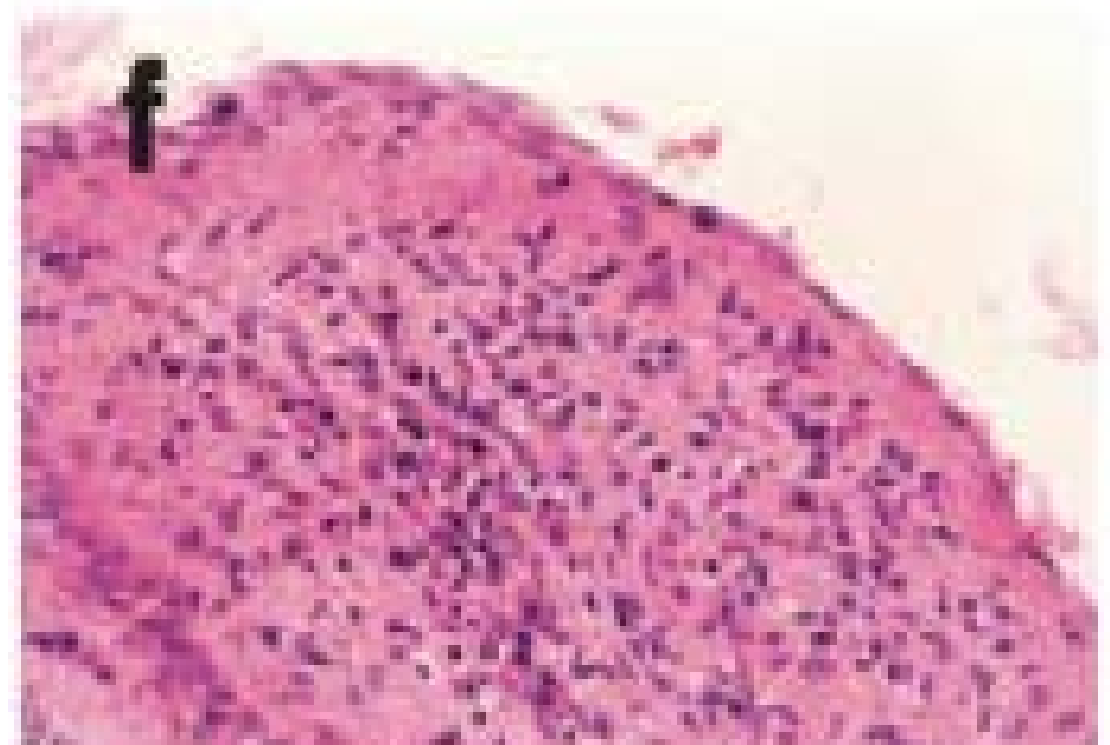
| Autoimmune disease | Polymorphism | Ethnic group | Referred studies |
|---|----------------|--------------------------------|--|
| Thyroiditis, Graves' disease and Hashimoto's disease | CTLA-4 | European | Ueda, Nature 2003 [8] Vaidya, Rheumatology 2002 [72] |
| Diabetes mellitus | CTLA-4 | European Asian | Ueda, Nature 2003 [8] Zhernakova, Hum Genet, 2005 [73] Zalloua PA, Hum Immunol 2004 [10] Jin, P of Endocrinol Investig, 2014 [74] Zhernakova, Hum Genet, 2005 [73] Song, Hum Immunol, 2013 [75] |
| Celiac disease | CTLA-4 | European | Fernández-Mestre, Hum. Immunol. 2009 [76] Hudson, Hum Genet, 2002 [77] Prokunina, Nat Gene, 2002 [9] Bertsias, Arthritis Rheum. 2009 [78] |
| Myasthenia gravis | CTLA-4 | South American | Vaidya, rheumatology 2002 [72] |
| Systemic lupus erythematosus | CTLA-4 PD-1 | Asian European and Mexicans | Lee, Z. Rheumatol. 2015 [79] |
| Rheumatoid arthritis | CTLA-4 PD-1 | European European and Asian | Blomhoff, J Clin Endocrinol Metabol 2004 [8] |
| Addison's disease | CTLA-4 | European | |

CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; PD-1: programmed cell death protein.

PD-1 Knockout und Autoimmunreaktion



Kontrolle

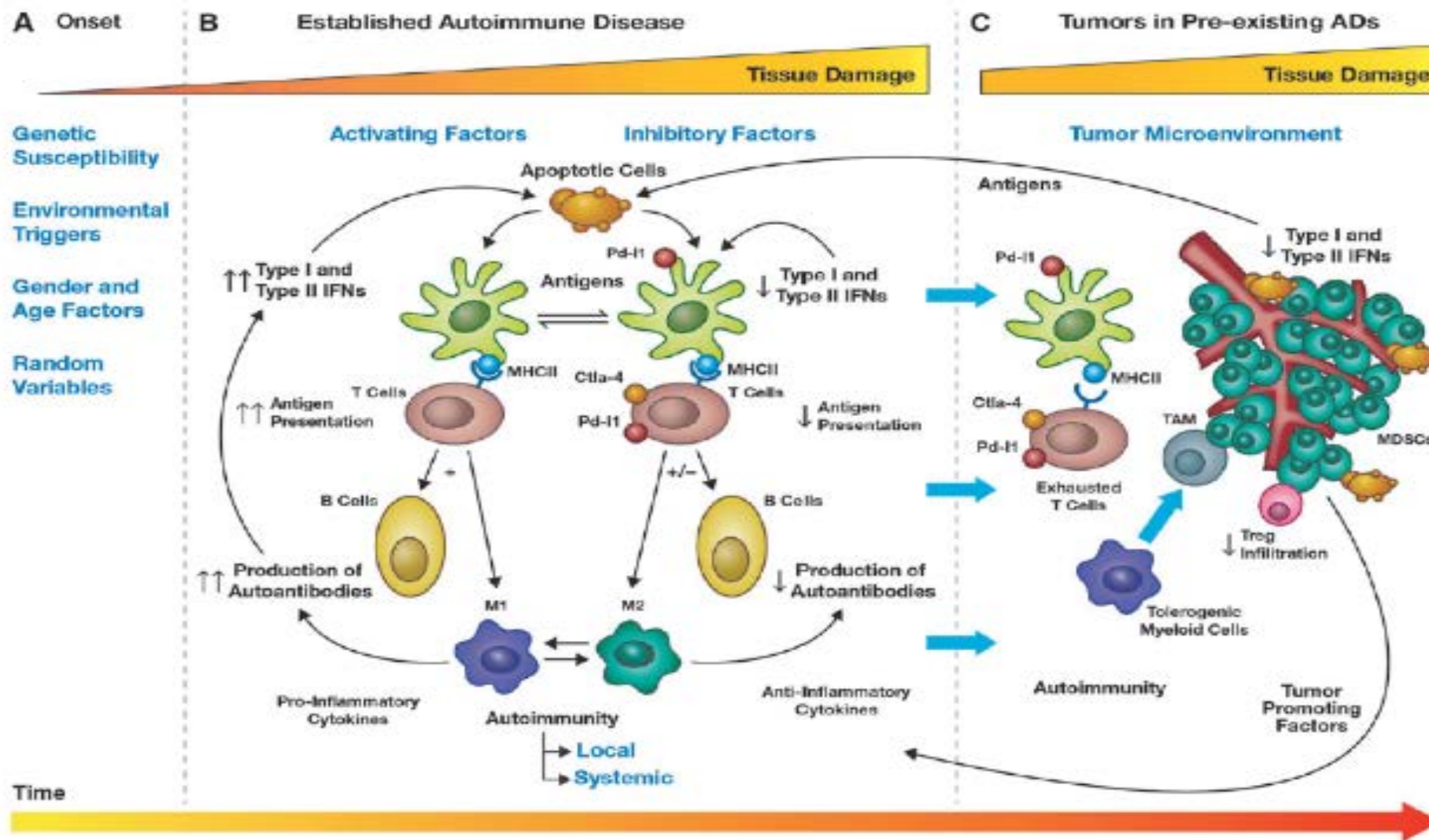


PD-1 Knockout

| <i>Autoimmune disease</i> | <i>Nonhematological malignancies</i> | <i>Hematological malignancies</i> | <i>References</i> |
|------------------------------|--------------------------------------|--|--|
| Systemic lupus erythematosus | Cervical, lung, breast | Hodgkin and non-Hodgkin lymphoma | Giati and others (2017); Malaguarnera and others (2012) |
| Rheumatoid arthritis | Lung, breast, ovary | T cell non-Hodgkin lymphoma, lymphoma (follicular or diffuse large B cell) | Giati and others (2017); Malaguarnera and others (2012); Bernatsky and others (2006) |
| Primary Sjogren syndrome | Oropharynx | Mucosa-associated lymphoid tissue type B cell lymphoma | Malaguarnera and others (2012); Bernatsky and others (2006) |
| Inflammatory bowel disease | Colorectal cancer | Non-Hodgkin lymphoma | Franks and Slansky(2012); Axelrad and others (2016) |
| Systemic sclerosis | Lung, skin, esophageal | | Malaguarnera and others (2012) |
| Wagner's granulomatosis | Bladder | | Giati and others (2017) |



AID und Krebs: Warum?



Spezialfall: AID und NSCLC

Table 1. Characteristics of Lung Cancer Patients With Autoimmune Disease

| Patient Characteristics | All Patients, No. | With Autoimmune Disease, No. (%) | P Value ^a |
|-------------------------|-------------------|----------------------------------|----------------------|
| Total | 210 509 | 28 453 (13.5) | |
| Age | | | |
| <75 | 94 804 | 11 664 (12.3) | <.001 |
| ≥75 to <85 | 92 045 | 13 529 (14.7) | <.001 |
| ≥85 | 23 660 | 3260 (13.8) | <.001 |
| Sex | | | |
| Female | 97 494 | 16 374 (16.8) | <.001 |
| Male | 113 015 | 12 079 (10.7) | <.001 |
| Stage (AJCC) | | | |
| I | 36 152 | 6331 (17.5) | <.001 |
| II | 6758 | 1028 (15.2) | <.001 |
| III | 51 542 | 6692 (13) | <.001 |
| IV | 77 833 | 9302 (12) | <.001 |
| Other | 38 224 | 5100 (13.3) | <.001 |



Spezialfall: AID und NSCLC



Table 2. Prevalence of the 10 Most Common Individual Autoimmune Diseases Among 210 509 Patients With Lung Cancer

| Autoimmune Disease | Prevalence, % |
|--------------------------------|---------------|
| Rheumatoid arthritis | 5.9 |
| Psoriasis | 2.8 |
| Polymyalgia rheumatic | 1.8 |
| Addison disease | 1.0 |
| Systemic lupus erythematosus | 0.9 |
| Ulcerative colitis | 0.8 |
| Giant cell arteritis | 0.8 |
| Sicca syndrome | 0.6 |
| Regional enteritis | 0.5 |
| Ménière disease, unspecified | 0.5 |
| Total (any autoimmune disease) | 13.5 |



