

Biologika - Die Zukunft der Pharmakotherapie in der Pneumologie?

QUADRIMED, 26.01.2024

Prof. Thomas Geiser,
Universitätsklinik für Pneumologie, Allergologie und
klinische Immunologie
Inselspital Bern
thomas.geiser@insel.ch

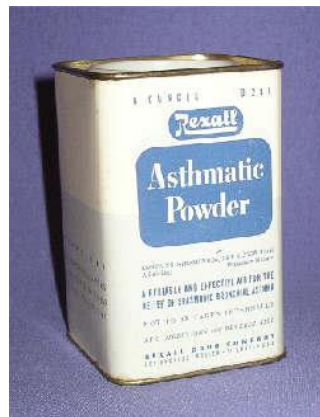


DE LA SAIGNÉE À L'IMMUNOTHÉRAPIE SPRITZEN, PILLEN, SALBEN HELFEN ALLENTHALBEN



Biologikas bei
obstruktiven Lungenerkrankungen

- **Asthma**
- **COPD**



Corpus Hippocraticum, 4th century BC

Ailments characterised by spasms of breathlessness occurring more frequently in anglers, tailors, and metal workers.

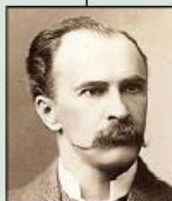
Sir John Floyer, 1698³³

"When the Muscles labour much for Inspiration and Expiration thro' some Obstruction, or Compression of the Bronchia, etc. we properly call this a Difficulty of Breath: but if this Difficulty be by the Constriction of the Bronchia, 'tis properly the Periodic Asthma: And if the Constriction be great, it is with Wheezing; but if less, the Wheezing is not so evident."



Sir William Osler, 1894³⁵

Osler highlighted the following features: spasm of the bronchial muscles; swelling of the bronchial mucous membrane; a special form of inflammation of the smaller bronchioles; similarities with hay fever; running in families; often beginning in childhood and sometimes lasting into old age; symptoms occurring in a variety of circumstances which at times induce a paroxysm; a relationship with climate, atmosphere (ie, hay, dust, cat), violent emotion, diet, and colds; and distinctive sputum containing rounded gelatinous masses (perles), Curschmann spirals, and octahedral crystals of Leyden.



Global Initiative for Asthma, 2002³⁶

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread airflow obstruction that is typically reversible either spontaneously or with treatment.



Maimonides, 12th century AD

Patient's symptoms often started as a common cold during the wet months. Eventually the patient gasped for air and coughed until phlegm was expelled. Maimonides noted that the dry months of Egypt helped asthma sufferers.



Henry Hyde Salter, 1860³⁴

"Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration between attacks."

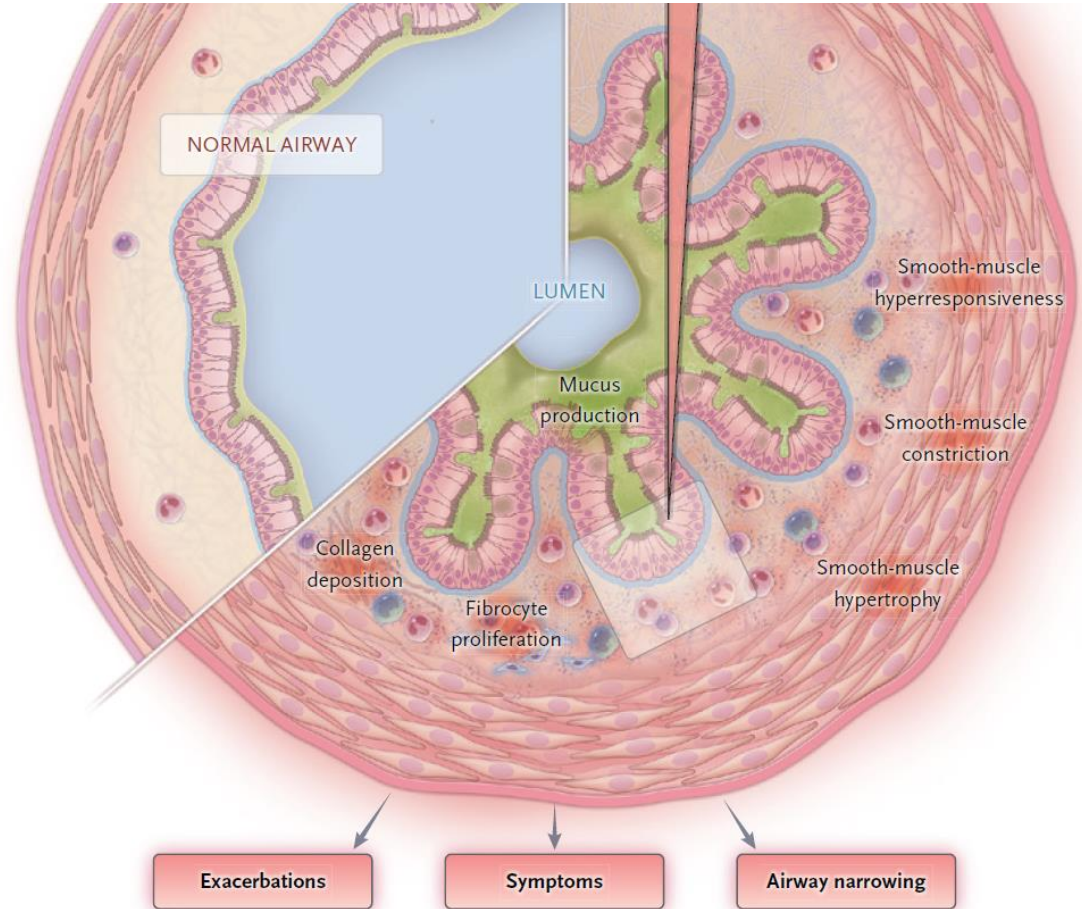
Ciba symposium, 1958²³

Asthma refers to the condition of subjects with widespread narrowing of the bronchial airways, which changes its severity over short periods of time either spontaneously or under treatment, and is not due to cardiovascular disease.

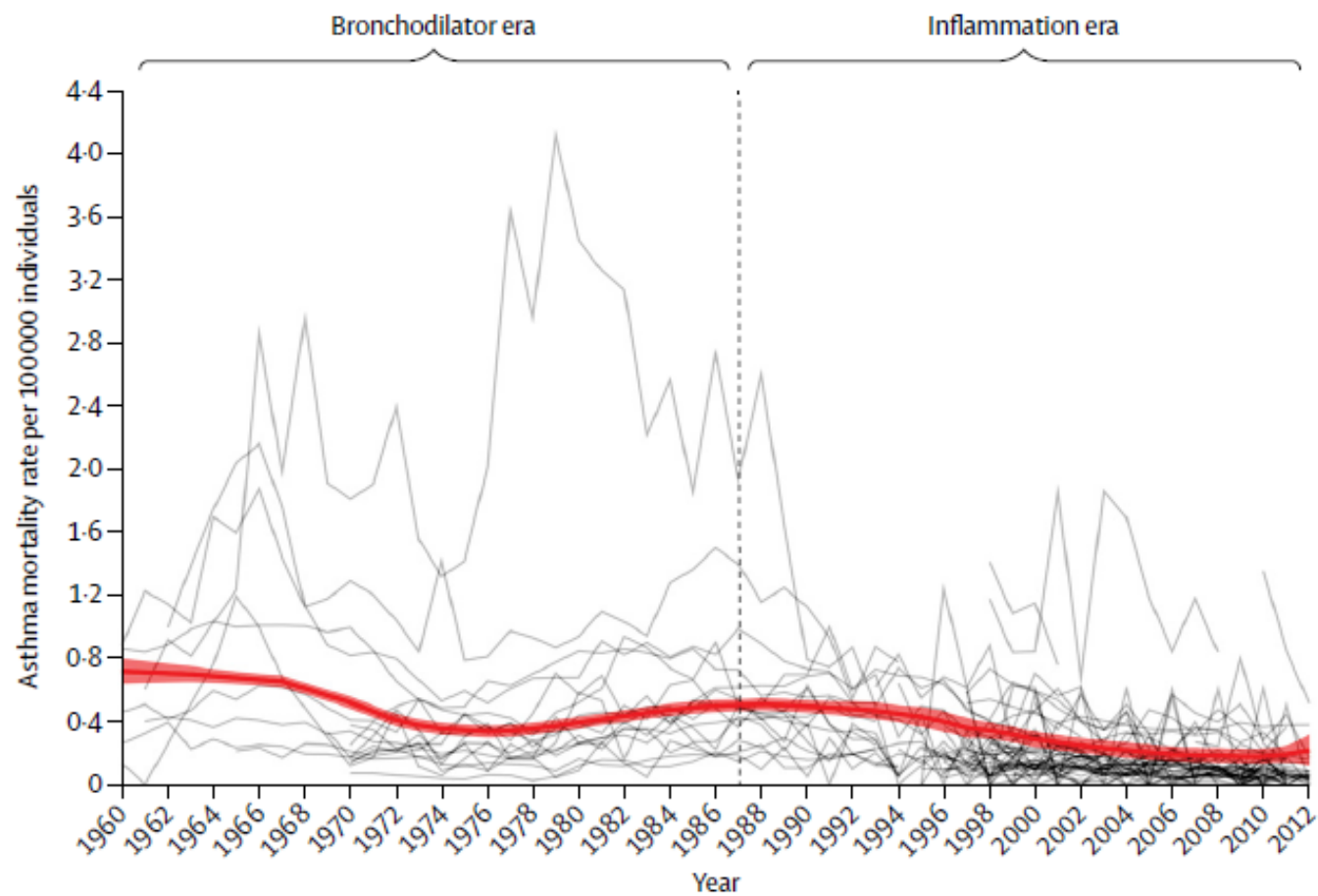
Global Initiative for Asthma 2017³⁷

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation.

