Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

13.– 16. Juni 2019

KML-Experten berichten vom EHA 2019 in Amsterdam

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT EHA Amsterdam 13.– 16. Juni 2019

Prof. Dr. med. Björn Chapuy

Aggressive B-Zell-Lymphome

Klinik für Hämatologie und Onkologie
der Universitätsmedizin Göttingen

Kapitel 1

Diffus großzelliges Lymphom (DLBCL)

Neue Therapien bei rezidivierten und/oder refraktären Erkrankungen

Diffus großzelliges Lymphom (DLBCL)

➔ Interim Analyse der Anti-CD47 plus Rituximab Therapie

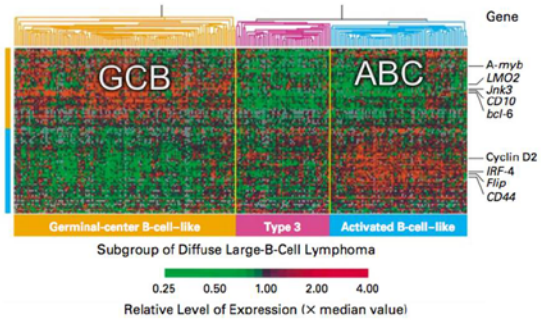
THE FIRST-IN-CLASS ANTI-CD47 ANTIBODY HU5F9-G4 WITH RITUXIMAB INDUCES DURABLE RESPONSES IN RELAPSED/REFRACTORY DLBCL AND INDOLENT LYMPHOMA: INTERIM PHASE 1B/2 RESULTS

Author(s): Ranjana Advani, Nancy Bartlett, Sonali Smith, Mark Roschewski, Leslie Popplewell, Ian Flinn, Graham Collins, Nilanjan Ghosh, Ann LaCasce, Adam Asch, Justin Kline, Murali Kesavan, Thu Tran, Judith Lynn, Jenny Huang ,Balaji Agoram, Jens-Peter Volkmer, Chris Takimoto, Mark Chao, Amitkumar Mehta

Diffuse Large B-cell Lymphoma (DLBCL)

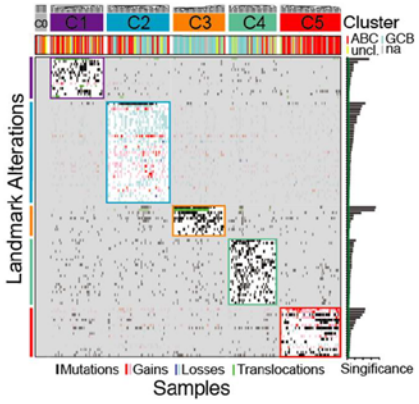
- Most common non-Hodgkin lymphoma in adults (7-8 new cases per 100k people per year).
- Treated with a combination of anti-CD20 antibody (rituximab) and chemotherapy (CHOP)
  ➔ Curable in over 60% of patients

Transcriptional Heterogeneity



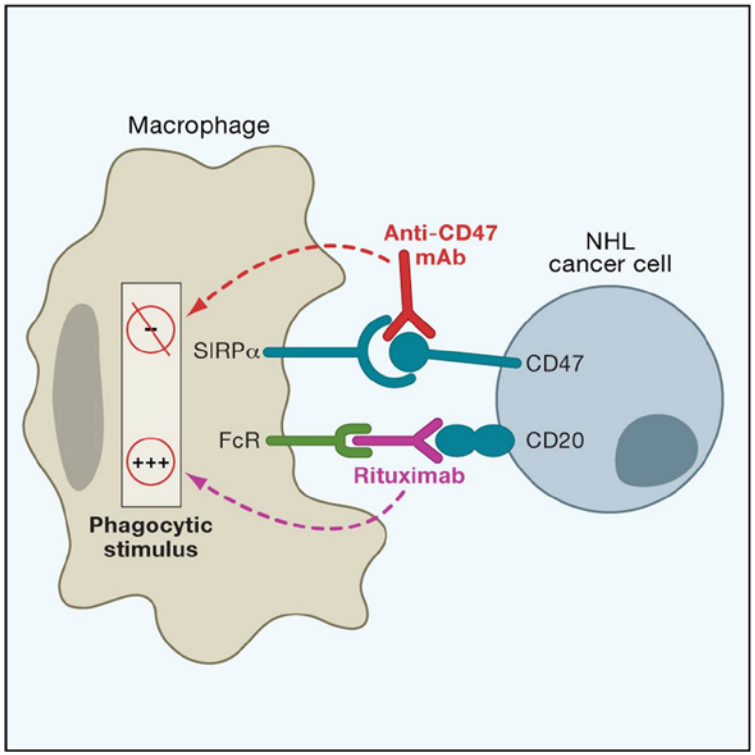
Alizadeh et al., Nature 2000
Rosenwald et al., NEJM 2002