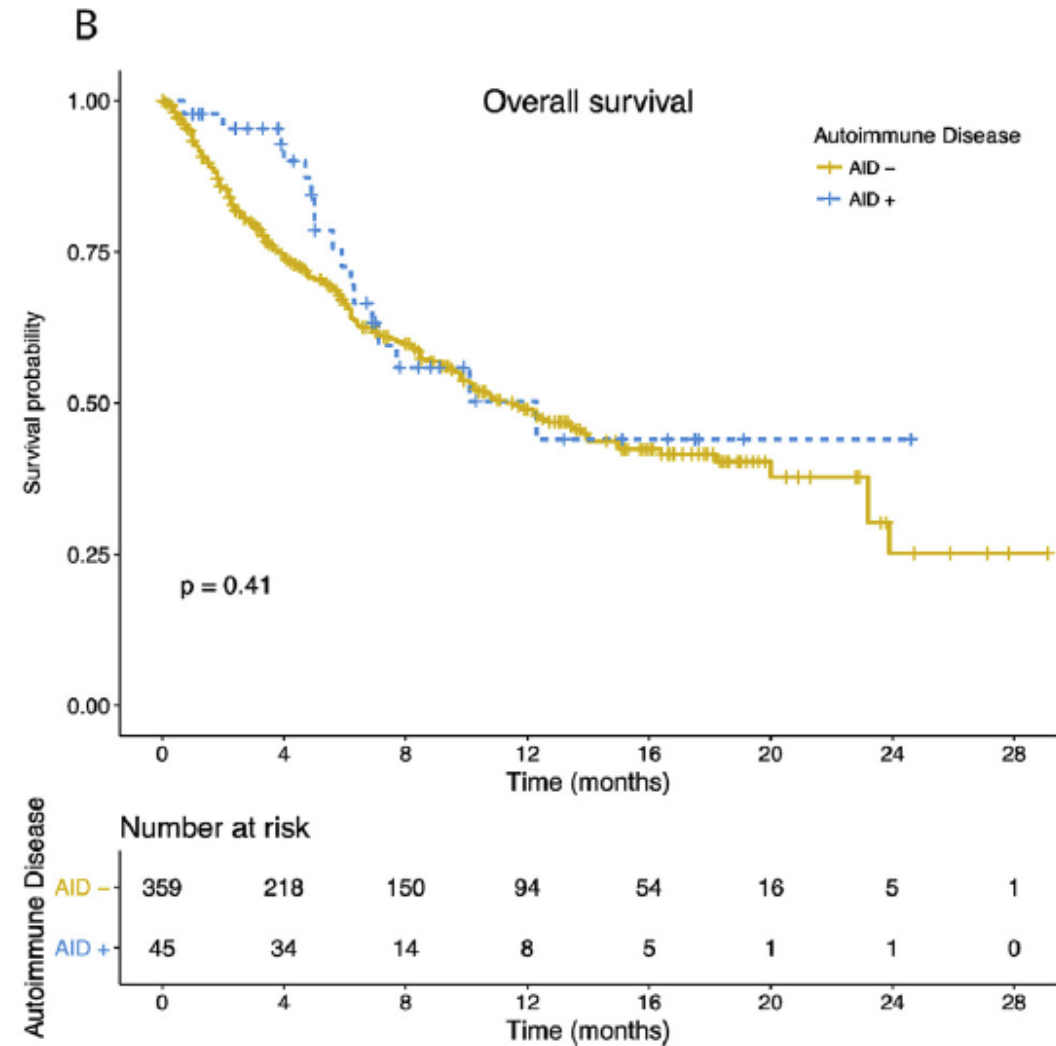
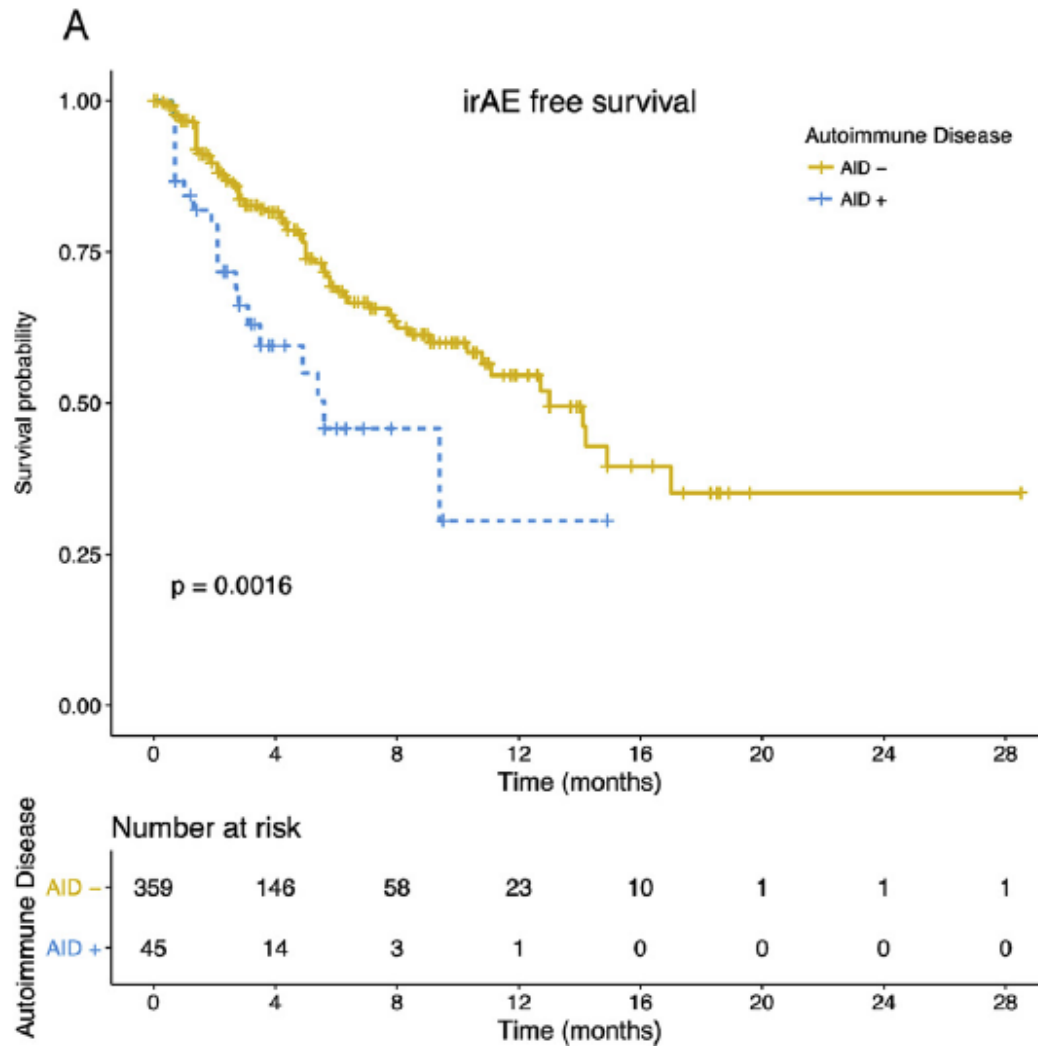
Spezialfall: AID und CPI



| Cancer | Target | AD | Type of Study | No. | Source | Efficacy | Safety |
|----------|---------|--------------------|----------------|--------|-----------------------------------|--|---|
| Melanoma | CTLA-4 | MS, RA | Case report | 2 | Kyi 2014 ¹⁸ | PR in 1 patient | No exacerbation of AD |
| | | Ulcerative colitis | Case report | 1 | Pedersen 2014 ¹⁹ | PR in 1 patient | No exacerbation of AD |
| | | MS | Case report | 1 | Gettings 2015 ²⁰ | PR in 1 patient | Severe exacerbation of AD |
| | | RA | Patient series | 8 | Lee 2016 ²¹ | 4 PRs, 3 SDs | 2 AD flares, 4 grade 3 irAEs |
| | | Various | Retrospective | 30 | Johnson 2016 ²² | ORR: 6 (20%), including 1 durable CR | 15 AD flares or irAEs (50%); 1 patient death |
| | PD-1 | Various | Retrospective | 41 | Kahler 2018 ²³ | ORR: 5 (12.2%), including 1 CR and 4 PRs | 12 AD flares (29.3%), 12 irAEs (29.3%) |
| | | BP | Case report | 1 | Beck 2016 ²⁴ | SD in 1 patient | Moderate AD exacerbation |
| | | RA | Case report | 1 | Puri and Homsy 2017 ²⁵ | CR in 1 patient | No exacerbation of AD |
| | | Various | Retrospective | 19 | Gutzmer 2017 ²⁶ | 6 PRs (32%), 2 SDs (11%) | 8 AD flares (42%), 3 irAEs (16%) |
| | | Various | Retrospective | 52 | Menzies 2017 ²⁷ | ORR: 33% | 20 AD flares (38%), 15 irAEs (29%) |
| NSCLC | PD-(L)1 | Various | Retrospective | 56 | Leonardi 2018 ¹⁴ | ORR: 22% | 13 AD flares (23%), 21 irAEs (38%) |
| RCC | N/A | Various | Retrospective | 25 | Chanza 2018 ²⁸ | ORR: 44%, including 1 CR and 10 PRs | 8 AD flares (32%), 12 irAEs (48%) |
| RCC, UC | N/A | Various | Retrospective | 25, 27 | Chanza 2019 ²⁹ | Similar for patients with AD and patients without AD | 12 AD flares (44%) in patients with UC |
| Various | Various | Various | Review | 123 | Abdel-Wahab 2018 ³ | N/A | 75% developed AD flares, irAEs, or both; 2.4% of patients died. |
| Various | PD-1 | Various | Prospective | 45 | Danlos 2018 ³⁰ | Similar for patients with AD and patients without AD | 11 AD flares (24%), 9 irAEs (20%) |
| Various | PD-1 | Various | Retrospective | 85 | Cortellini 2019 ³¹ | Similar for patients with AD and patients without AD | 40 AD flares (47%), 56 irAEs (66%) |