Asthma als Entzündungskrankheit der Atemwege

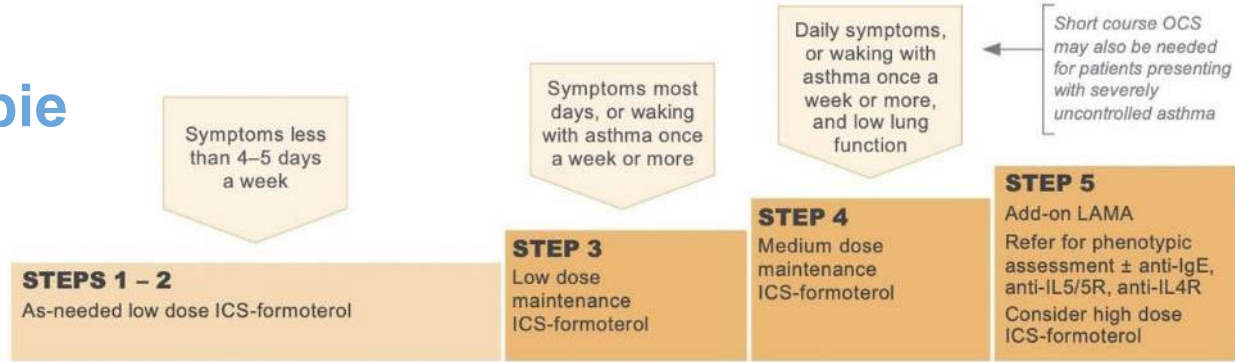


1/31/2024



Stufentherapie

CONTROLLER and **PREFERRED RELIEVER**



RELIEVER: As-needed low-dose ICS-formoterol

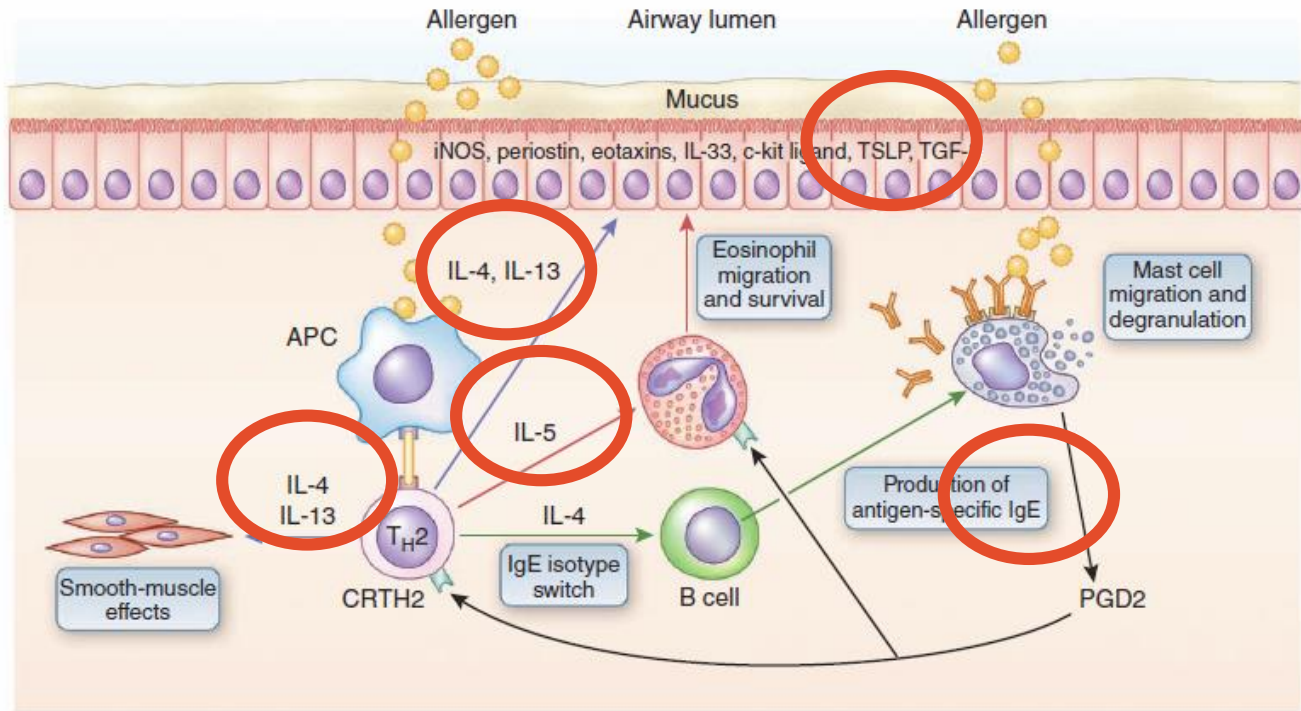
Maintenance and reliever therapy (MART)

- Formoterol: langwirksamer Beta-2-Agonist mit schnellem Wirkungseintritt
- Inhalative Kortikosteroide (ICS)

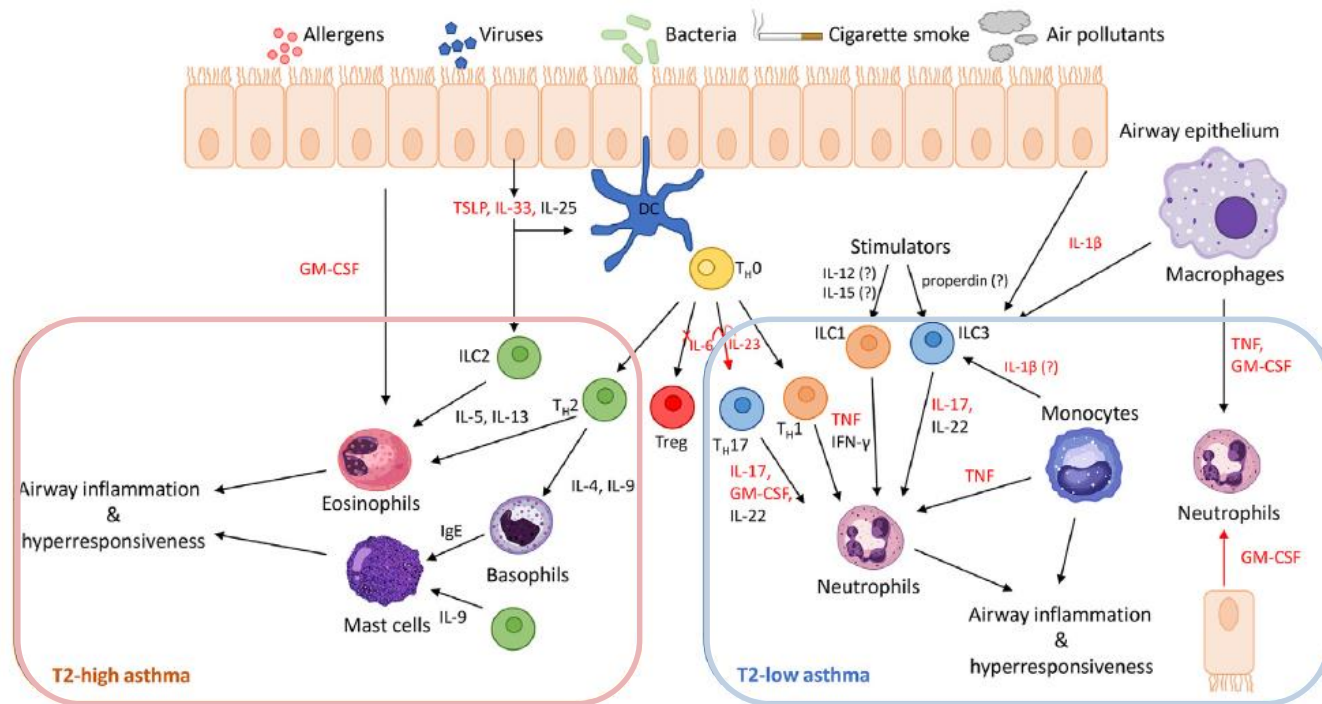
CONTROLLER and **ALTERNATIVE RELIEVER**



Pathophysiologie bei Asthma



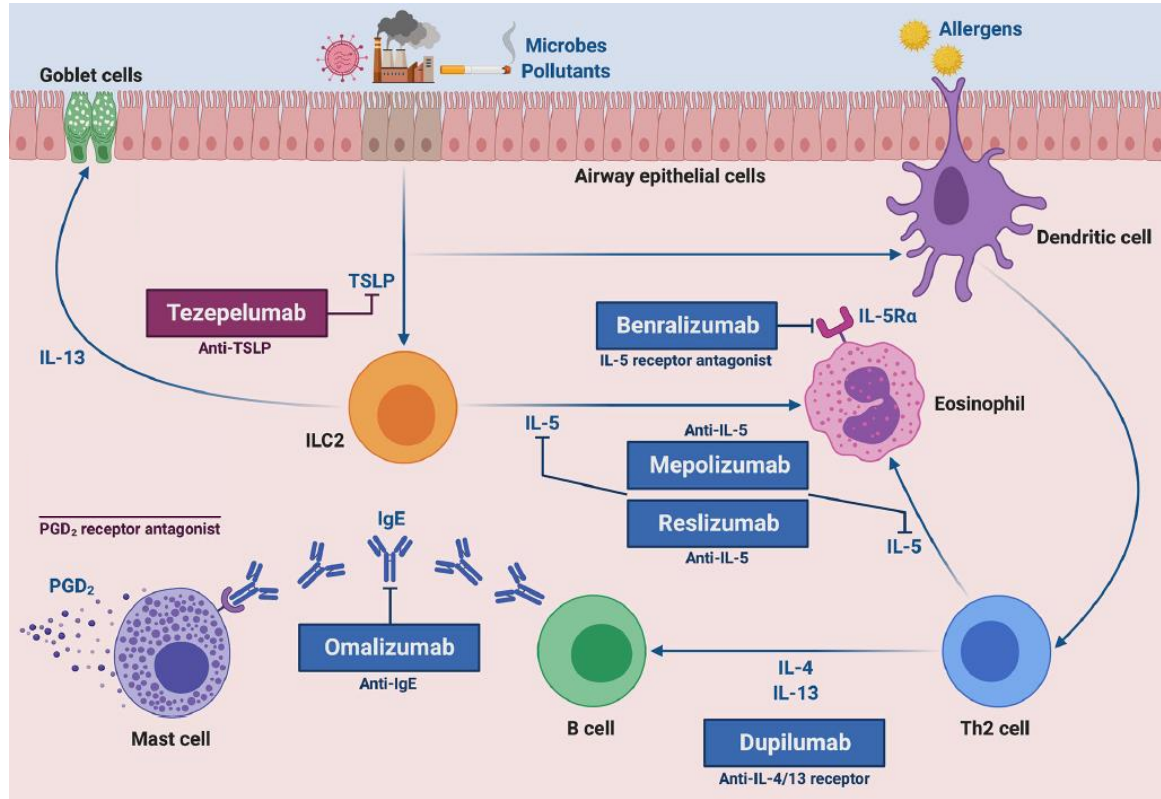
Schweres Asthma: Konzept T2 high vs. T2 low