Genetic Heterogeneity



Chapuy et al., Nature Medicine 2018

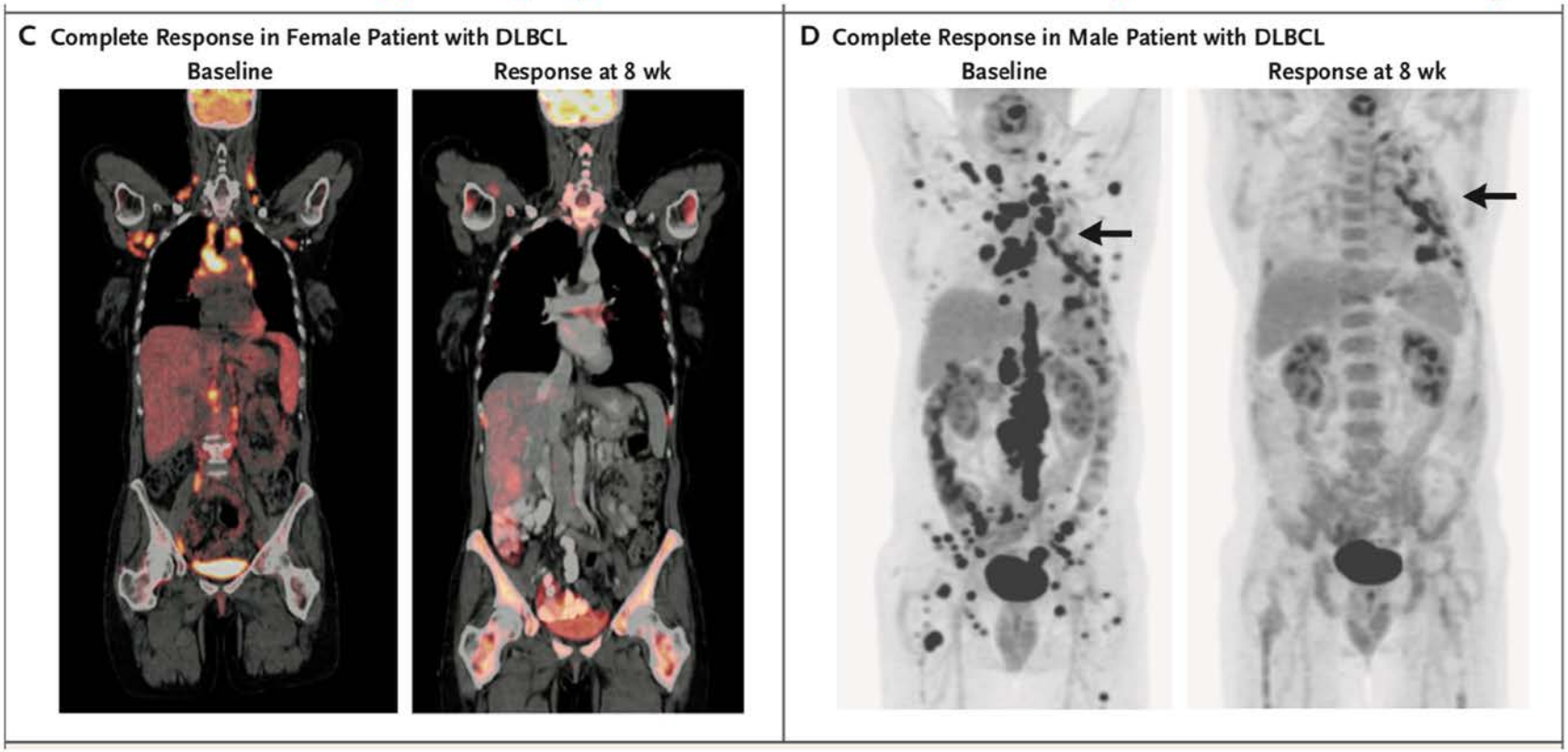
Myeloid Immune-checkpoint Inhibition – Overcoming an Innate Immune Checkpoint