Spezialfall: AID und CPI

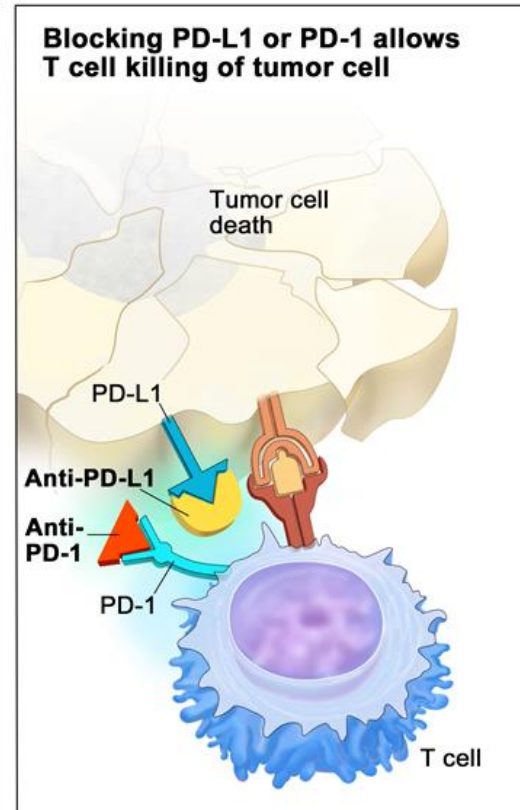
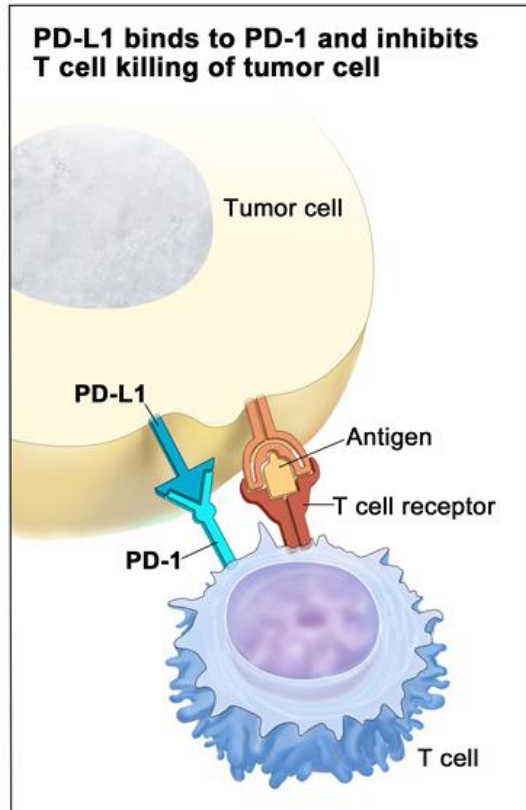


Spezialfall: AID und CPI

| ICIs May Be Considered | Avoid ICIs |
|---|---|
| 1. Consult with appropriate autoimmune subspecialist | 1. Autoimmune neurologic or neuromuscular disease |
| 2. Low level of or no immunosuppression with good control of underlying autoimmune disorder | 2. Life-threatening autoimmune disease |
| 3. Patient informed consent | 3. Patients with poor control of autoimmune disease OR requiring high doses of immunosuppressants for control |



Pat. mit Autoimmunerkrankungen



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Spezialfall: Rechallenge nach irAEs

Warum Rechallenge?

| First Author | No. of Patients | Immunotherapy Agent | Malignancy | Statistical Analysis of PFS and OS Between Patients With or Without irAEs |
|----------------------|-----------------|---------------------|--|---|
| Horvat ¹⁷ | 298 | CTLA-4 | Melanoma | No significant difference |
| Wang ¹⁸ | 117 | CTLA-4, PD-1, PD-L1 | Melanoma, solid tumors, hematologic malignancies | $P < .001$, HR not reported |
| Indini ¹⁹ | 173 | PD-1 | Melanoma | PFS HR, 0.47 (95% CI, 0.26 to 0.86) OS HR, 0.39 (95% CI, 0.18 to 0.81) |
| Maher ¹⁵ | 1,747 | PD-1, PD-L1 | Urothelial carcinoma | OS HR, 0.53 (95% CI, 0.43 to 0.66) |

2/2019 (Letzte Immuntherapie 1/19)

Klinische Chemie

| | | | | |
|--------------------------|---|------|--------------|--------|
| > Natrium | ↓ | 134 | 136 - 145 | mmol/L |
| > Kalium | | 4.46 | 3.5 - 5.1 | mmol/L |
| > Chlorid | ↓ | 93 | 98 - 107 | mmol/L |
| > Kalzium | | 2.37 | 2.20 - 2.55 | mmol/L |
| > Anorganisches Phosphat | | 0.84 | 0.81 - 1.45 | mmol/L |
| > Magnesium | ↓ | 0.64 | 0.66 - 1.07 | mmol/L |
| > Kreatinin | | 0.96 | 0.70 - 1.20 | mg/dL |
| > Harnstoff - N | | 11.2 | 8 - 23 | mg/dL |
| > Harnsäure | | 5.2 | 3.4 - 7.0 | mg/dL |
| > Gesamt Bilirubin | | 0.57 | 0.0 - 1.2 | mg/dL |
| > Hämolyseindex | | 1 | | |
| > Eiweiß, gesamt | | 66.4 | 64 - 83 | g/L |
| > Albumin | | 39.1 | 35 - 52 | g/L |
| > Cholinesterase | ↓ | 4.74 | 5.32 - 12.92 | kU/L |
| > Alkalische Phosphatase | ↑ | 702 | 40 - 130 | U/L |
| > ASAT (GOT) | ↑ | 271 | < 50 | U/L |
| > ALAT (GPT) | ↑ | 316 | < 50 | U/L |
| > Gamma - GT | ↑ | 1978 | < 60 | U/L |
| > LDH | | 179 | < 250 | U/L |

Immunologie

| | | | | |
|---------------------------|---|------|-------|-------|
| > C-reaktives Protein CRP | ↑ | 3.64 | < 0.5 | mg/dL |
|---------------------------|---|------|-------|-------|



3/2019- Pat. unter Kortison 2mg/kg/KG

Klinische Chemie

| | | | | |
|--------------------------|---|------|--------------|--------|
| > Natrium | ↓ | 128 | 136 - 145 | mmol/L |
| > Kalium | | 5.03 | 3.5 - 5.1 | mmol/L |
| > Chlorid | ↓ | 89 | 98 - 107 | mmol/L |
| > Kalzium | | 2.48 | 2.20 - 2.55 | mmol/L |
| > Anorganisches Phosphat | | 0.89 | 0.81 - 1.45 | mmol/L |
| > Magnesium | | 0.66 | 0.66 - 1.07 | mmol/L |
| > Kreatinin | | 0.94 | 0.70 - 1.20 | mg/dL |
| > Harnstoff - N | ↓ | 7.7 | 8 - 23 | mg/dL |
| > Harnsäure | ↓ | 3.3 | 3.4 - 7.0 | mg/dL |
| > Gesamt Bilirubin | | 0.35 | 0.0 - 1.2 | mg/dL |
| > Hämolyseindex | | 2 | | |
| > Eiweiß, gesamt | | 66.2 | 64 - 83 | g/L |
| > Albumin | | 37.0 | 35 - 52 | g/L |
| > Cholinesterase | ↓ | 4.82 | 5.32 - 12.92 | kU/L |
| > Alkalische Phosphatase | ↑ | 634 | 40 - 130 | U/L |
| > ASAT (GOT) | ↑ | 106 | < 50 | U/L |
| > ALAT (GPT) | ↑ | 214 | < 50 | U/L |
| > Gamma - GT | ↑ | 1768 | < 60 | U/L |
| > LDH | | 141 | < 250 | U/L |

Immunologie

| | | | | |
|---------------------------|---|------|-------|-------|
| > C-reaktives Protein CRP | ↑ | 4.45 | < 0.5 | mg/dL |
|---------------------------|---|------|-------|-------|

Virologie

Akt. Auftrag
27.02.2019
10647436

Hepatitis: virale Antigene und virusspezifische Antikörper

| | |
|---|---------|
| CMIA Hepatitis-A-Virus IgG | negativ |
| CMIA Hepatitis-A-Virus IgM | negativ |
| CMIA Hepatitis-B-Virus HBs Ag | negativ |
| CMIA Hepatitis-B-Virus HBs Ag quant. (IU/mL) | |
| CMIA Hepatitis-B-Virus HBs Ak | |
| CMIA Hepatitis-B-Virus HBs Ak quant. (mIU/mL) | |
| CMIA Hepatitis-B-Virus HBc Ak | negativ |
| CMIA Hepatitis-B-Virus HBc IgM | |
| CMIA Hepatitis-B-Virus HBe Ag | |
| CMIA Hepatitis-C-Virus Ak | negativ |
| CMIA Hepatitis-D-Virus Ak | |
| ELISA Hepatitis-E-Virus IgG | |
| ELISA Hepatitis-E-Virus IgM | |

HIV: virales Antigen und virusspezifische Antikörper

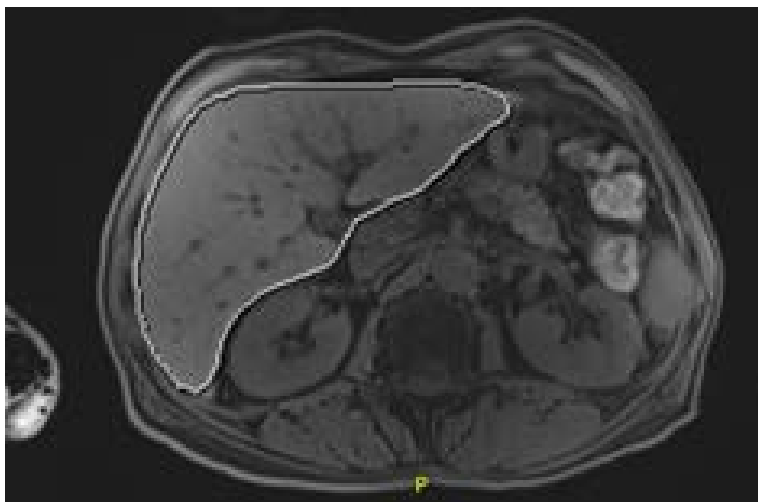
| | |
|--------------------|---------|
| CMIA HIV-1/2 Ag/Ak | negativ |
|--------------------|---------|

Autoimmunhepatitis Marker

AUTOANTIKÖRPER

| | | | |
|---------------------------|---|------------------------------|--|
| > ANA/ANF HEP-2 | ↑ | 1:160 | bis 1:80 |
| > ANA/ANF HEP-2 Muster | | nukleolär | |
| > ANA/ANF HEP-2 Muster | | cytoplasmatische Fluoreszenz | |
| > AK g. dsDNA (ELIA) | | 0.5 | < 10 IU/mL negativ 10 - 15 IU/mL grenzwertig > 15 IU/mL positiv |
| > c-ANCA Fluoreszenz | | negativ | negativ |
| > c-ANCA ELISA | | < 0.2 | Negativ: < 2.0 IU/mL Grenzwertig: 2.0 - 3.0 IU/mL Positiv: > 3.0 IU/mL |
| > p-ANCA Fluoreszenz | | negativ | negativ |
| > p-ANCA ELISA | | < 0.2 | Negativ: < 3.5 IU/mL Grenzwertig: 3.5 - 5.0 IU/mL Positiv: > 5.0 IU/mL |
| > X-ANCA | | negativ | |
| > AK g. glatte Muskulatur | | negativ | bis 1:80 |
| > AK g. Mitochondrien | | negativ | negativ |

MRCP



Zusammenfassung:

- 1.) Unauffällige Morphologie der Leber mit regulärer Perfusion und unauffälliger Funktion mit zeitgerechter Ausscheidung des hepatobiliären Kontrastmittels. Einzelne unkomplizierte Leberzysten bis 8mm Breite, exemplarisch im Lebersegment VII.
- 2.) Unauffällige Darstellung der intrahepatischen Gallenwege sowie des Ductus pancreaticus.