Type-2 high
 ANY of:
 Blood Eos ≥ 0.15
 Sputum Eos $\geq 2\%$
 FeNO ≥ 25 ppb
 ca. 80%

Type-2 low
 ALL of:
 Blood Eos < 0.15
 Sputum Eos $< 2\%$
 FeNO < 25 ppb
 ca. 20%

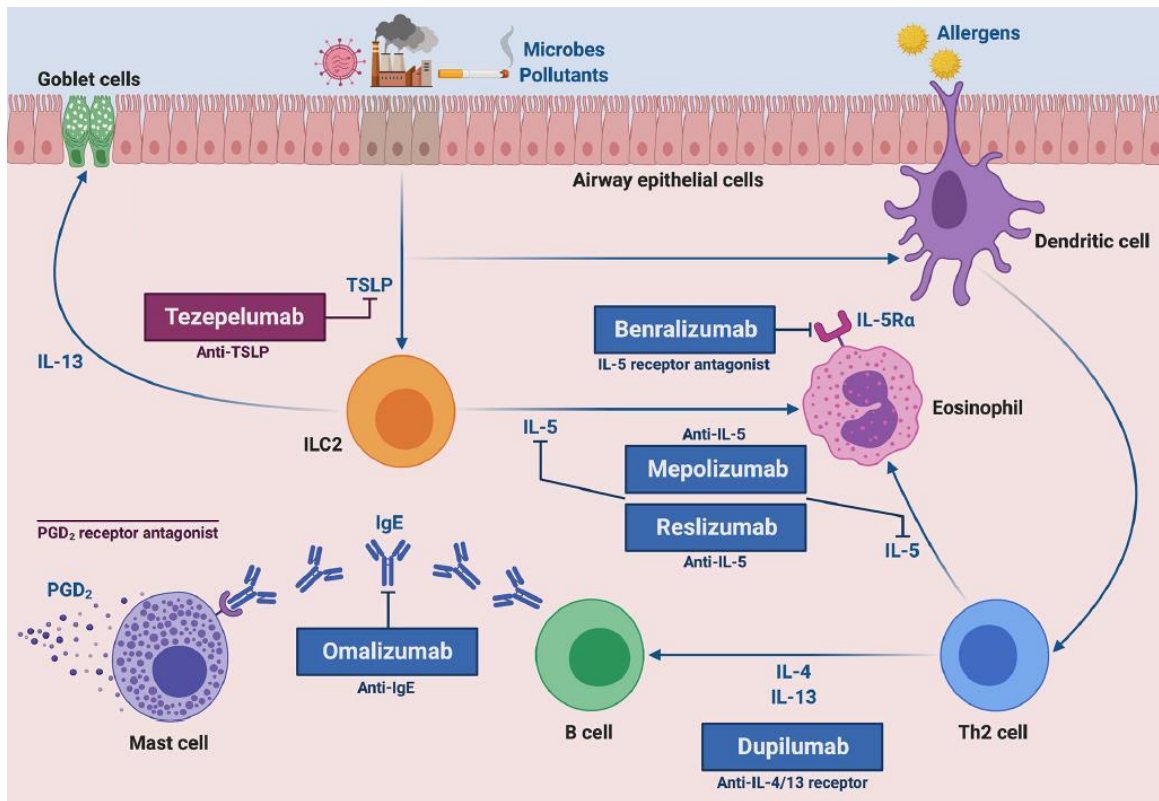
Niessen NM et al. Ann Allergy Asthma Immunol. 2022 Aug;129(2):150-159



| | |
|---|--|
| <p>Type-2 high <u>ANY of:</u> Blood Eos \geq 0.15 Sputum Eos \geq 2% FeNO \geq 25 ppb</p> | <p>Type-2 low <u>ALL of:</u> Blood Eos $<$ 0.15 Sputum Eos $<$ 2% FeNO $<$ 25 ppb</p> |
|---|--|

- Tezepelumab**
- Anti-TSLP
- Benralizumab**
- IL-5 receptor antagonist
- Mepolizumab**
- Anti-IL-5
- Reslizumab**
- Anti-IL-5
- Dupilumab**
- Anti-IL-4/13 receptor
- Omalizumab**
- Anti-IgE

- Tezepelumab**
- Anti-TSLP



| Biologic | Target | Effects |
|--------------|--------|--|
| Omalizumab | IgE | ↓ Exacerbations ↑ Quality of life and symptom control ↑ FEV1 |
| Mepolizumab | IL-5 | ↓ Blood and sputum eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↓ OCS intake ↑ FEV1 |
| Reslizumab | IL-5 | ↓ Blood and sputum eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↑ FEV1 |
| Benralizumab | IL-5Rα | ↓ Blood eosinophils ↓ Exacerbations ↑ Quality of life and symptom control ↓ OCS intake ↑ FEV1 |
| Dupilumab | IL-4Rα | ↓ Exacerbations ↓ OCS intake ↑ FEV1 |
| Tezepelumab | TSLP | ↓ Exacerbations ↓ Blood eosinophils ↑ FEV1 |

Pelaia C et al. Front Immunol. 2020 Nov 30;11:603312

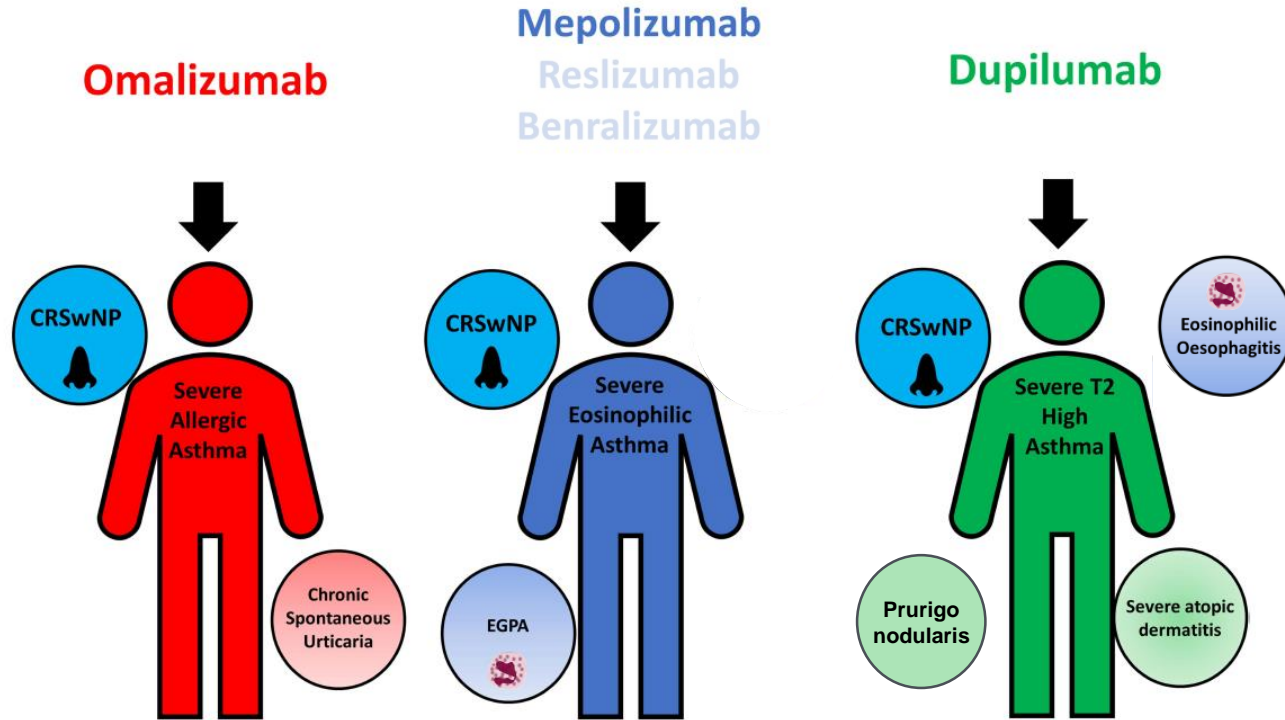
Zugelassene Biologika bei schwerem Asthma



| Biologikum | Ziel | Kriterien | Verabreichung |
|------------------------|----------------|----------------------------------|--|
| Mepolizumab (Nucala) | IL-5 | Type 2 High (Eos, FeNO) | 100 mg sc Alle 4 Wo |
| Benralizumab (Fasenra) | IL-5R α | Type 2 High | 30 mg sc, 3x alle 4, dann alle 8 Wo |
| Reslizumab (Cinqaero) | IL-5 | Type 2 High | 3 mg/kg iv alle 4 Wo |
| Omalizumab (Xolair) | IgE | Type 2 High Allergentest | 75-600 mg sc abhängig von IgE+ KG |
| Dupilumab (Dupixent) | IL-4/13 | Type 2 High | 300 mg sc alle 2 Wo (Loading dose 600 mg) |
| Tezepelumab (Tezspire) | TSLP | Type 2 High und Type 2 low | 210 mg sc Alle 4 Wo |