- **Rituximab** acts at least in part by engaging Fc receptors on immune effector cells stimulating effector functions such as **ADCC**
- **Phagocytic** cells **express** signal regulatory protein alpha (**SIRPa**), which **inhibits** phagocytosis **when bound to CD47**
- **Hypothesis:**
  Combination of a blocking **anti-CD47 antibody with a second FcR-activating antibody would both prevent an inhibitory signal.**

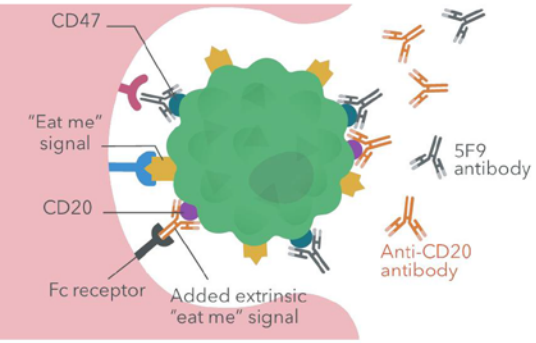
Chao and Alizadeh et al. *Cell* 2010; 142, 699-713 Mantovani and Longo, *NEJM* 2018 Van den Berg and Valerius, *Nat Rev Clin Oncol* 2018

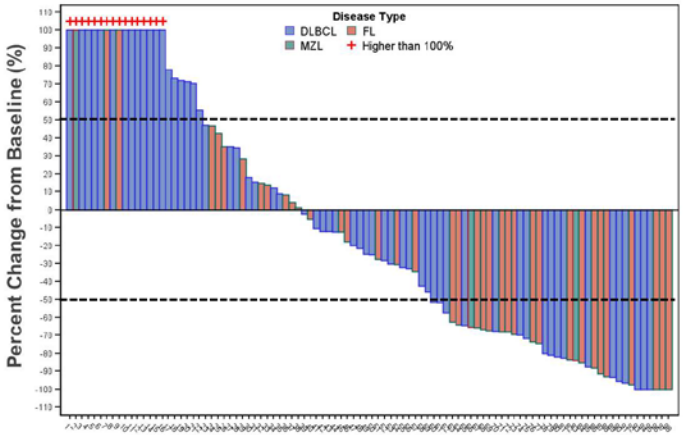
Anti-CD47 Antibody Synergizes with Rituximab to Promote Phagocytosis and Eradicate Non-Hodgkin Lymphoma – Clinical Studies (here two Patients)



Advani, et al *N Engl J Med.* 2018 Nov 1;379(18):1711-1721.

Interim Phase 1b/2: Anti-CD47 Ab Hu5F9-G4 + rituximab in rel/ref NHL



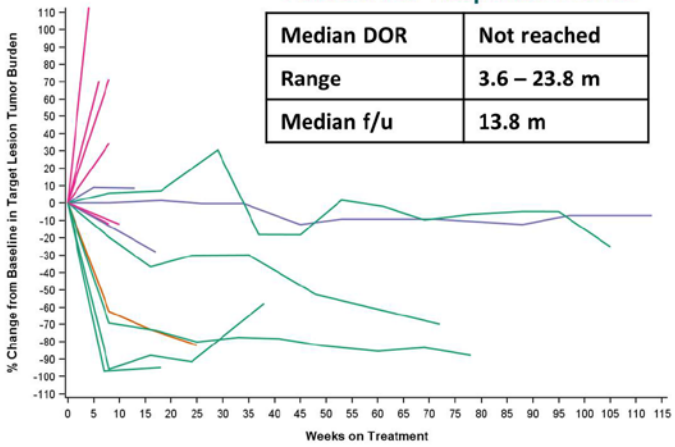


Best response	DLBCL N=59	Indolent (FL N=35, MZL N=3)
ORR	21 (36%)	23 (61%)
CR	9 (15%)	9 (24%)
PR	12 (20%)	14 (37%)
SD	7 (12%)	9 (24%)
PD	31 (53%)	6 (16%)