Leber-BX

Mikroskopie:

Histologisch Leberstanzzylinder mit gewahrter Architektur. Die Portalfelder sind geringgradig verbreitert und zeigen diskrete Zeichen der portalen und periportal Fibrose. Die eingelagerten Gefäße und Gallengänge sind regulär strukturiert und man sieht ein diskretes lymphomononukleäres Infiltrat. Die parenchymatöse Grenzplatte ist scharf, die Leberzellen liegen in trabekulärer Anordnung, sie sind regulär strukturiert und zeigen keine Verfettungszeichen. Im Bereich der Grenzzone zeigen sich teils immer wieder marginale Gallengangsproliferate.

Diagnose:

Geringgradiges hepatitisches Bild, morphologisch in erster Linie (medikamentös) toxischer Genese.

Diktirt am: 06.03.2019

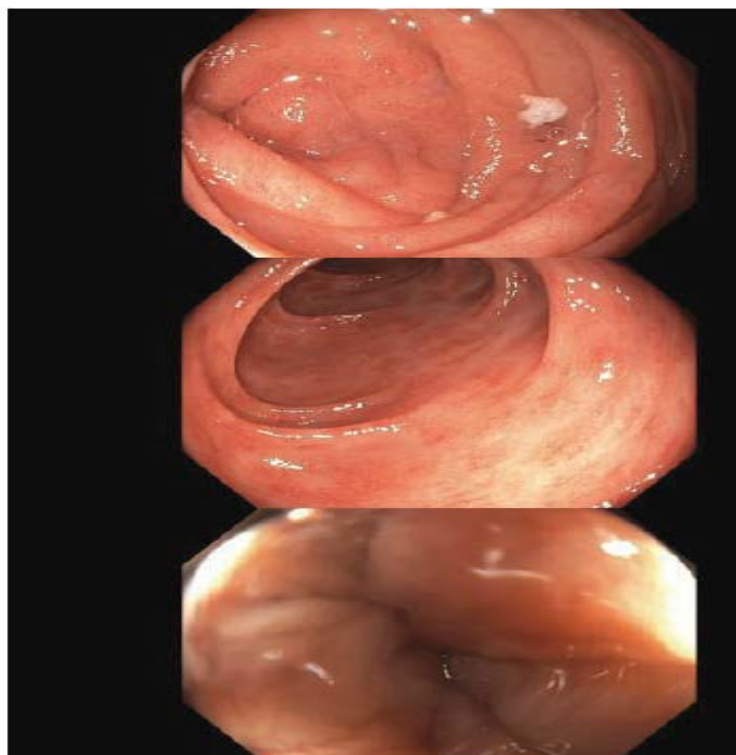
Geschrieben am: 07.03.2019

Kortison 2mg/kg/KG plus MMF 1000mg 1-0-1 bis 7/2019

Klinische Chemie

| | | | |
|--------------------------|--------|--------------|--------|
| > Natrium | 141 | 136 - 145 | mmol/L |
| > Kalium | 4.46 | 3.5 - 5.1 | mmol/L |
| > Chlorid | 103 | 98 - 107 | mmol/L |
| > Kalzium | 2.30 | 2.20 - 2.55 | mmol/L |
| > Anorganisches Phosphat | 1.27 | 0.81 - 1.45 | mmol/L |
| > Magnesium | 0.75 | 0.66 - 1.07 | mmol/L |
| > Kreatinin | 1.11 | 0.70 - 1.20 | mg/dL |
| > Harnstoff - N | ↑ 30.5 | 8 - 23 | mg/dL |
| > Harnsäure | 5.7 | 3.4 - 7.0 | mg/dL |
| > Gesamt Bilirubin | 0.19 | 0.0 - 1.2 | mg/dL |
| > Hämolyseindex | 0 | | |
| > Eiweiß, gesamt | 70.9 | 64 - 83 | g/L |
| > Albumin | 38.3 | 35 - 52 | g/L |
| > Cholinesterase | ↓ 4.26 | 5.32 - 12.92 | kU/L |
| > Alkalische Phosphatase | 63 | 40 - 130 | U/L |
| > ASAT (GOT) | 15 | < 50 | U/L |
| > ALAT (GPT) | 11 | < 50 | U/L |
| > Gamma - GT | 40 | < 60 | U/L |
| > LDH | 151 | < 250 | U/L |
| > CK | 76 | < 190 | U/L |

9/2019- Durchfälle+Übelkeit



Klinische Chemie

- > Material 06 ikterisch
- > Material 06 lipämisch

| | | | | |
|--------------------------|---|------|--------------|--------|
| > Natrium | ↓ | 135 | 136 - 145 | mmol/L |
| > Kalium | ↑ | 5.65 | 3.5 - 5.1 | mmol/L |
| > Chlorid | | 98 | 98 - 107 | mmol/L |
| > Kalzium | | 2.40 | 2.20 - 2.55 | mmol/L |
| > Anorganisches Phosphat | | 1.05 | 0.81 - 1.45 | mmol/L |
| > Magnesium | | 0.76 | 0.66 - 1.07 | mmol/L |
| > Kreatinin | | 1.07 | 0.70 - 1.20 | mg/dL |
| > Harnstoff - N | | 11.3 | 8 - 23 | mg/dL |
| > Harnsäure | | 3.5 | 3.4 - 7.0 | mg/dL |
| > Gesamt Bilirubin | ↑ | 2.79 | 0.0 - 1.2 | mg/dL |
| > Hämolyseindex | | 0 | | |
| > Eiweiß, gesamt | | 75.9 | 64 - 83 | g/L |
| > Albumin | | 37.4 | 35 - 52 | g/L |
| > Cholinesterase | ↓ | 4.92 | 5.32 - 12.92 | kU/L |
| > Alkalische Phosphatase | ↑ | 1624 | 40 - 130 | U/L |
| > ASAT (GOT) | ↑ | 209 | < 50 | U/L |
| > ALAT (GPT) | ↑ | 149 | < 50 | U/L |
| > Gamma - GT | ↑ | 1098 | < 60 | U/L |
| > LDH | | 180 | < 250 | U/L |

Immer wieder geringe fleckige Rötung. Es werden Stufenbiopsien entnommen.

Histo:

Zusammenfassende Diagnose:

1: Dünndarmschleimhaut (Ileum) mit deutlich gesteigerter regenerativer Aktivität und follikulärer lymphatischer Reaktivität - siehe Folgepräparate.

2-7: Der Gesamtaspekt passt am ehesten zum Bild einer sogenannten lymphozytären Colitis - siehe Anmerkung.

Anmerkung:

Diesbezüglich zu überlegen wäre, ob dies vielleicht auch mit eventuell stattgehabter Immuntherapie zusammenhängen könnte.

Diktiert am: 25.09.2019

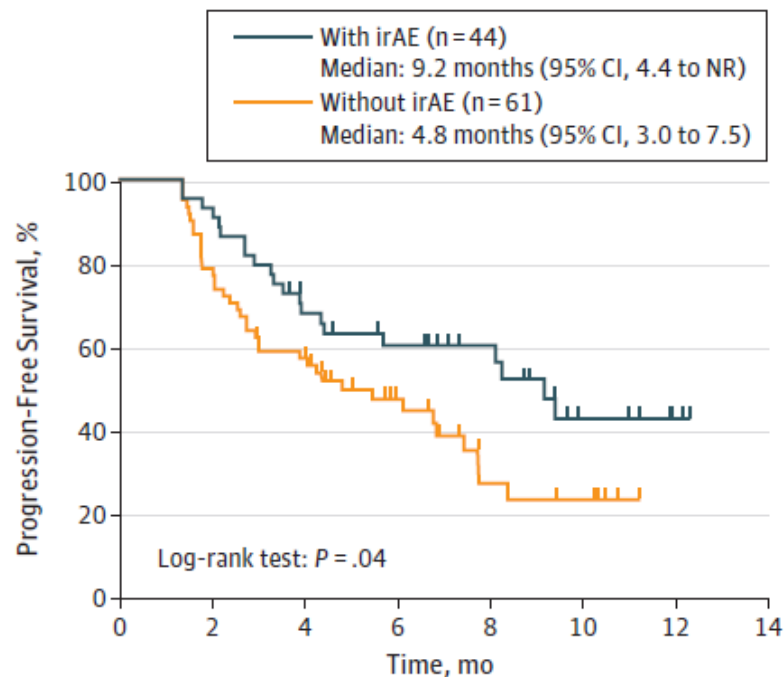
Geschrieben am: 26.09.2019



Nebenwirkung und Outcome-NSCLC

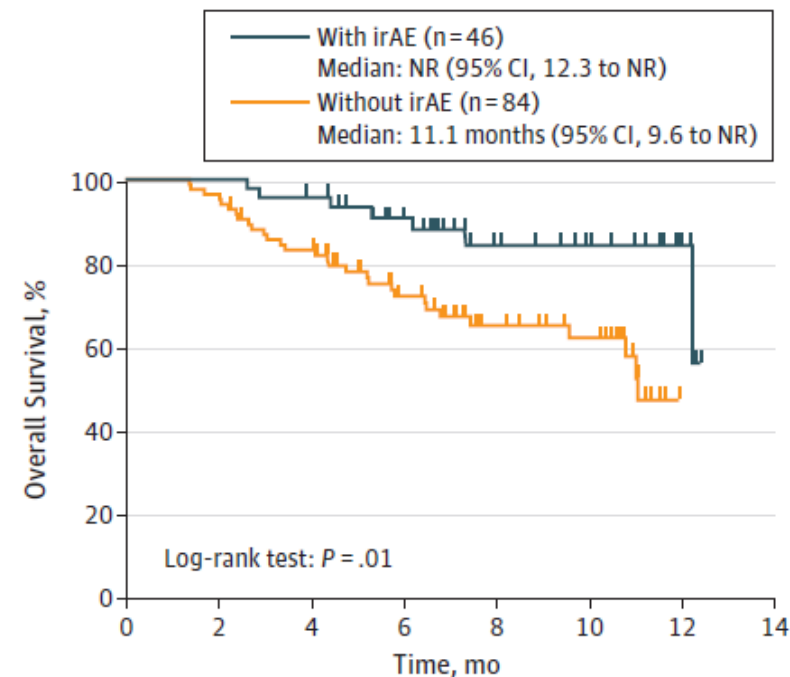


A Progression-free survival



| No. at risk | 0 | 2 | 4 | 6 | 8 | 10 | 12 |
|--------------|----|----|----|----|----|----|----|
| With irAE | 44 | 41 | 28 | 22 | 15 | 6 | 2 |
| Without irAE | 61 | 48 | 34 | 17 | 7 | 5 | 0 |