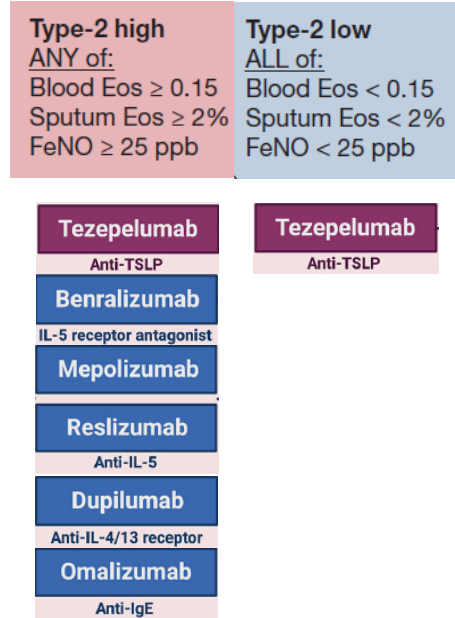
Biologika für schweres Asthma & Komorbiditäten

Interdisziplinäres Board für schweres Asthma

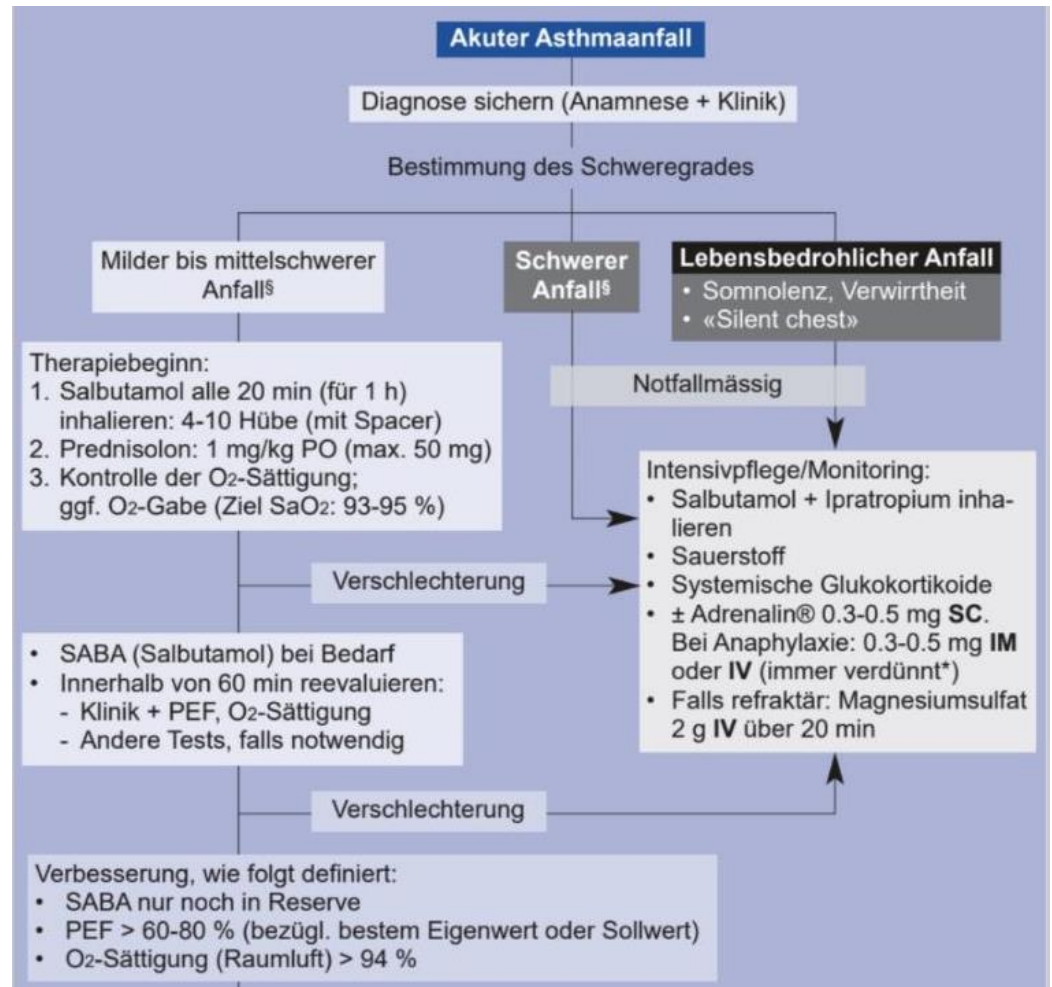


Biologika – was muss ich wissen?

- Keine Interaktionen bekannt
- Keine immunsuppressive Wirkung
- Bei Eosinophilie Empfehlung zum Ausschluss einer asymptomatischen *Strongyloides stercoralis* Infektion vor Beginn einer Biologikatherapie
- Häufigste Nebenwirkungen: lokale Reaktionen an der Injektionsstelle, Kopfschmerzen, Pharyngitis
- Sehr geringes Risiko einer anaphylaktischen Reaktion
- Konjunktivitis/Blepharitis unter Dupilumab (nur bei AD)
- CAVE: Eosinophilie unter Dupilumab

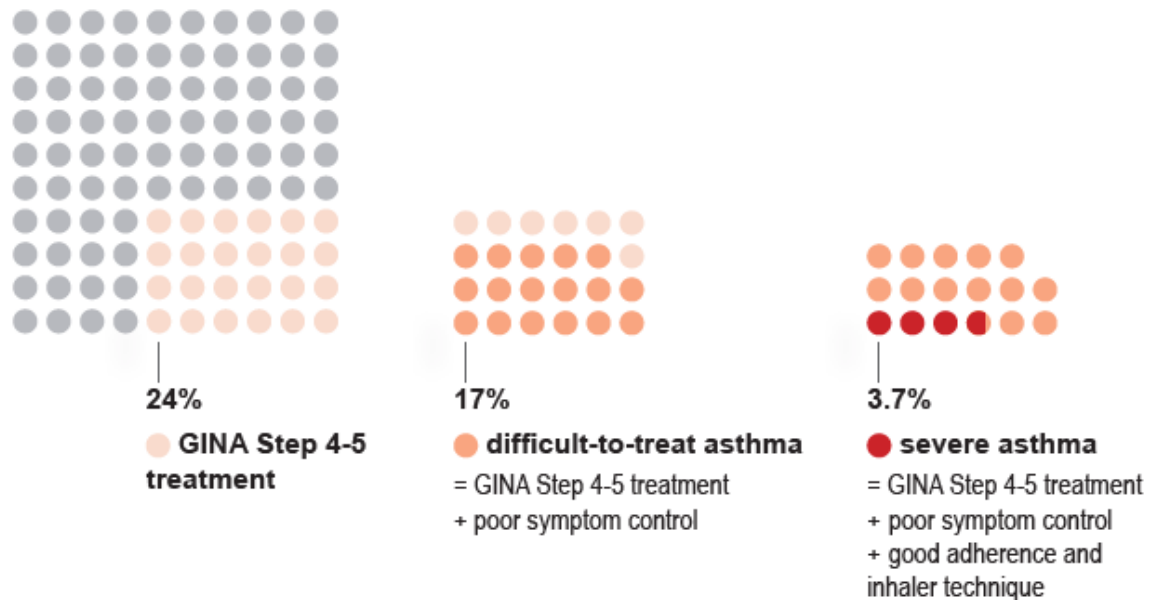


- Biologica haben in der Notfallsituation (akute Exazerbationen, Status asthmaticus) keinen Stellenwert



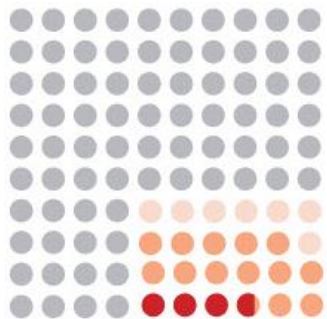
Wie häufig ist schweres Asthma ?

Box 1. What proportion of adults have difficult-to-treat or severe asthma?



These data are from a Dutch population survey of people ≥ 18 years with asthma²

Difficult-to-treat vs. schweres Asthma



24%
 ● GINA Step 4-5 treatment

17%
 ● difficult-to-treat asthma

3.7%
 ● severe asthma

Medium oder high-dose ICS/LABA

- 'Difficult Asthma'**
 GINA Step 4-5 treatment + Uncontrolled asthma
- Inhalation technique
 - Adherence
 - Tobacco exposure
 - Comorbidity
 - Allergen and other environmental exposures
 - Psycho-social triggers

- Severe Asthma**
 Asthma diagnosis confirmed + Contributory factors optimized:
- GINA Step 4-5 treatment
 - Good inhaler technique
 - Good adherence
- + Uncontrolled Asthma
- Frequent (≥ 2) severe asthma attacks in the previous year
 - ACQ score ≥ 1.5

Biologika?



Asthma – wann Biologika?