Median time to response =1.8 m

Duration of Response DLBCL

Median DOR	Not reached
Range	3.6 – 23.8 m
Median f/u	13.8 m

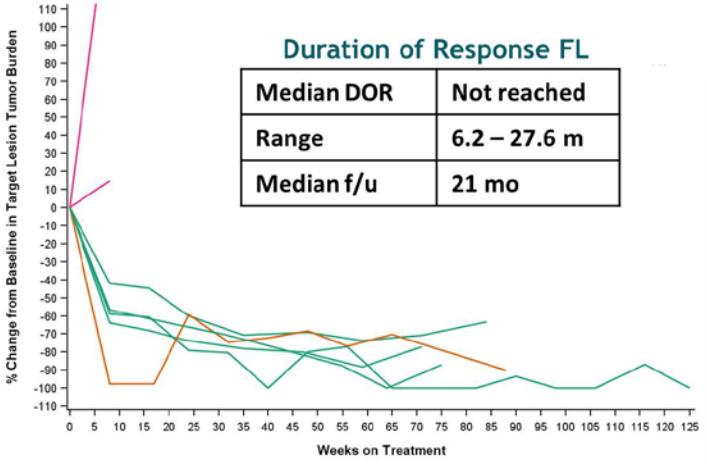


Progressive disease
Partial response
Stable disease
Complete response

No emergence of late toxicities

Duration of Response FL

Median DOR	Not reached
Range	6.2 – 27.6 m
Median f/u	21 mo



DLBCL Efficacy According to Subtype and Prior Lines of Therapy

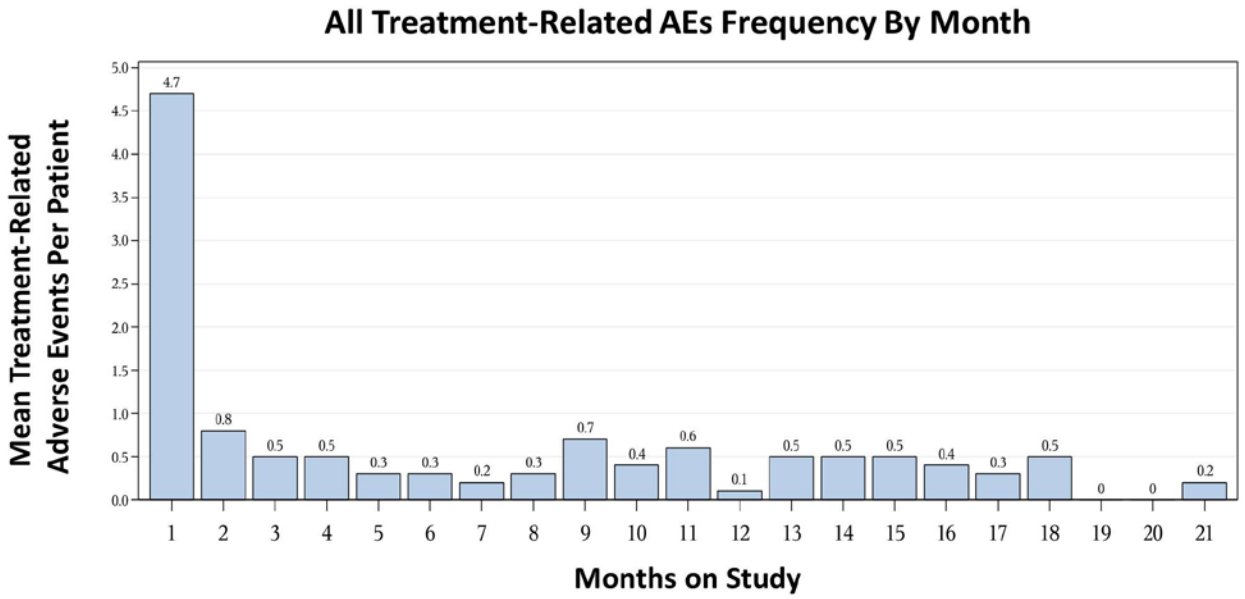
	DLBCL (N=59)					
Population	All DLBCL N=59 (%)	ABC N=14 (%)	GCB N=30 (%)	Cell of origin unknown N=15 (%)	De novo N=38 (%)	Transformed DLBCL N=21 (%)
Objective Response Rate (ORR)	21 (36%)	5 (36%)	9 (30%)	6 (46%)	13 (34%)	8 (38%)

	DLBCL (N=59)			
Population	All DLBCL N=59 (%)	Primary refractory N=35 (%)	≥ 2 prior lines of therapy N=57 (%)	≥ 3 prior lines of therapy N=39 (%)
Objective Response Rate (ORR)	21 (36%)	12 (34%)	20 (35%)	15 (38%)

Patient evaluable for efficacy are shown ABC: activated B cell-like COO: cell of origin GCB: germinal center B cell-like

- Similar responses observed across multiple DLBCL subtypes and primary refractory patients
- Similar responses observed irrespective of prior lines of therapy