B Overall survival

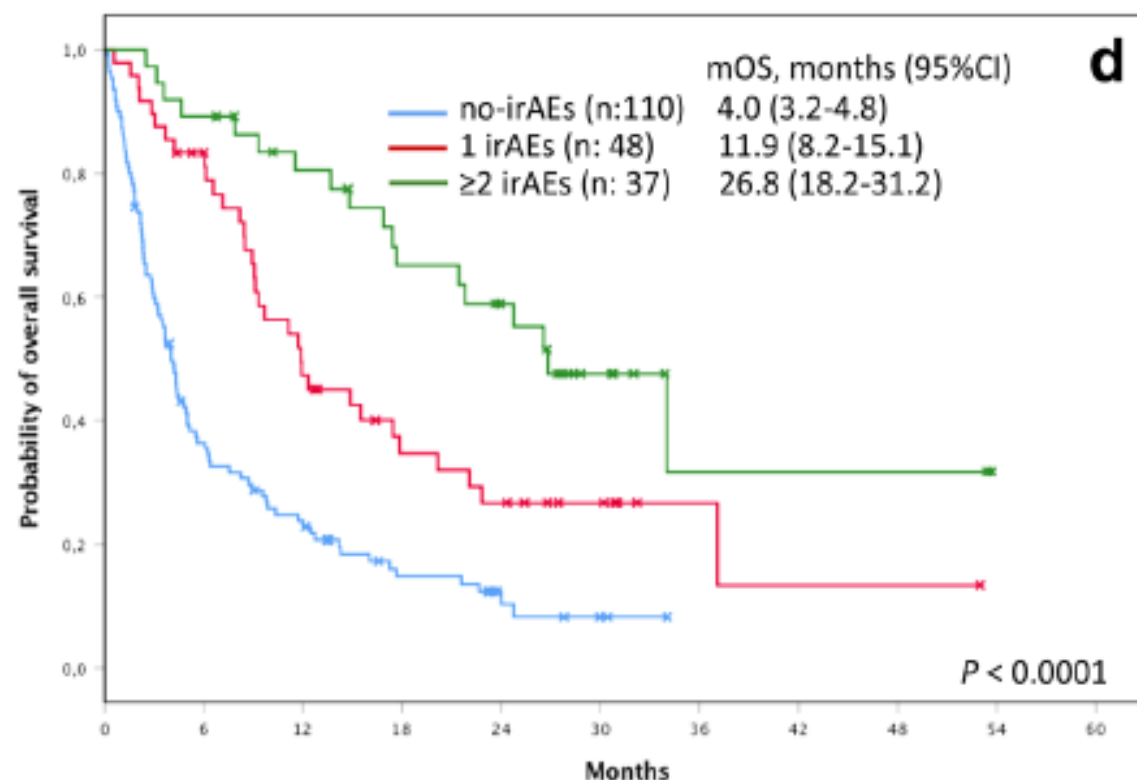
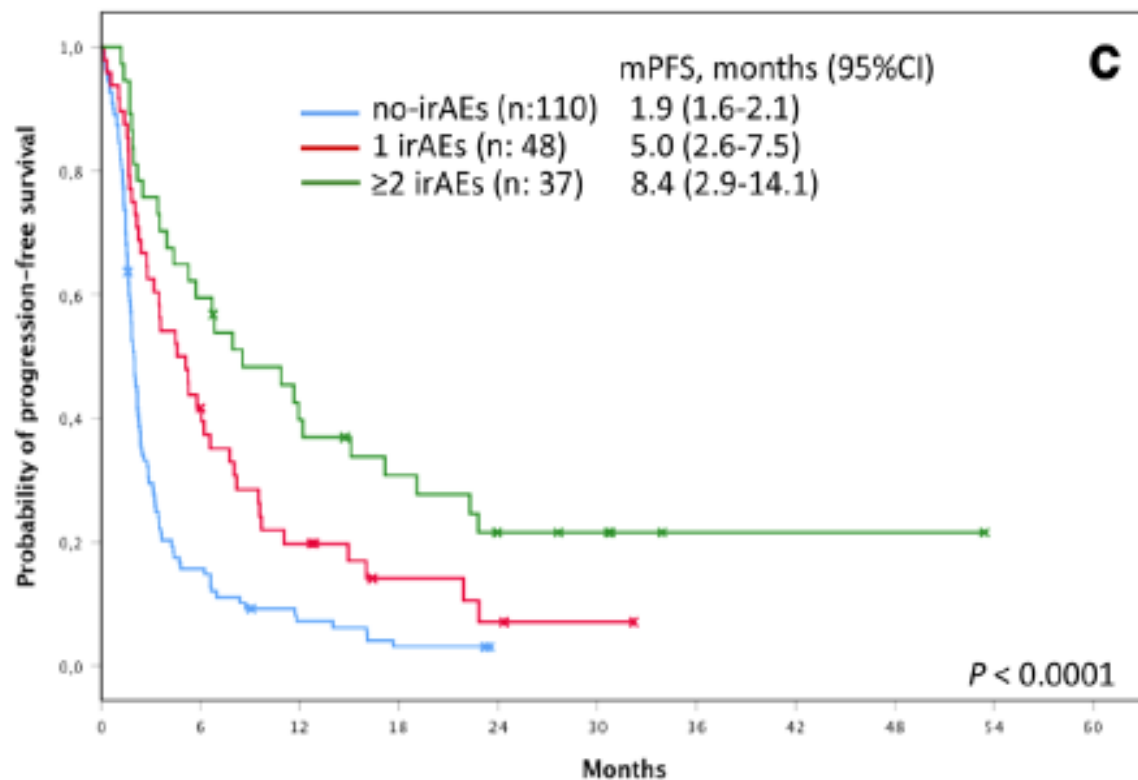


| No. at risk | 0 | 2 | 4 | 6 | 8 | 10 | 12 |
|--------------|----|----|----|----|----|----|----|
| With irAE | 46 | 46 | 43 | 33 | 19 | 13 | 4 |
| Without irAE | 84 | 81 | 68 | 46 | 28 | 21 | 0 |

Kaplan-Meier curves with 6-week landmark analysis for (A) progression-free survival (B) and overall survival in patients with or without irAEs. irAEs indicates immune-related adverse events; NR, not reached.



Anzahl Nebenwirkungen und Outcome- NSCLC



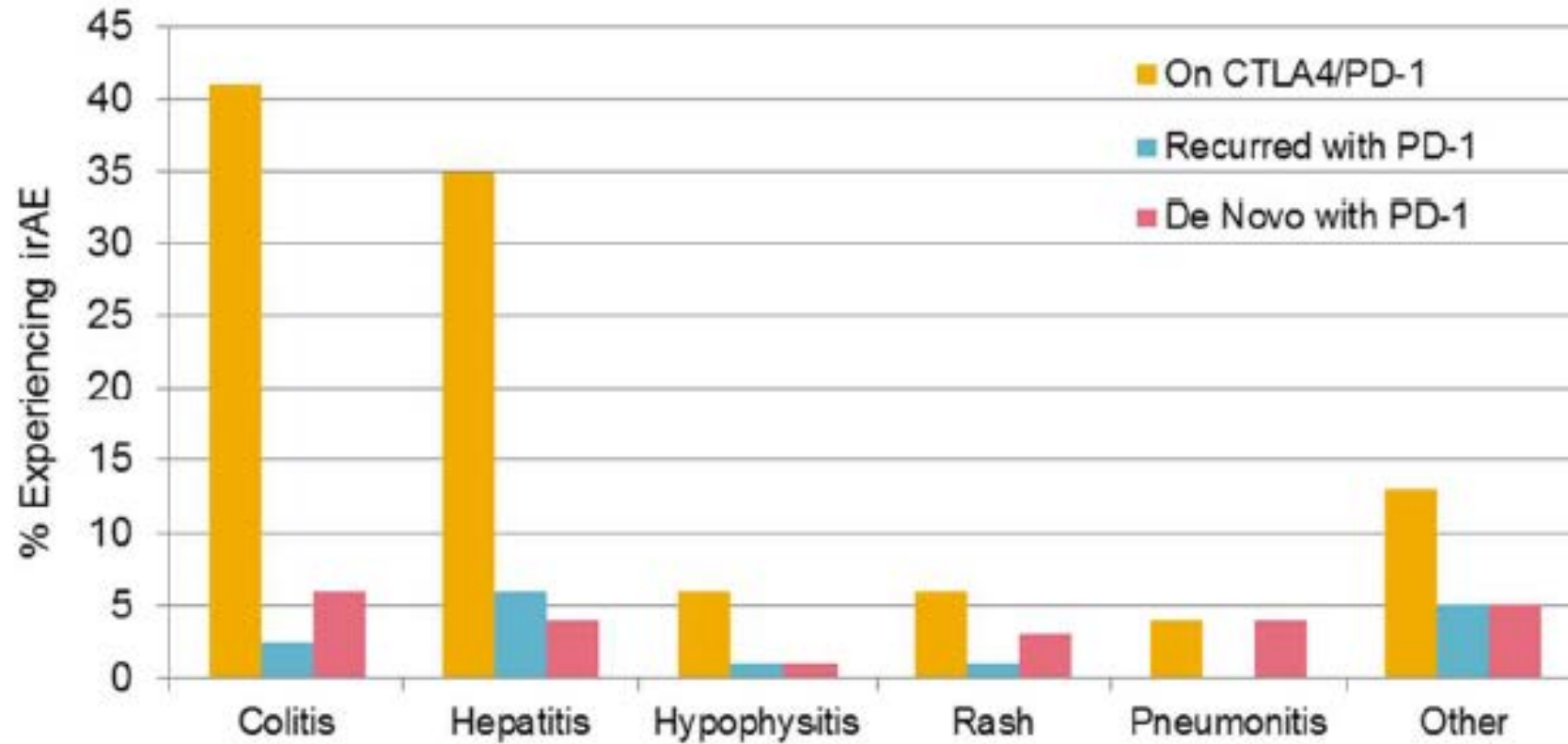
Spezialfall: Rechallenge nach irAEs

| First Author | No. of Patients With irAE | No. of Patients Rechallenged | Immunotherapy Target | Malignancy | Patients With Any irAE Recurrence After Immunotherapy Rechallenge, % | Patients With Identical irAE Recurrence, % |
|--------------------------|---------------------------|------------------------------|----------------------|--|--|--|
| Pollack ¹¹ | 80 | 80 | PD-1 | Melanoma | 39 | 18 |
| Santini ¹² | 68 | 38 | PD-L1 | NSCLC | 52 | 26 |
| Abu-Sbeih ¹⁰ | 167 | 167 | CTLA-4, PD-1, PD-L1 | Melanoma, NSCLC, other solid tumors and hematologic malignancies | | 34 |
| Simonaggio ¹³ | 93 | 40 | PD-1, PD-L1 | Melanoma, lung, colorectal, lymphoma | 55 | 42 |