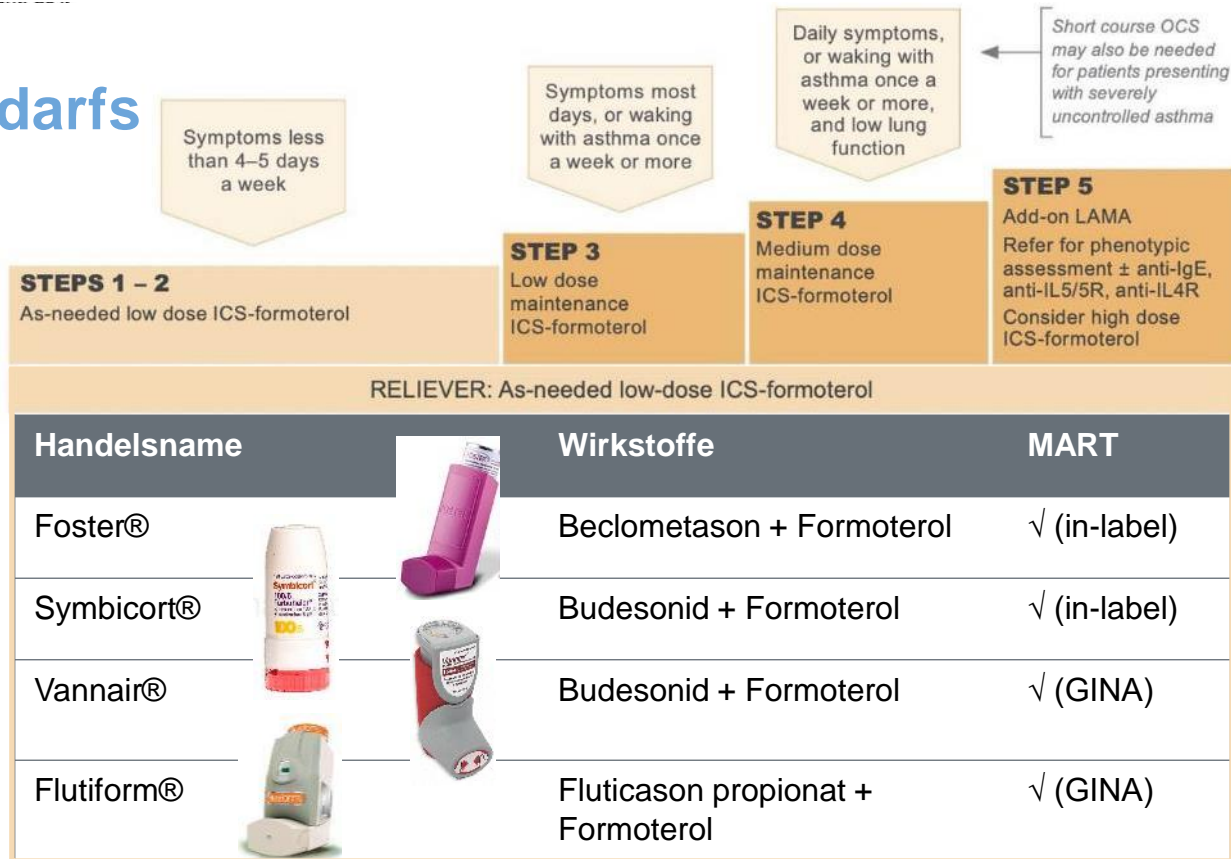
Therapieziele



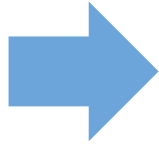
- Gute Symptomkontrolle
- Keine Limitation in den Alltagsaktivitäten
- Weniger/keine Exazerbationen
- Minimiertes Risiko einer persistierenden Obstruktion
- Minimiertes Risiko von Nebenwirkungen der Therapie

Optimale Bedarfs therapie

CONTROLLER and
PREFERRED RELIEVER

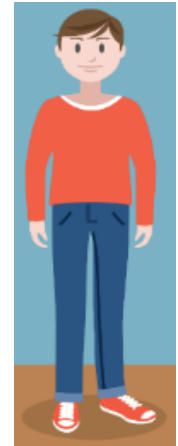
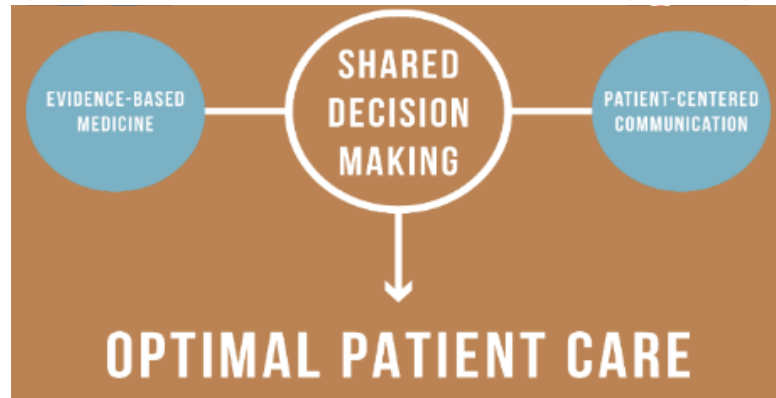


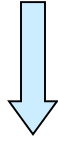
«Difficult-to-treat Asthma» – korrekt inhaliert ?



Patientenschulung in der korrekten
Inhalationstechnik und Inhaler überprüfen

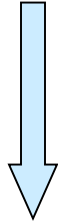
Asthma – was inhalieren?





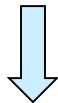
(2) Differentialdiagnosen erwägen

- COPD / Emphysem
- Stimmbanddysfunktion
- Fremdkörper / Tumor
- Obstruktives Schlafapnoesyndrom
- Kardiopathie
- Interstitielle Pneumopathie
- Allerg. bronchopulm. Aspergillose
- EGPA
- Cystische Fibrose



(3) Asthmaunterhalt. Faktoren suchen und behandeln

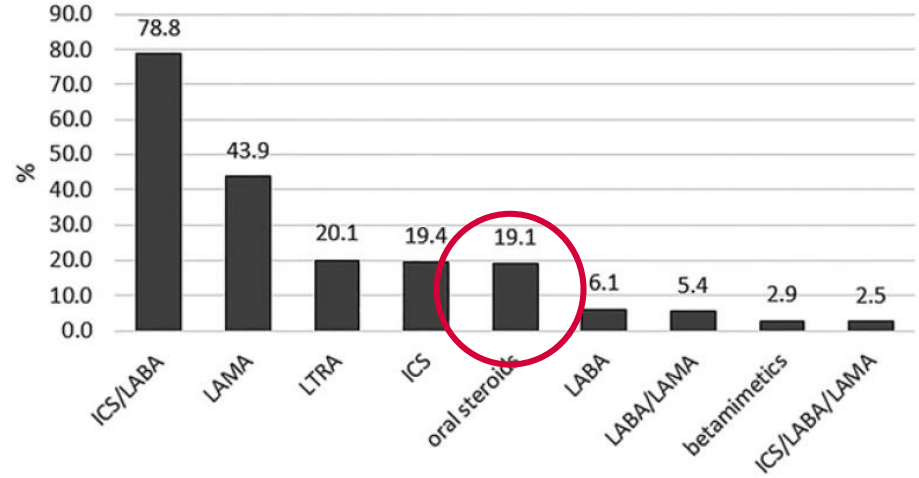
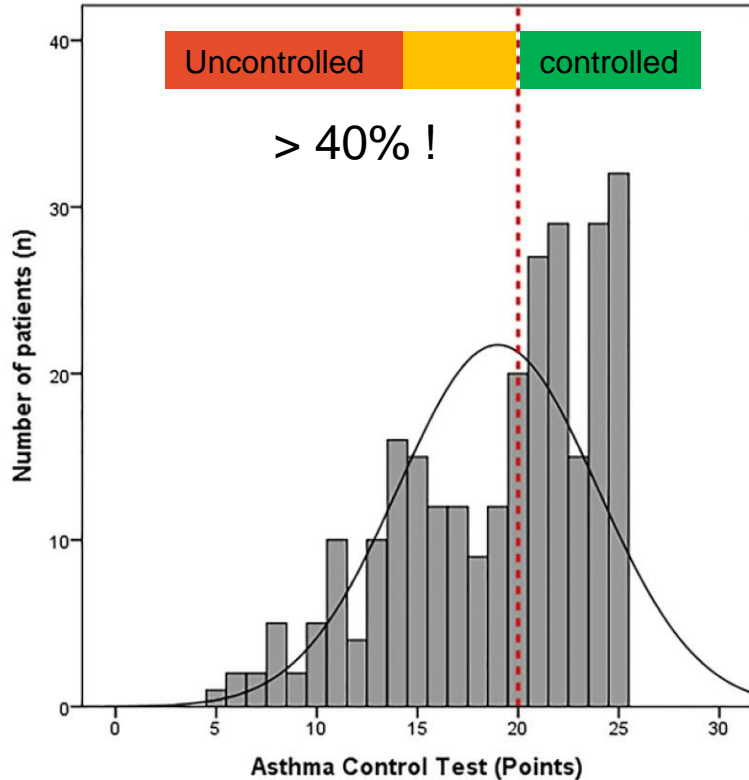
- Allergie
- HNO (Sinusitis/Polypen)
- Reflux



(4) Umgebungsfaktoren vermeiden

- Rauchen
- Allergene
- Virale Infekte
- berufl. Exposition
- Luftverschmutzung
- Stress

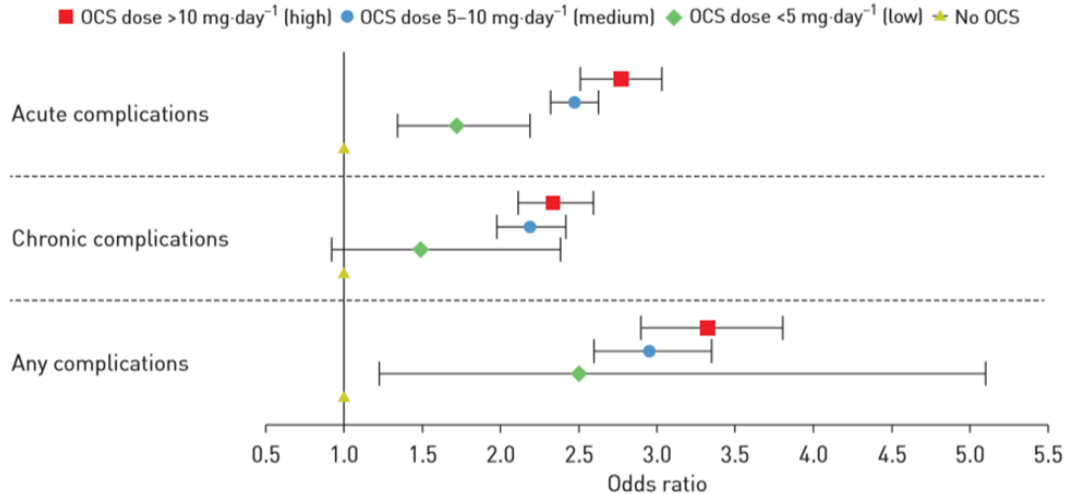
Patienten mit schwerem Asthma in der Schweiz