Long-term safety for 5F9+rituximab



- Most AEs occurred with the priming dose, with minimal AEs thereafter
- Patients treated long term (up to 24+ months) without any significant late safety signals

Kapitel 2

Primär Mediastinales großzelliges Lymphom (PMBL)

Neue Therapien bei rezidivierten und/oder refraktären Erkrankungen

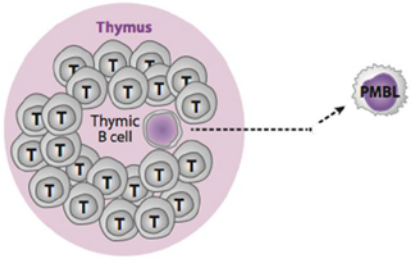
Primär Mediastinales großzelliges Lymphom (PMBL)

➔ Zielgerichtete Kombinationstherpie mit anti-PD-1/anti-CD30 (BV)

NIVOLUMAB COMBINED WITH BRENTUXIMAB VEDOTIN FOR RELAPSED/REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA: EFFICACY AND SAFETY RESULTS FROM THE PHASE 2 CHECKMATE 436 STUDY

Author(s): Pier Luigi Zinzani, Armando Santoro, Giuseppe Gritti, Pauline Brice ,Paul M. Barr, John Kuruvilla, David Cunningham, Justin Kline, Nathalie A. Johnson,Neha A. Mehta-Shah, Thomas Manley, Stephen Francis, Manish Sharma, Alison J. Moskowitz

Primary Mediastinal Large B-Cell Lymphoma (PMBL)



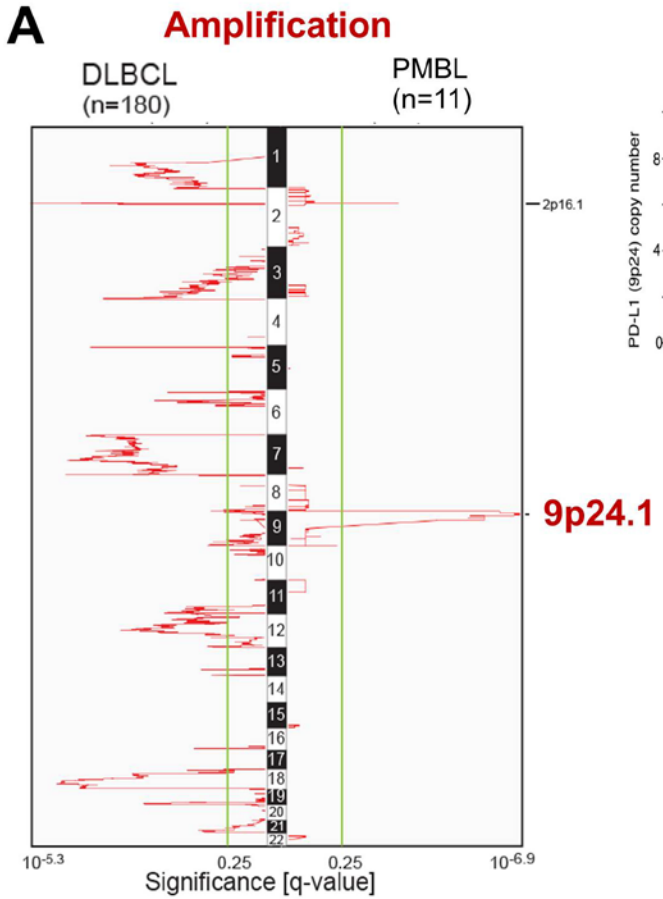
- Arise from thymic medullary, asteroid B-cells
- Shares clinical, pathomorphological, transcriptional and genetic features with classical Hodgkin lymphoma (cHL)
- Occurs in young adults and presents with large mediastinal masses at diagnosis
- More frequent in females
- Frequently CD30 positive and harbors frequently alterations of 9p24/*PD-L1/PD-L2*