Abbreviations: CTLA-4, cytotoxic T-cell lymphocyte 4; irAE, immune-related adverse event; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

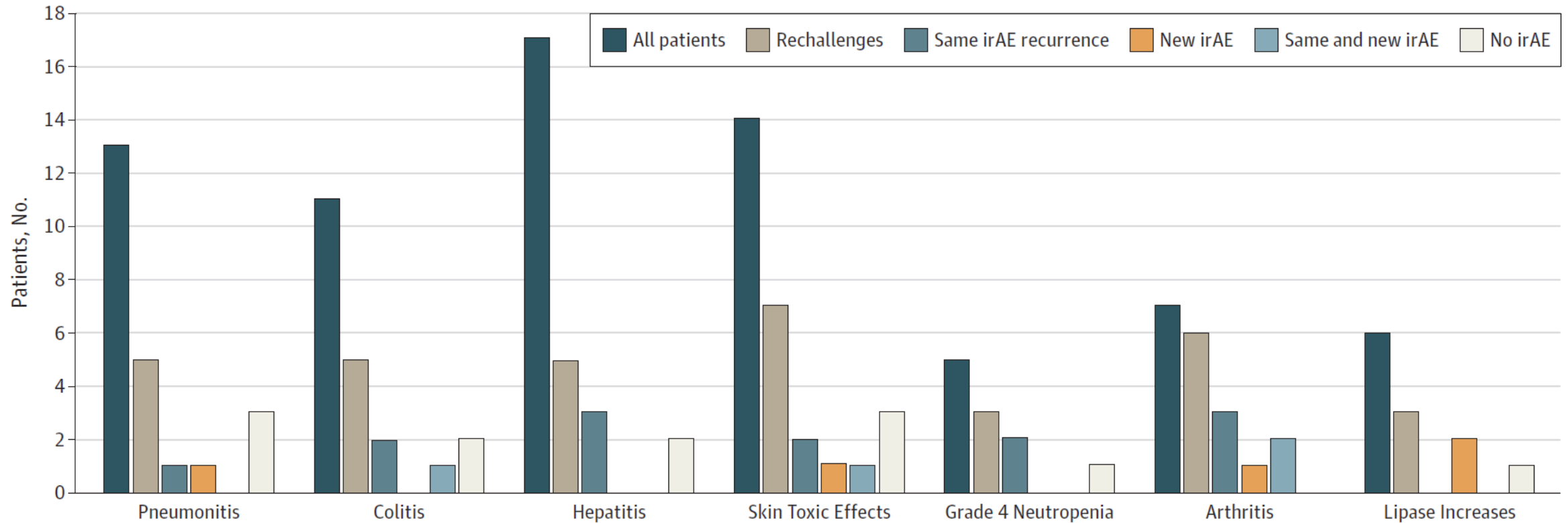


Spezialfall: Rechallenge nach irAEs



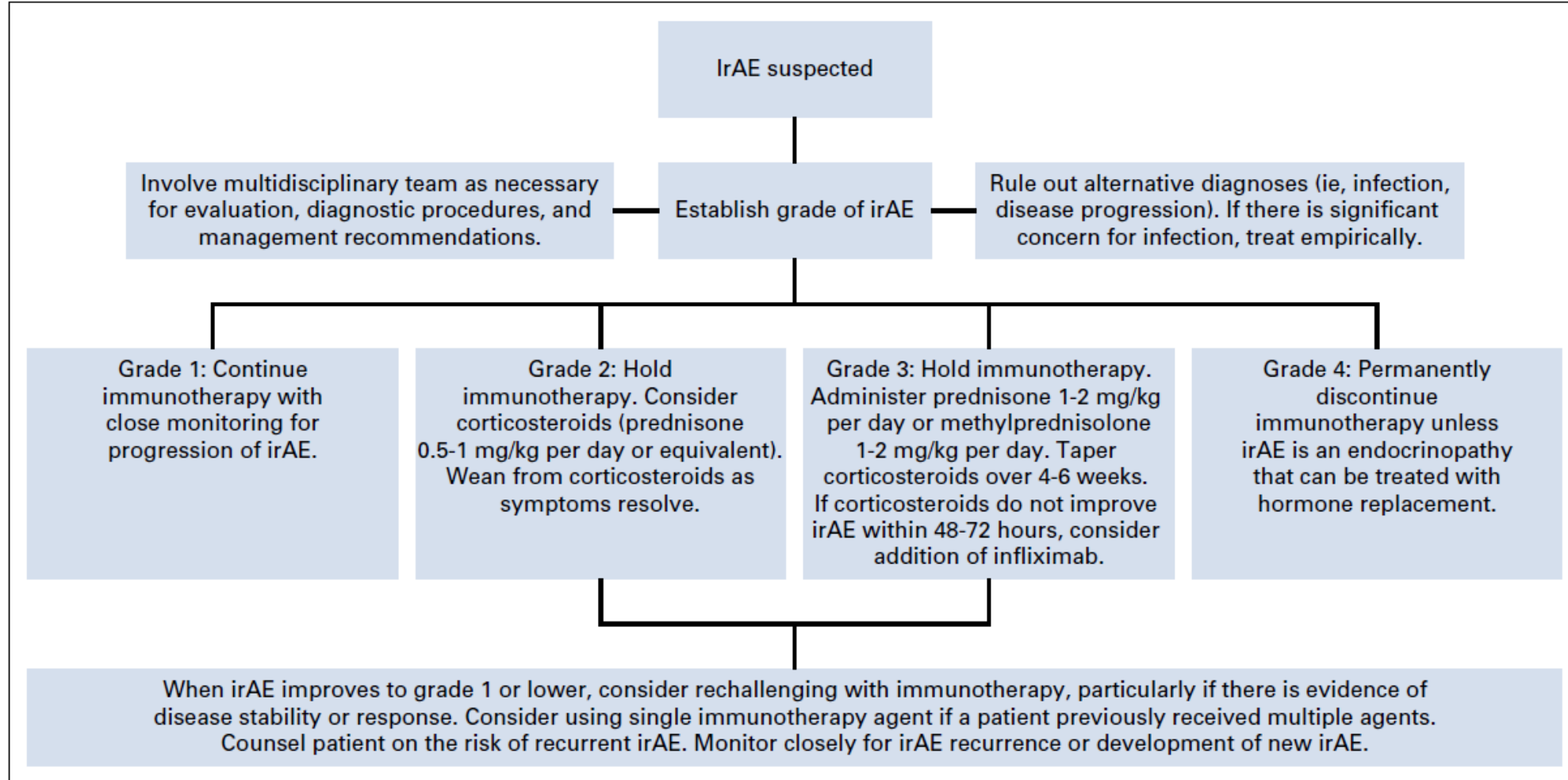
Spezialfall: Rechallenge nach irAEs

Figure. Patient Outcomes After Anti-PD-1 or Anti-PD-L1 Rechallenge as a Function of Immune-Related Adverse Event (irAE) Type



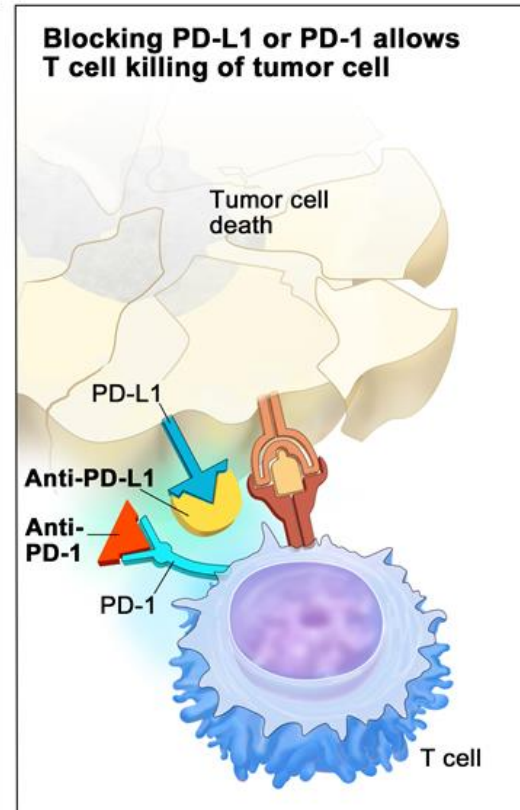
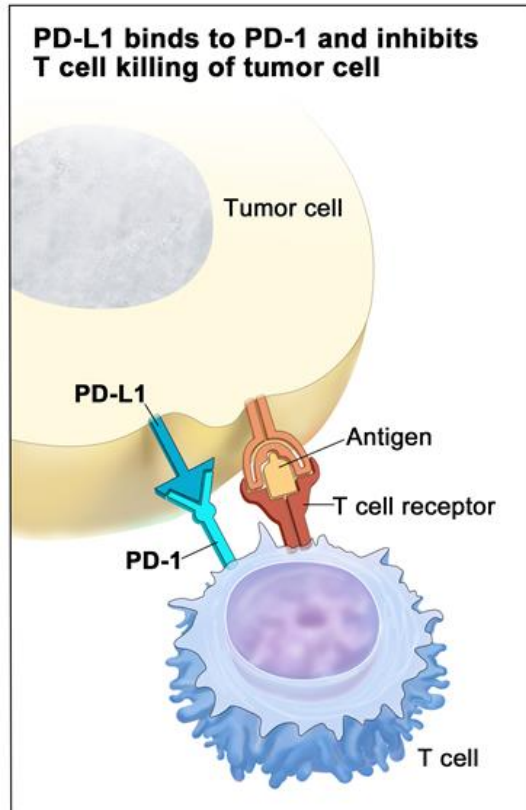


Spezialfall: Rechallenge nach irAEs





Rechallenge nach Nebenwirkungen



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60 jährige Pat. Melanom met.; PD nach BRAF/MEK Inhibition St.p. NTX 2000

| | | Resultat | Referenzbereich | Einheit |
|------------------------------|---|----------|-----------------|-----------------------------------|
| Chlorid | ↓ | 97 | 98 - 107 | mmol/L |
| Kalzium | | 2.34 | 2.15 - 2.50 | mmol/L |
| Anorganisches Phosphat | | 1.05 | 0.81 - 1.45 | mmol/L |
| Magnesium | | 0.74 | 0.66 - 1.07 | mmol/L |
| Kalzium - Phosphat - Produkt | | 2.46 | | mmol ² /L ² |
| Kreatinin | ↑ | 3.22 | 0.50 - 0.90 | mg/dL |
| Harnstoff - N | ↑ | 49.2 | 6 - 20 | mg/dL |
| Albumin | | 45.5 | 35 - 52 | g/L |
| LDH | ↑ | 307 | < 250 | U/L |
| GFR (MDRD-IDMS) | ↓ | 14.88 | > 90 | mL/min/1,73m ² |