- 82% unter Biologica

Data from the **Swiss Severe Asthma Registry**
Jaun et al, Respiration 2023

Orale Kortikosteroide bei Asthma

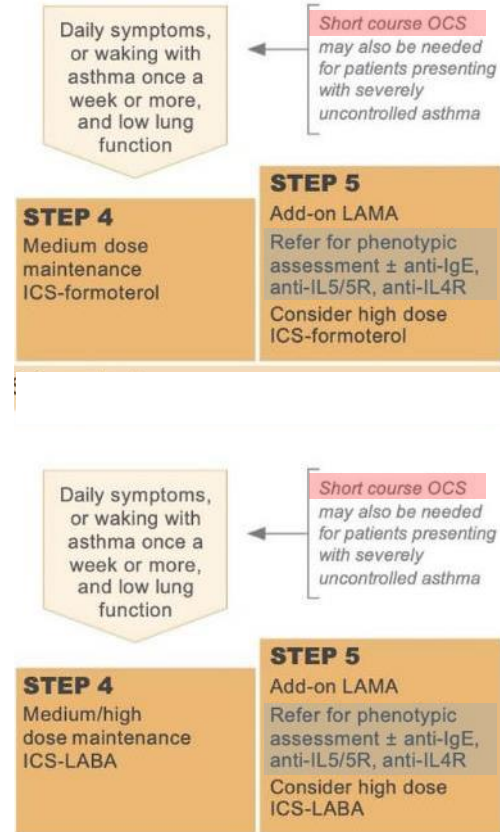


- Osteoporose → Frakturen
- Diabetes
- Adipositas
- Immunsuppression → Infektionen
- Osteonekrose
- Muskelschwäche
- NNR-Insuffizienz, Cushing-Syndrom
- Cardiovasculäre Erkrankungen
- Dyslipidämie
- Magenulkus
- Pergamenthaut → Hautwunden
- Gestörte Wundheilung
- Katarakt
- Glaukom
- Psychiatrische Störungen

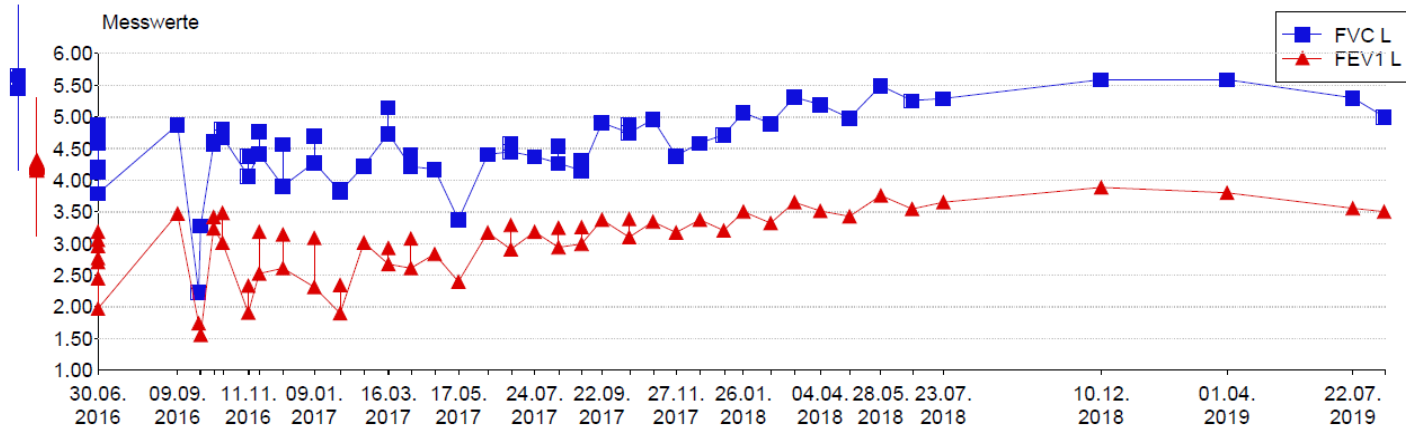
Schweres Asthma: Therapie

Keine dauerhafte systemische Steroidtherapie!

→ Evaluation einer Biologikatherapie



Therapieverlauf eines schweren Asthmas (Type 2 High) unter Biologika

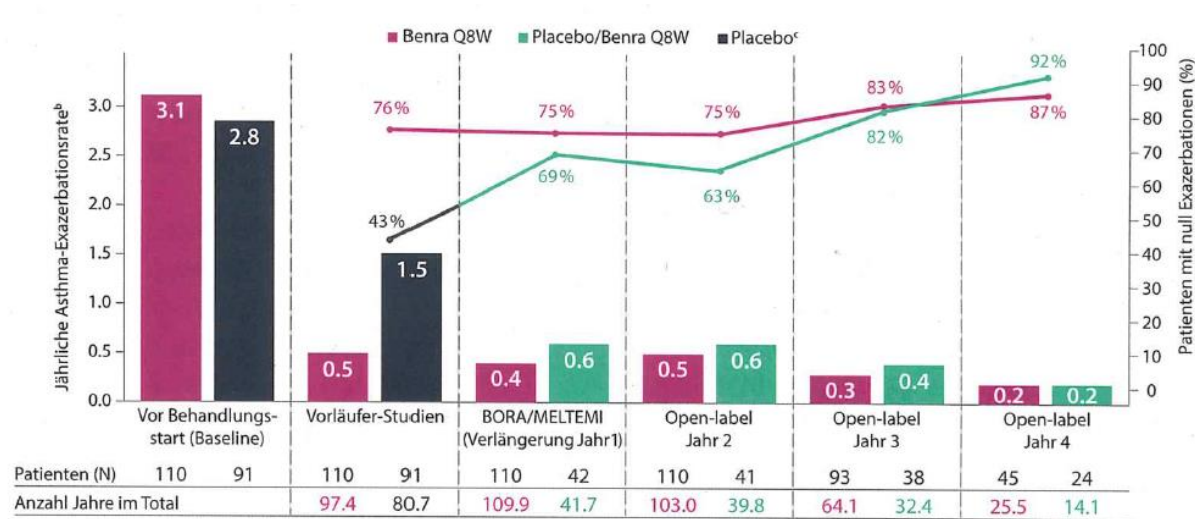


Mepolizumab 100 mg sc →

Eos 2.35G/l 0.01 0.05 0.02 0.01 0.00 0.01 0.01 0.00

Prednison 60 40 30 20 15 10 5 0

Wie lange hält der Therapieeffekt von Biologika an ?



- Erhaltene Therapieeffekte über (2-) 5 Jahre
- Medikamentensicherheit gegeben, minimale Nebenwirkungen
- Symptomfreiheit langfristig möglich

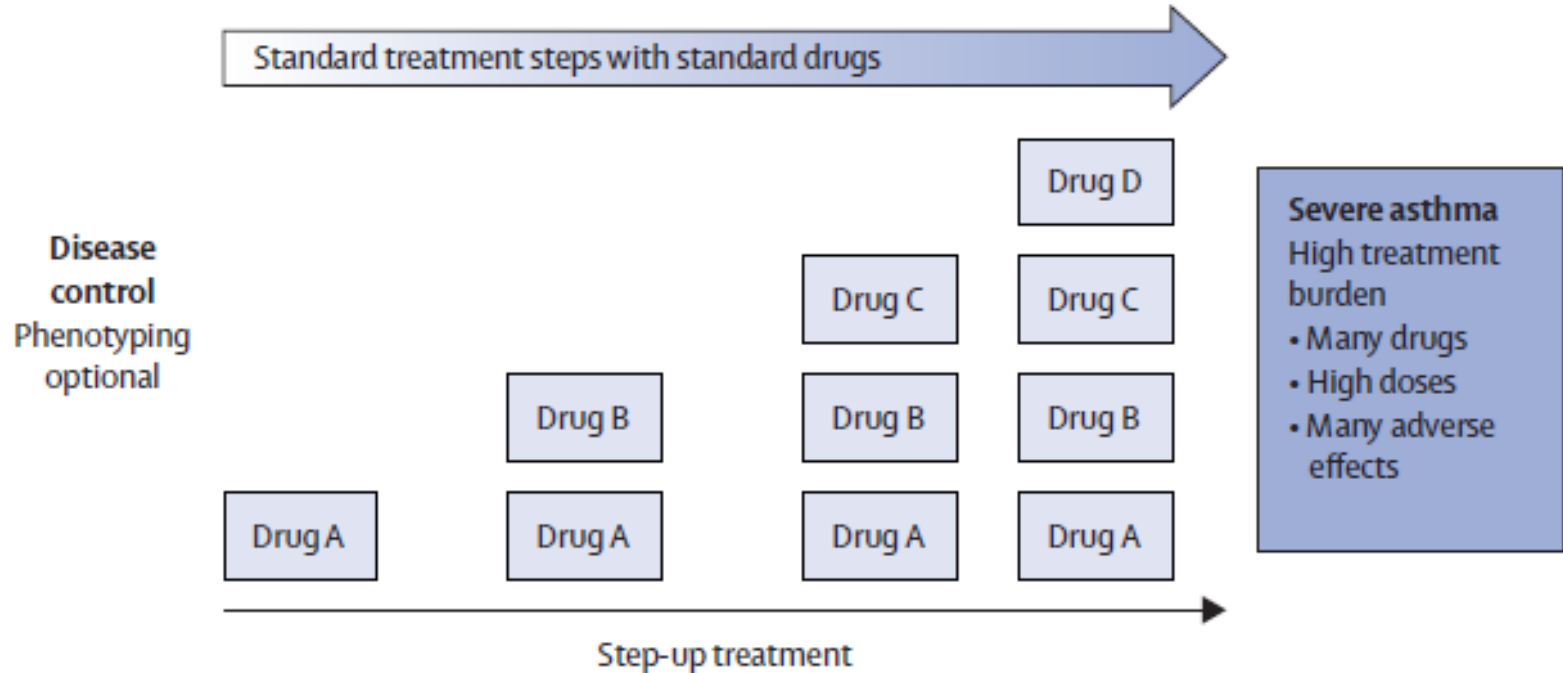
mod. nach Korn et al, J Allergy Clin Immunol 2021