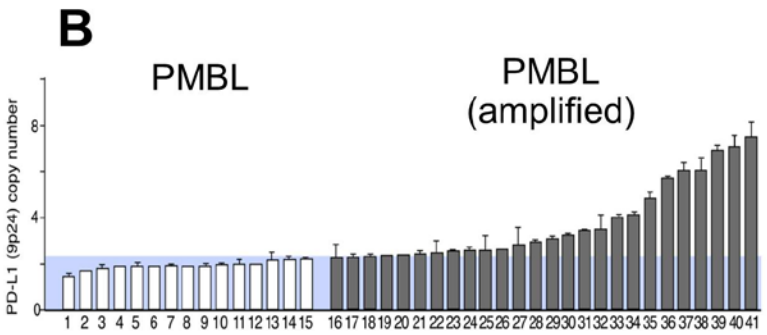
Hofmann et al., *Human Pathol* 1988
Isaacson et al., *Lancet* 1987
Leithauser et al., *Blood* 2001
Shaffer et al., *Ann Rev Immunol* 2012

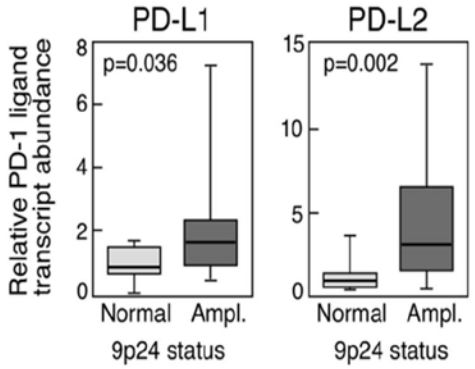
Popov et al., *Cell* 2007
Swerdlow et al., *WHO Classification* 2008
Steidl and Gascoyne., *Blood* 2011

Green et al., *Blood* 2010
Chapuy et al., *Blood* 2016
Moldenhauer et al., *Blood* 2006

9p24.1 Amplification and PD-1 Ligand Overexpression in PMBL



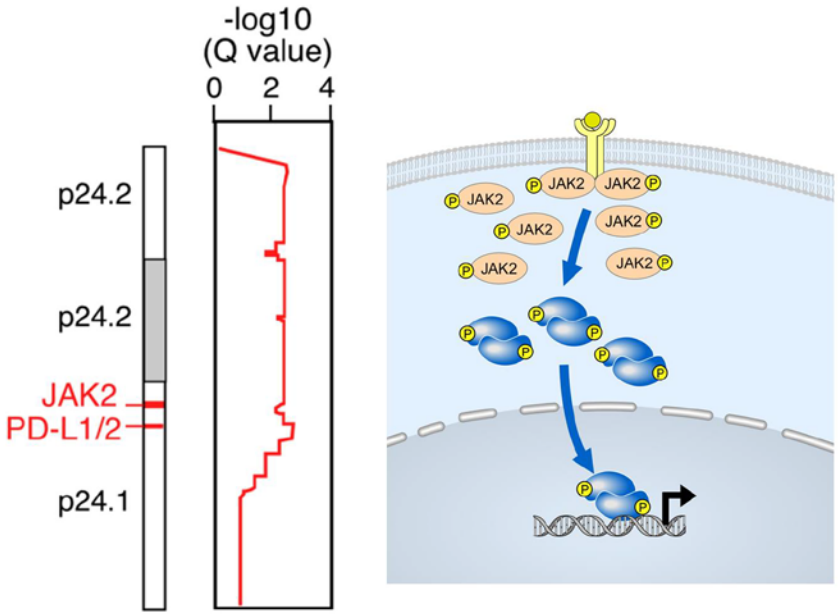




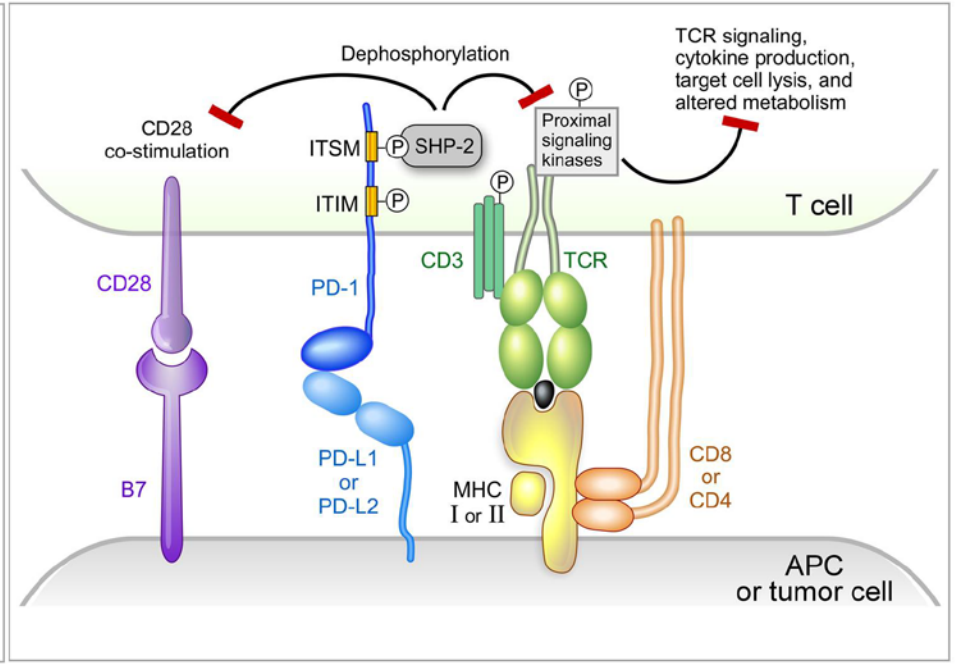
Green *et al.*, *Blood* 2010; 116:3268
Monti and Chapuy *et al.*, *Cancer Cell* 2012; 22:359-72
Chapuy and Roemer et al. *Blood 2016;* 127:869-881