Spezialfall: Organtransplantation

Tumor Inzidenz nach Organtransplantation

| Cancer site (ICD code[s]) | Up to 5 years before RRT | | During dialysis | | After transplantation | |
|--|-----------------------------|------------|-----------------|--------------|-----------------------|---------------|
| | SIR | 95% CI | SIR | 95% CI | SIR | 95% CI |
| Lip (C00) | 1.87 | 1.17–2.83 | 3.68 | 2.46–5.28 | 47.08 | 41.75–52.89 |
| Tongue (C01–C02) | 0.53 | 0.06–1.93 | 3.28 | 1.69–5.72 | 7.17 | 4.38–11.07 |
| Mouth (C03–C06) | 1.34 | 0.43–3.13 | 2.15 | 0.98–4.08 | 4.58 | 2.51–7.69 |
| Salivary gland (C07–C08) | 2.11 | 0.57–5.40 | 1.2 | 0.15–4.34 | 7.71 | 3.33–12.20 |
| Esophagus (C15) | 1.05 | 0.28–2.68 | 1.68 | 0.96–2.74 | 3.82 | 2.26–6.03 |
| Stomach (C16) | 0.81 | 0.35–1.60 | 1.52 | 1.01–2.19 | 1.84 | 1.07–2.94 |
| Small intestine (C17) | 1.25 | 0.15–4.53 | 3.06 | 1.12–6.67 | 1.73 | 0.21–6.25 |
| Colon (C18) | 1.33 | 1.06–1.65 | 1.18 | 0.93–1.47 | 2.36 | 1.87–2.92 |
| Rectum (C19–C20) | 1.33 | 0.98–1.77 | 1.02 | 0.72–1.40 | 0.63 | 0.33–1.07 |
| Anus (C21) | 0.33 | 0.07–0.96 | 0.23 | 0.03–0.82 | 2.76 | 1.51–4.64 |
| Liver (C22) | 2.87 | 0.78–7.34 | 2.25 | 1.23–3.77 | 3.19 | 1.53–5.87 |
| Gallbladder (C23–C24) | 0 | - | 1.55 | 0.67–3.05 | 4.34 | 2.16–7.76 |
| Pancreas (C25) | 2.16 | 0.87–4.45 | 1.17 | 0.69–1.85 | 1.21 | 0.56–2.30 |
| Larynx (C32) | 0.96 | 0.42–1.90 | 1.02 | 0.41–2.11 | 2.1 | 0.96–3.98 |
| Trachea; bronchus and lung (C33–C34) | 1.07 | 0.74–1.49 | 1.59 | 1.33–1.88 | 2.45 | 2.00–2.97 |
| Melanoma (C43) | 1.02 | 0.81–1.27 | 1.06 | 0.81–1.38 | 2.53 | 2.08–3.05 |
| Mesothelioma (C45) | 0.61 | 0.02–3.37 | 1.73 | 0.75–3.40 | 1.32 | 0.27–3.85 |
| Kaposi sarcoma (C46) (Nalesnik et al. 2011) | 19.64 | 4.05–57.40 | 57.88 | 21.24–125.98 | 207.9 | 113.66–348.82 |



Spezialfall: Organtransplantation

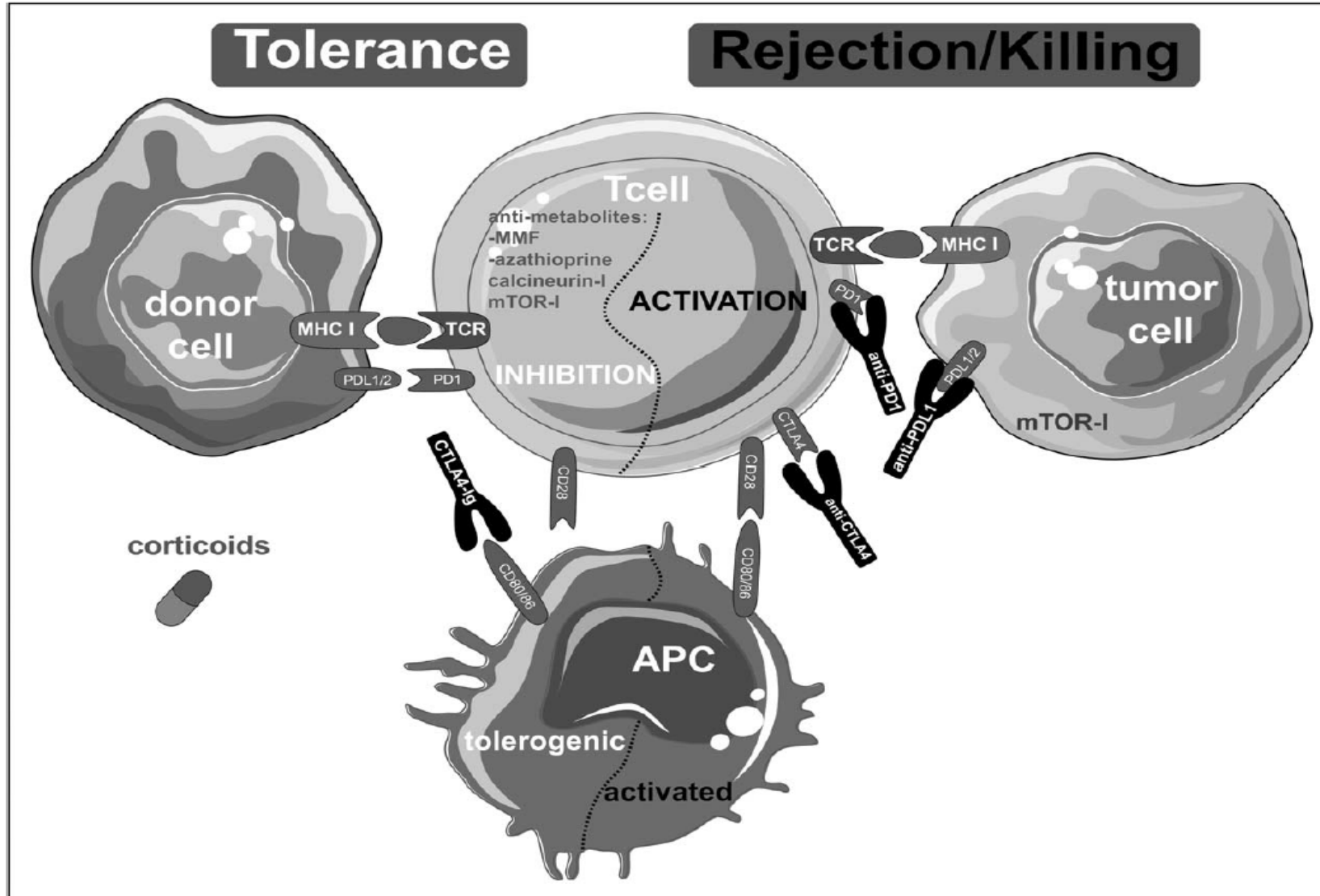


Table 2 Checkpoint Inhibitor-Induced Allograft Rejection in Patients with Cancer and Prior Solid Organ Transplantation

| Prior organ transplantation | Checkpoint inhibitor | Allograft rejection, no./ reported cases (%) | Median time to rejection, days (range) |
|-----------------------------|--|--|--|
| All | | 16/39 (41) | 15.5 (5–60) |
| Renal | Ipilimumab | 2/4 (50) | 21 |
| | Nivolumab | 2/5 (40) | 18.5 (7–30) |
| | Pembrolizumab | 4/9 (44) | 21 (5–60) |
| | Ipilimumab + nivolumab | 1/1 (100) | 8 |
| | Ipilimumab followed by nivolumab or pembrolizumab ^a | 2/4 (50) | 14.5 (8–21) |
| | All | | 11/23 (48) |
| Hepatic | Ipilimumab | 1/3 (33) | 13 |
| | Nivolumab | 2/4 (50) | 12.5 (7–18) |
| | Pembrolizumab | 1/3 (33) | 7 |
| | Ipilimumab followed by pembrolizumab ^a | 0/1 (0) | |
| | All | | 4/11 (36) |
| Cardiac | Ipilimumab | 0/1 (0) | |
| | Nivolumab | 1/2 (50) | 5 |
| | Pembrolizumab | 0/1 (0) | |
| | Ipilimumab followed by pembrolizumab ^a | 0/1 (0) | |
| | All | | 1/5 (20) |

Spezialfall: OTR und CPI

| Immunosuppression at initiation of checkpoint inhibitor therapy | Allograft rejection, no./reported cases (%) | Tumor response ^a , no./reported cases (%) |
|---|---|--|
| All patients ^b | 15/38 (40) | 15/32 ^c [47] |
| Single-agent immunosuppressive therapy | | |
| Prednisone (≤ 10 mg/day) | 7/9 (78) | 5/8 (63) |
| mTOR inhibitors | 2/3 (67) | 1/2 (50) |
| Calcineurin inhibitors | 1/9 (11) | 2/8 (25) |
| Combination immunosuppressive therapy | 5/17 (29) | 7/14 (50) |