Therapieziele

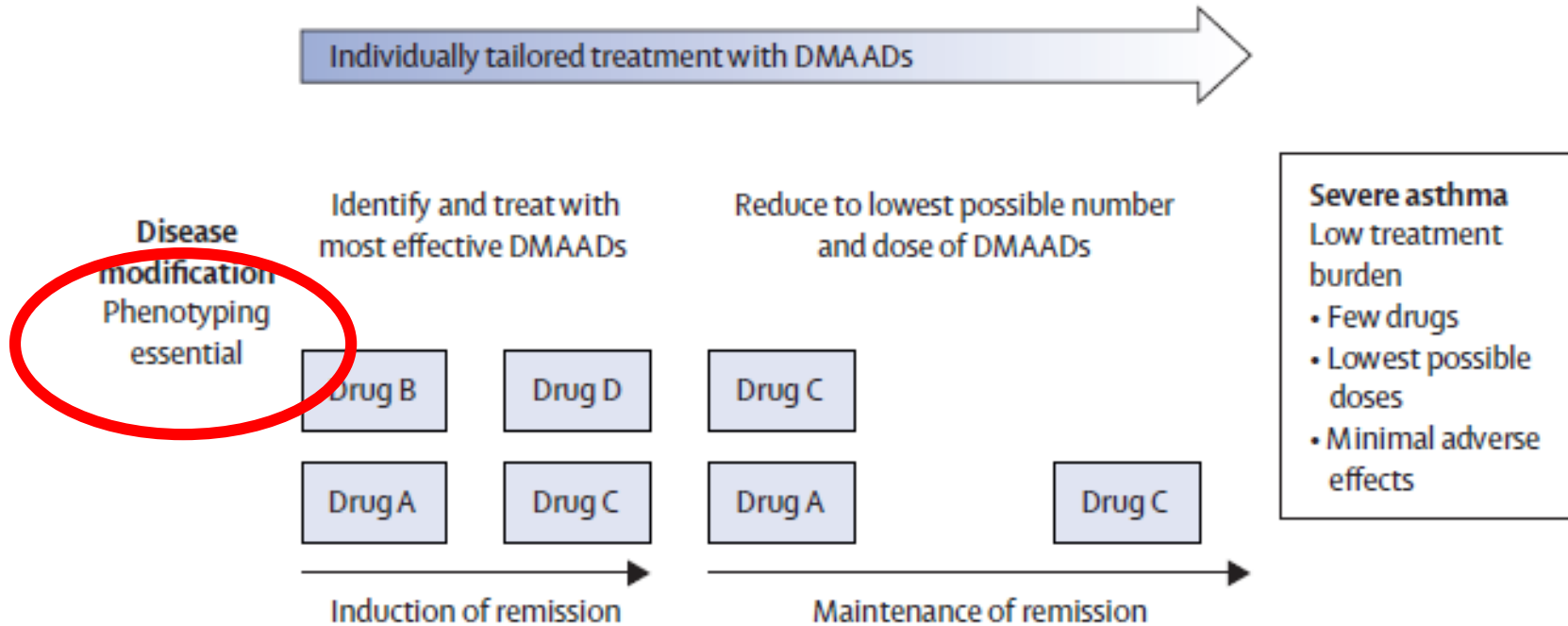


- Gute Symptomkontrolle
- Keine Limitation in den Alltagsaktivitäten
- Weniger/keine Exazerbationen
- Minimiertes Risiko einer persistierenden Obstruktion
- Minimiertes Risiko von Nebenwirkungen der Therapie
- **Vollständige Remission des Asthmas ?**

Remission als neues Therapieziel



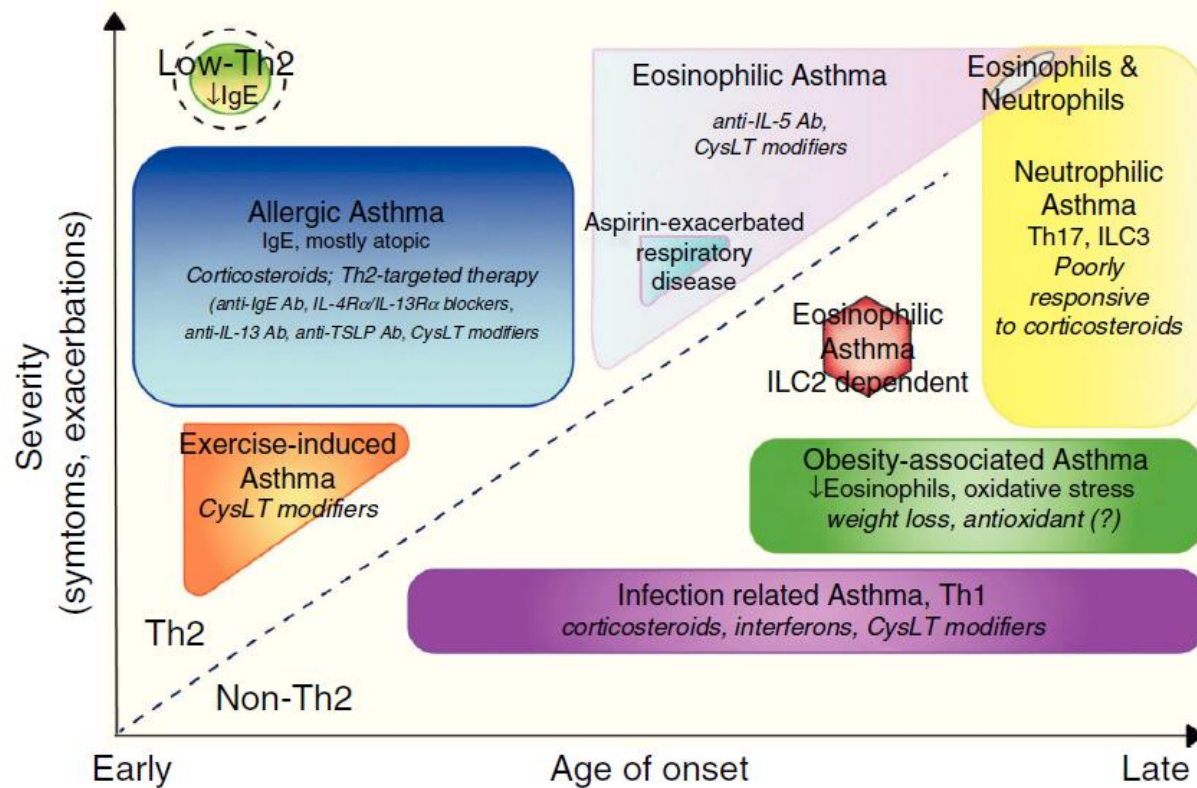
Remission des Asthmas als neues Therapieziel