9p24.1 Amplicon Block and PD-1-mediated T-cell Exhaustion

9p24.1 Amplicon Block



PD-1/PD-1 Ligand Interaction



➔ *PD–L1* and *PD-L2* copy gain and further induction via JAK2/STAT signaling

Green *et al., Blood* 2010; 116:3268
Green et al., *Clin. Cancer Res.* 2012; 18(7):2117
Hao *et al., Clin. Cancer Res.* 2014; 20:2674

➔ Increased PD-1 ligand expression on tumor cells results in a reversible T-cell exhaustion and ineffective immune surveillance.

Modified from Baumeister *et al.* 2016; *Annu. Rev. Immunol.* 34:539-73

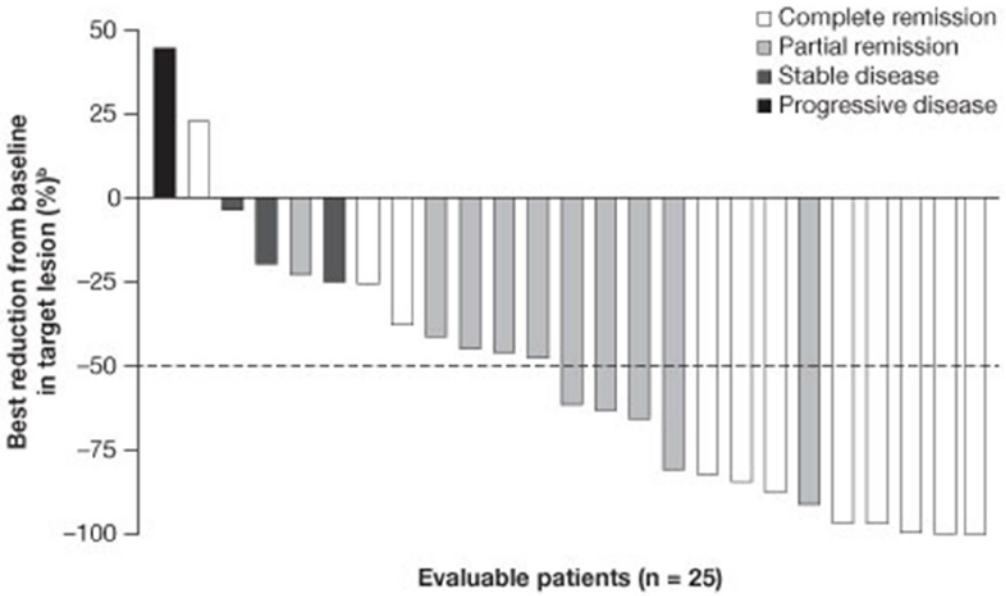
Nivolumab combined with Brentuximab – CheckMate 436

Aims: To investigate the efficacy and safety of nivolumab + BV in pts with R/R PMBL

Methods

- CheckMate 436 is an **international, open-label, phase 1/2 study of nivolumab + BV** to treat CD30+ NHLs
- R/R disease after auto-HCT or ≥ 2 prior multi-agent chemotherapy regimens if ineligible for auto-HCT.
- Pts received nivolumab (240 mg IV) and BV (1.8 mg/kg IV, pre-specified dose modifications allowed) every 3 weeks until disease progression or unacceptable toxicity.
- Primary endpoints were investigator-assessed ORR per the Lugano 2014 classification and safety.
- Tumor response was assessed by PET-CT at weeks 6 and 12, every 9 weeks for the following 4 assessments, and every 12 weeks after the first year until disease progression.