Spezialfall: OTR und CPI

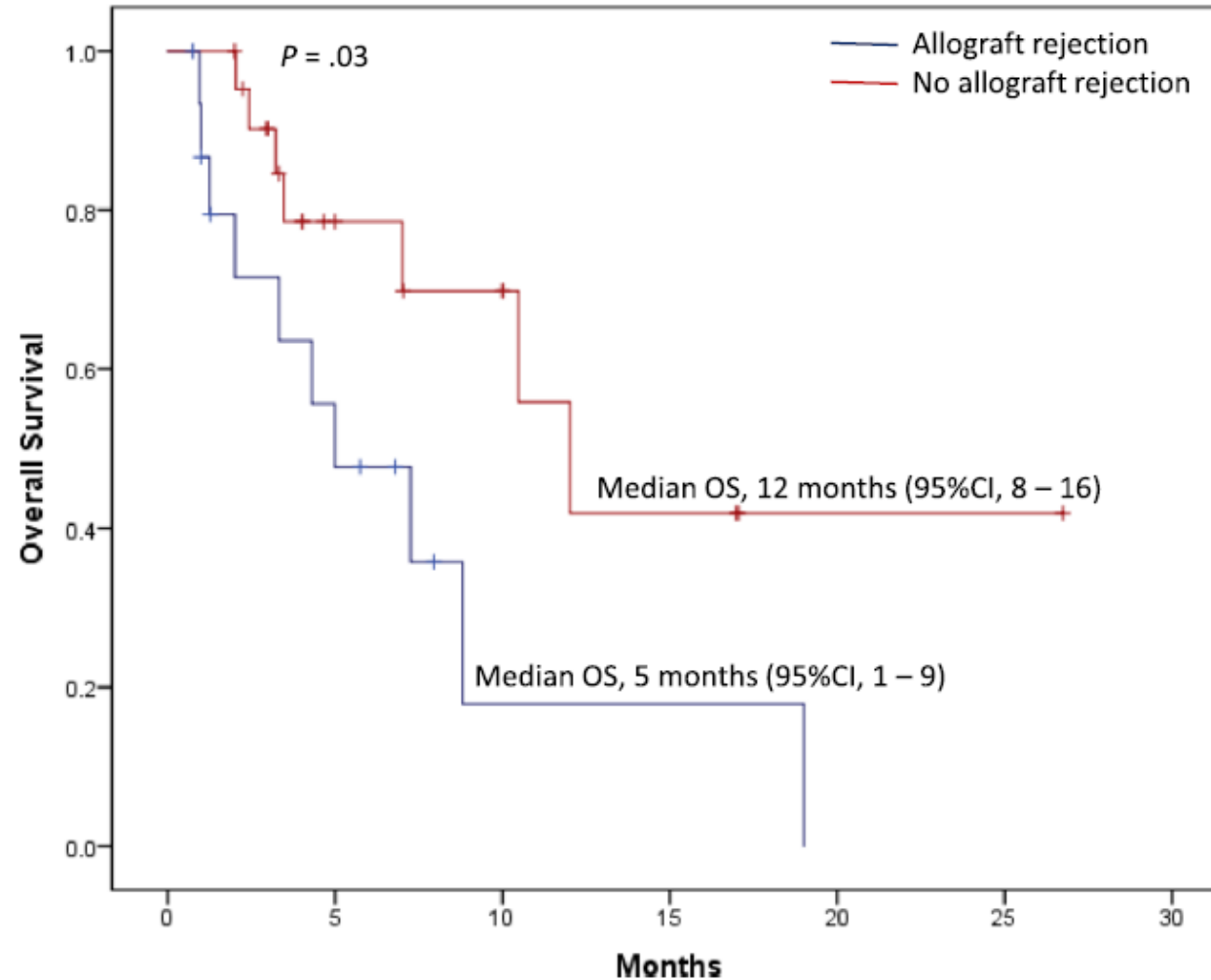


Table III. Rate of rejection by organ type

| Transplant type | Rejection, n (%) | Death secondary to rejection, n (%) |
|------------------------|-----------------------------|--|
| Kidney, n = 32 | 13 (41) | 2 (6) |
| Liver, n = 20 | 7 (35) | 6 (30) |
| Cardiac, n = 5 | 1 (20) | 0 (0) |



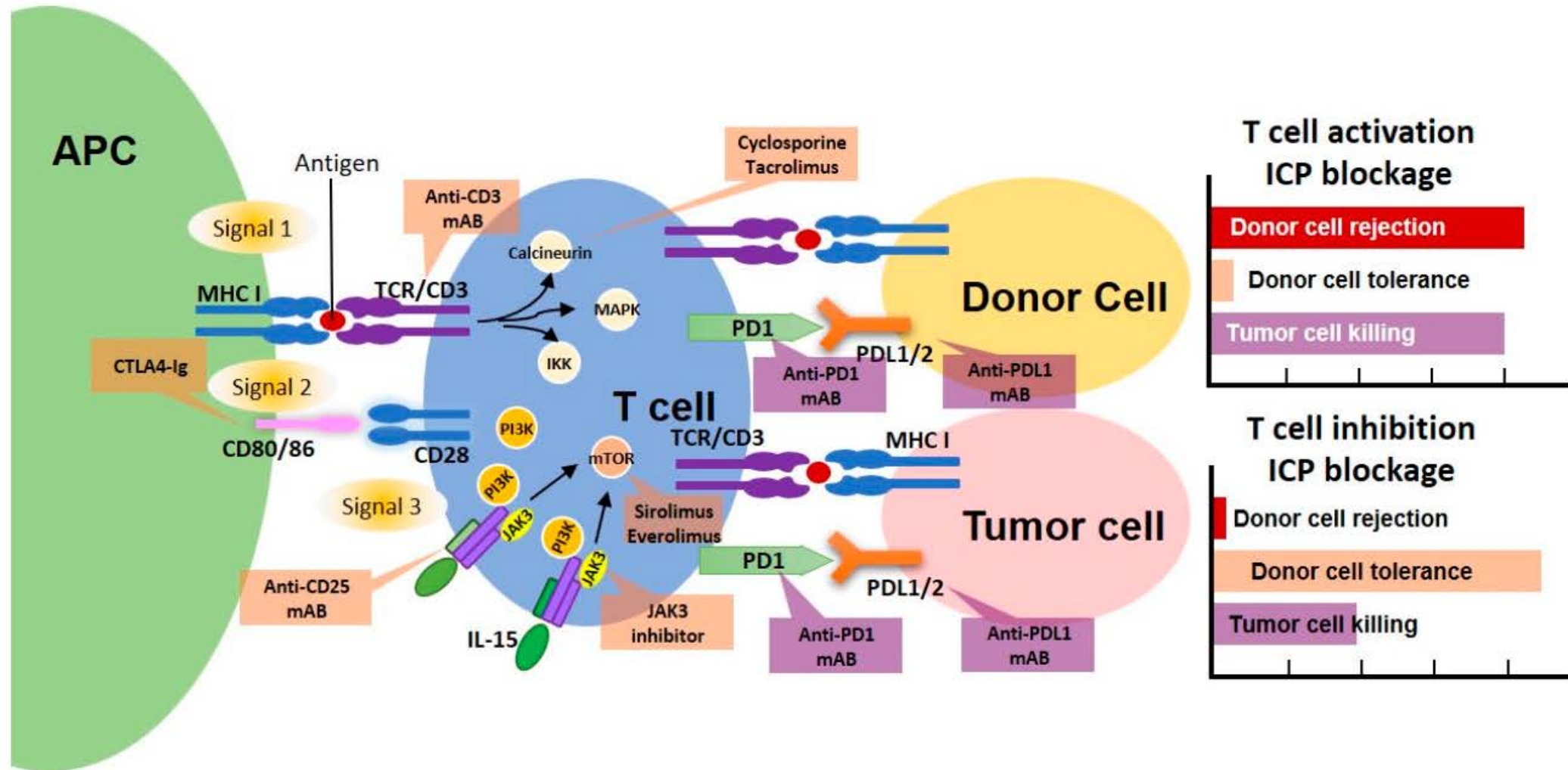
Case



| | | | | |
|---|---|-----------------|-------------|-----------------------------------|
| Natrium | ↓ | 133 | 136 - 145 | mmol/L |
| Kalium | | 4.89 | 3.5 - 5.1 | mmol/L |
| Chlorid | | 101 | 98 - 107 | mmol/L |
| Kalzium | ↓ | 1.78 | 2.15 - 2.50 | mmol/L |
| Anorganisches Phosphat | | 1.35 | 0.81 - 1.45 | mmol/L |
| Magnesium | | 0.90 | 0.66 - 1.07 | mmol/L |
| Kalzium - Phosphat - Produkt | | 2.40 | | mmol ² /L ² |
| Kreatinin | ↑ | 4.56 | 0.50 - 0.90 | mg/dL |
| Harnstoff - N | ↑ | 39.4 | 6 - 20 | mg/dL |
| Harnsäure | | 5.0 | 2.4 - 5.7 | mg/dL |
| Gesamt Bilirubin | | < 0.1 | 0.0 - 1.2 | mg/dL |
| Eiweiß, gesamt | ↓ | 46.4 | 64 - 83 | g/L |
| Albumin | ↓ | 19.3 | 35 - 52 | g/L |
| Alpha - Amylase, gesamt | | 50 | 28 - 100 | U/L |

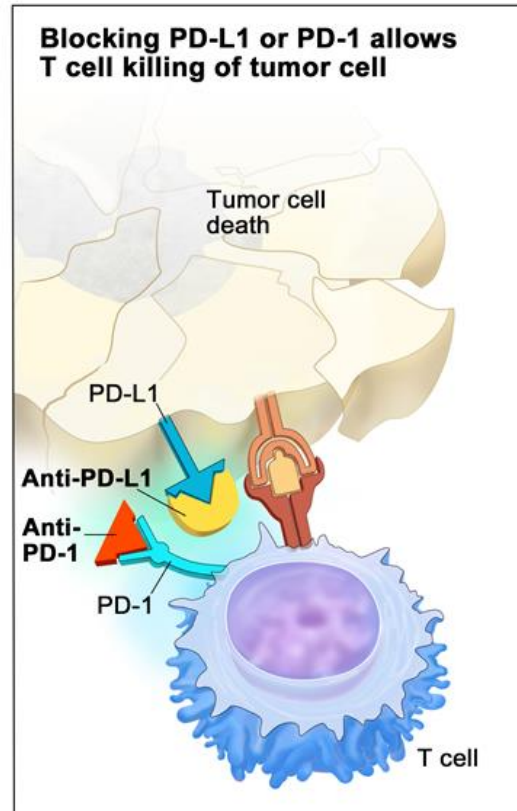
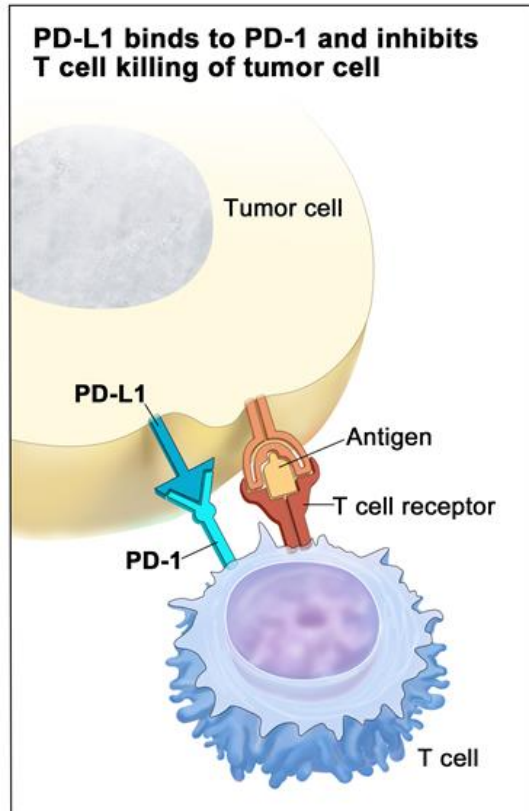


Spezialfall: OTR und CPI





Organtransplantierte Patienten



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Fragen?