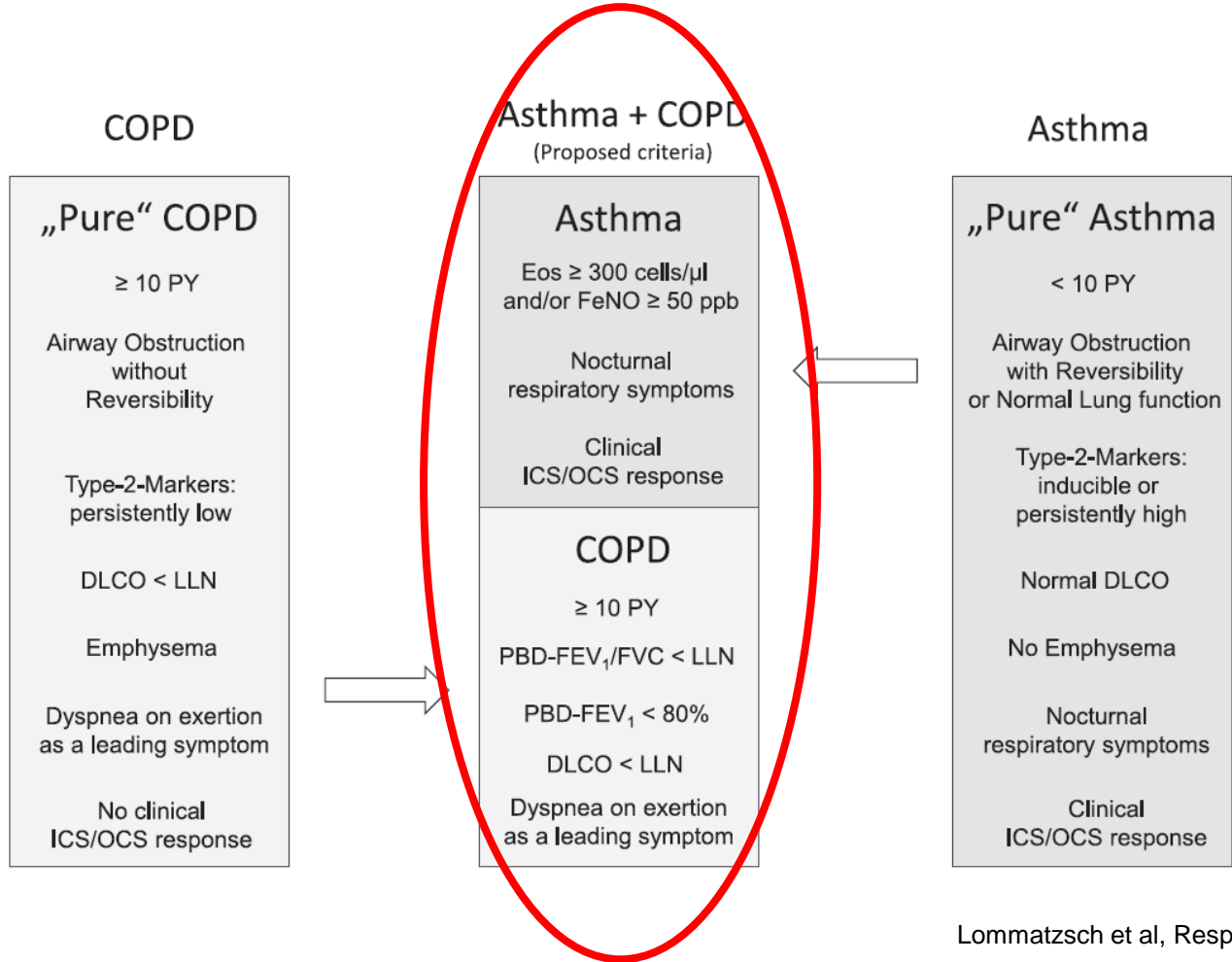


DMAAD : Disease modifying anti-asthmatic drugs

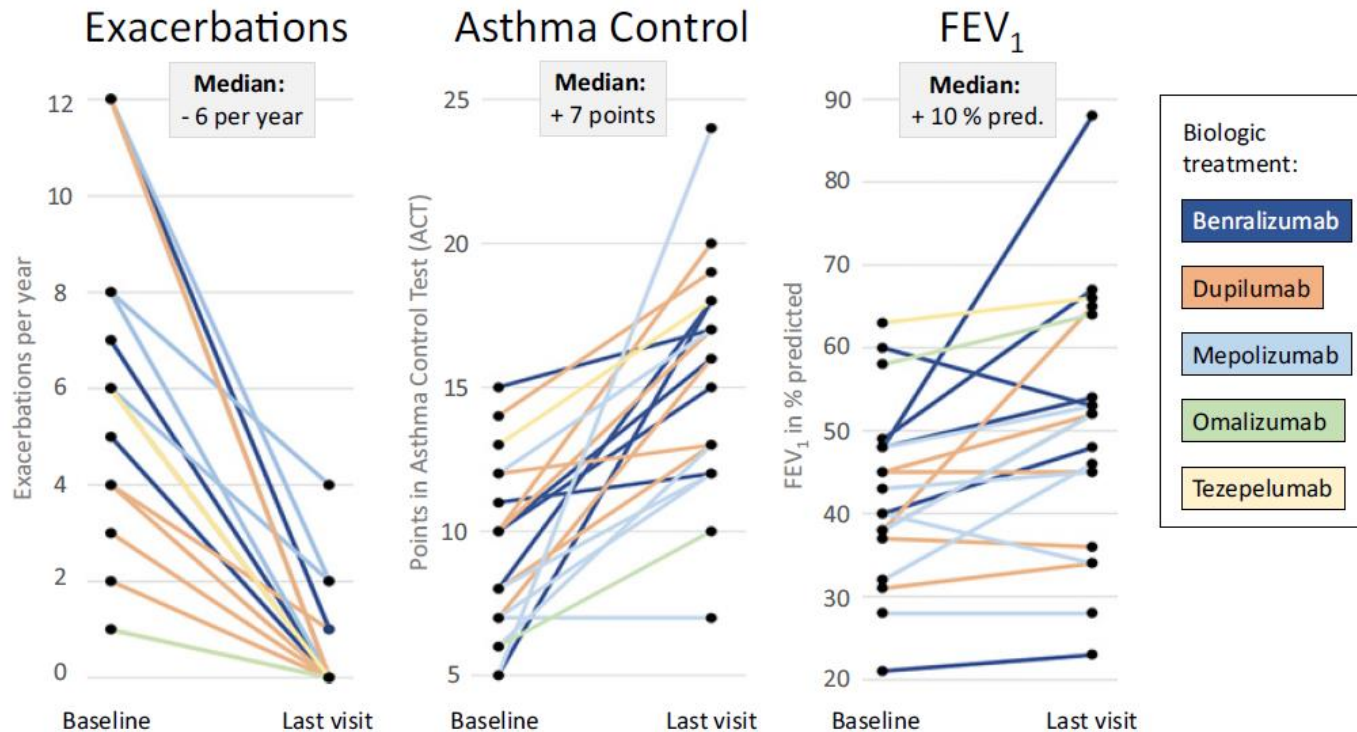
Lommatzsch et al, Lancet Resp Med 2023

Diagnostik & Phänotypen

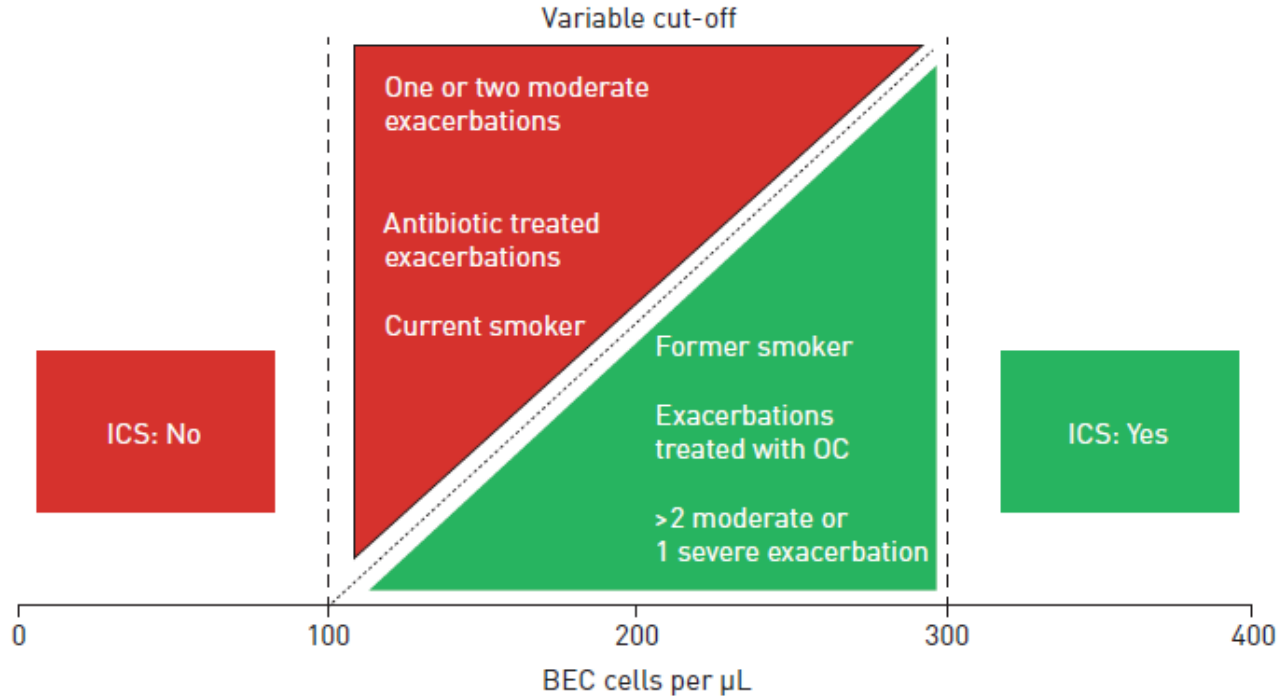




Lommatzsch et al, Respiration 2023



Bluteosinophilie als Biomarker bei COPD



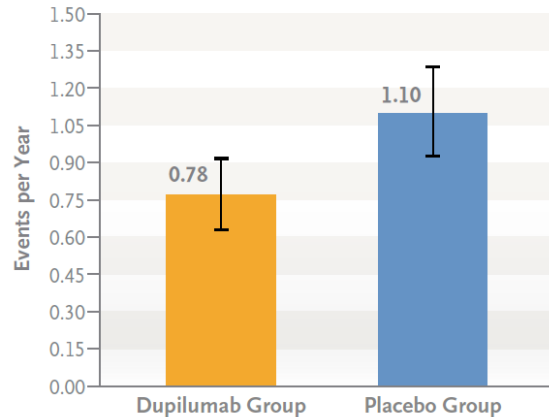
Biologicals bei COPD ?

Einschlusskriterien:

- Rez. Exazerbationen trotz Tripeltherapie
- Eos > 300 Zellen/ul

Adjusted Annualized Rate of Moderate or Severe Exacerbations of COPD

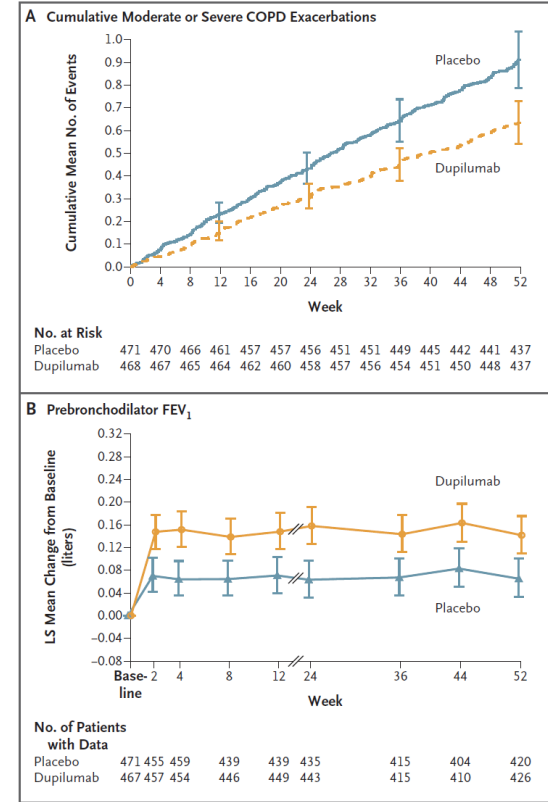
Rate ratio, 0.70; 95% CI, 0.58–0.86; P<0.001



Definitions

Moderate exacerbations:
Requiring treatment with systemic glucocorticoids, systemic antibiotics, or both.

Severe exacerbations:
Leading to hospitalization, an emergency medical visit, or death.



Biologika in der Pneumologie

- Neue Therapieoption bei **schwerem unkontrolliertes Asthma** mit rezidivierenden Exazerbationen (oder oralen Kortikosteroiden)
- **Patientenselektion** entscheidend !
- Sehr **günstiges** Wirkungs-/Nebenwirkungsprofil
- Bei gutem Ansprechen hält die Wirkung in der Regel über Jahre an (**Remission ?**)
- Erweiterung der Indikationsstellung der zugelassenen Biologicals für Asthma für andere Lungenerkrankungen mit vergleichbaren Pathomechanismen (Eos !)
- Weitere Biologicals in der Pipeline (Phase II Studien, zB interstitielle Lungenerkrankungen, pulmonale Hypertonie)



Vielen Dank für die Aufmerksamkeit !