Nivolumab combined with Brentuximab - Best Overall Response



[a]Per Lugano 2014 criteria incorporating FDG-PET scan;
[b]Sum of the product of the diameters, based on CT scan.

Results

- 30 pts were treated with nivolumab + BV
- Age: 35.5 (19, 83) years
- Prior systemic therapies: 2 (2, 5) - 4 (13%) prior auto-HCT.
- Median follow-up: 11.1 months
- ORR (95% CI): 73% (54–88)
  - 11 pts (37%) CR
  - 13 (52%) of the 25 evaluable pts had a best reduction in target lesion of > 50%
- Median duration of response - not reached

Nivolumab combined with Brentuximab – CheckMate 436

Treatment-related AEs (TRAEs) reported in 25 (83%) pts. :

- Grade 3–4 TRAEs were reported in 16 (53%) pts, including 9 (30%) with neutropenia, 3 (10%) each with thrombocytopenia or peripheral neuropathy, 2 (7%) with decreased neutrophil count, and 1 (3%) each with hypersensitivity, colitis, rash, maculopapular rash, or immune-mediated hepatitis.
- Four pts (13%) had treatment-related serious AEs, including 2 pts with grade 3–4 colitis, maculopapular rash, or immune-mediated hepatitis.

Conclusion

- In pts with R/R PMBL, nivolumab + BV demonstrated a high investigator-assessed ORR of 73%, with 37% CR.
- TRAEs were consistent with the safety profiles of nivolumab and BV treatment alone.
- The combination of nivolumab + BV may be synergistic and is active in pts with R/R PMBL.

Kapitel 3

Extranodale NK-/T-Zell Lymphome (ENKTL)

Neue Therapien bei rezidivierten und/oder refraktären Erkrankungen

EXTRANODAL NK/T CELL LYMPHOMA (ENKTL)

➔ Anti-PD-1 Blockade

SINTILIMAB FOR RELAPSED/REFRACTORY (R/R) EXTRANODAL NK/T CELL LYMPHOMA (ENKTL): A MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL (ORIENT-4)

Author(s): Rong Tao, Lei Fan, Yongping Song, Yu Hu, Wei Zhang, Yafei Wang, Linxinyu Xu, Hui Zhou, Jianyong Li

SINTILIMAB FOR R/R ENKTL: A MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL (ORIENT-4)

Background

- ENKTL account for more than 20% of the peripheral T-cell lymphoma in Asia.
- Patients with r/r ENKTL have a poor prognosis after failing an L-asparaginase based regimen, and the median overall survival is less than 6 months.
- The overexpression of PD-L1 induced by EBV infection is a potential mechanism for ENKTL to avert immune surveillance,

Aims

This multicenter, single-arm, phase 2 study aims to validate the efficacy and safety of sintilimab monotherapy in patients with r/r ENKTL in China.

Methods

- Patients with pathologically confirmed r/r ENKTL were enrolled.
- Sintilimab was given 200 mg IV Q3W, until PD, death, unacceptable toxicity, or withdrawal from study.
- Tumor response evaluation was performed by both PET-CT and CT/MRI with contrast.
- The primary endpoint was objective response rate based on LUGANO 2014 criteria.

SINTILIMAB FOR R/R ENKTL: A MULTICENTER, SINGLE-ARM, PHASE 2 TRIAL (ORIENT-4)

Results

- 28 patients failed L-asparaginase based regimen were enrolled
- 68% of patients were stage IV and 89.3%
- Median lines of previous therapy were 3 (range: 1~13).
- Median duration of therapy was 14.04 (range: 1.4~17.3) months and 19 patients are still on sintilimab.

- 68% (19/28, 95%CI: 47.6%~84.1%) of patients achieved response (CR+PR)
- 14% (4 pats) progress
- 1-year OS rate was 82.1% and the median OS has not been reached.
- Most TRAEs were G1~2 (67.9%). No patients died from AEs.

Conclusion

Sintilimab is effective and well tolerated in r/r ENKTL might be a promissing treatment option for ENKTL patients.

Die Kurzpräsentationen sind online unter

www.lymphome.de/eha2019

Für den Inhalt verantwortlich:

Prof. Dr. med. Björn Chapuy

Klinik für Hämatologie und Onkologie • Universitätsmedizin Göttingen

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