Nowości w leczeniu zespołów mieloproliferacyjnych Ph(-) ASH 2018

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IFN r-alfa-2a vs HU, PV

3-year analysis of DALIAH trial, dr. Knudsen

Table 1

	HU age > 60 y (n=19)	r-IFNα age ≤ 60 y (n=33)	r-IFNα age > 60 y (n=33)
Type of r-IFNα (r-IFNα-2a/r-IFNa-2b)	N/A	15/18	16/17
Age, median years	67 (62-72)	47 (42-55)	68 (65-71)
Sex, men	14/19 (74)	15/33 (45)	19/33 (58)
History of major thrombotic event	1/19 (5)	7/33 (21)	12/33 (36)
Patients positive for JAK2 V617F	19/19 (100)	29/33 (88)	33/33 (100)
Median JAK2 V617F allele burden	44 (26-57)	41 (21-56)	44 (20-63)
Abnormal karyotype	0/12 (0)	0/22 (0)	3/22 (14)
Hemoglobin (g/dL)	17.7 (15.5-20.8)	17.2 (16.0-19.3)	18.4 (16.1-19.5)
EVF (vol %)	53 (47-63)	52 (46-57)	56 (50-59)
WBC ($\times 10^9$/L)	10.5 (8.4-12.8)	10.2 (8.1-13.1)	9.7 (7.4-12.8)
Platelets ($\times 10^9$/L)	573 (450-914)	604 (367-722)	420 (319-659)
LDH (U/L)	253 (221-356)	236 (190-303)	222 (184-287)
Splenomegaly by ultrasound (≥13mm)	7/11 (64)	13/25 (52)	10/18 (56)
Spleen size (mm)	122 (105-140)	130 (114-150)	115 (100-130)
Microcirculatory disturbances	5/19 (26)	12/33 (36)	10/33 (30)
Hypermetabolic symptoms	5/19(26)	12/33 (36)	7/33 (21)
Pruritus	7/19 (37)	10/33 (30)	10/33 (30)
Phlebotomy before inclusion	13/19 (68)	28/33 (85)	28/33 (85)
Low risk	0/19 (0)	29/33 (88)	0/33 (0)

Data are median (IQR) and n (%)

IFN r-alfa-2a vs HU PV n=85

3-year analysis of Daliah trial

	HU	IFNα >60y	IFNα <60y	
ORR	68%	42%	39%	ns
PHR	53%	33%	30%	ns
CHR	11%	21%	18%	ns
PMR	21%	18%	24%	ns

MPN-RC 112 Trial n=168

Pegylated IFN-α-2a versus HU with HR PV/ET

Arm A HU; 86 pts

	ET	PV	Total
CR	19 (45%)	13 (29%)	32 (37%)
PR	11 (26%)	17 (38%)	28 (32%)
NR	1	2	3
UE	11	12	23

Arm B Peg:82 pts

	ET	PV	Total
CR	17(43%)	12 (27%)	29 (35%)
PR	10 (25%)	25 (58%)	35 (42%)
NR	3	2	5
UE	9	4	13

Final analysis at 12 and 24 months CR rates in pts treated with HU and Peg were similar

PROUD/CONTI-PV trials n= 254
Ropeginterferon α-2b versus HU

	Ropeg N=83	HU N=70	p
CHR	70%	51%	p= 0.0122
CHR + symptom improvement and spleen size reduction	52%	37%	p=0.0437

PROUD/CONTI-PV trials n= 254
Ropeginterferon α-2b versus HU

Adverse events;

- Most common AE: anemia, thrombocytopenia, leukopenia occured in both arms, more frequently under HU

- Ropeg arm: GGT increase

PROUD/CONTI-PV trials n= 254
Ropeginterferon α-2b versus HU

Secondary malignancies

- HU cohort: 2 AML, 1 melanoma, 2 basalioma

- Ropeg: 1 glioblastoma, 1 seminoma, 1 adrenal neoplasm

PROUD/CONTI-PV trials n= 254 Ropeginterferon α-2b versus HU

- JAK2V617F after 36 months molecular responses ($p < 0.0001$)
- 66% in Ropeg
- 27% in HU

Non-JAK mutations involved TET2 (15% of pts), DNMT3A,ASXL1,CUX1,CEBPA and EZH2;

- Ropeg was able to reduce non-JAK allele burden including TET2
- HU lack that ability

PROUD/CONTI-PV trials n= 254
Ropeginterferon α-2b versus HU

Ropeginterferon- α -2b provide durable hematologic response and symptom control with good tolerability.

Safe , new long-term treatment option.

RUXOPEG Trial 1/ 2 phase MF
Pegylated IFNα-2a + Ruxolitinib

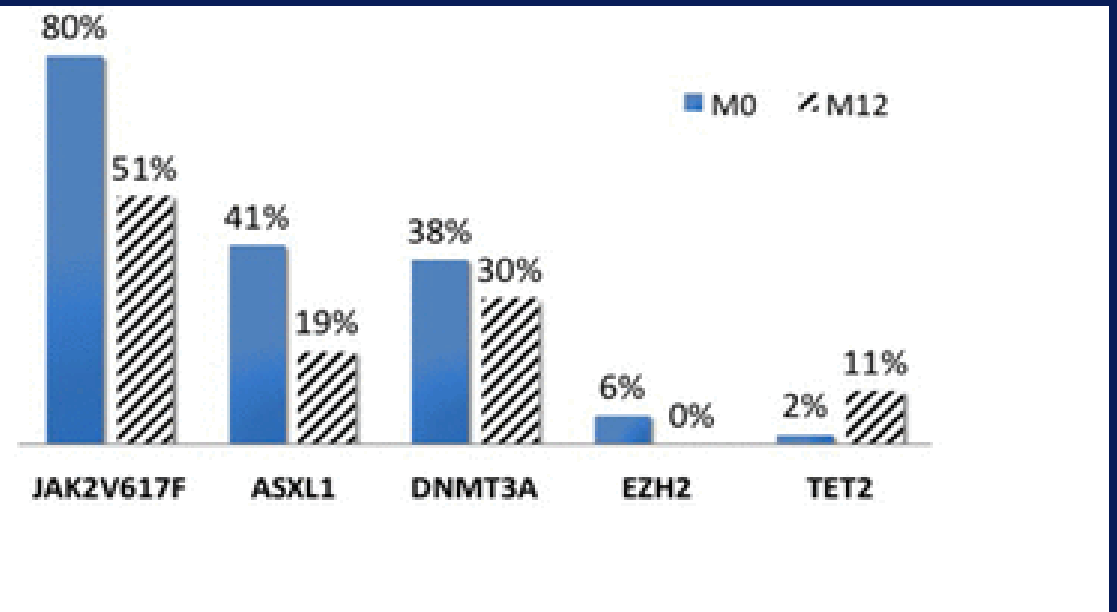

Figure 1: Evolution of 5 mutations found in one patient after 12 months of therapy

Enrolment: 42 pts.

Promising results: all pts responded (partial response and hematological improvement)

Clear decrease of 5 tested mutation

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Ruxolitinib+ Azacitidine
Phase 2, MF

Single institutional

Prospective

N=52, 2013-2017

IWG-MRT 2013	N (%)
Overall response	36 (73)
Partial remission (PR)	2 (4)
Clinical improvement (CI) spleen + total symptom score (TSS)	10 (19)
CI TSS + CI hemoglobin	2 (4)
CI TSS or CI spleen + complete cytogenetic response	3 (6)
CI TSS only	14 (27)
CI spleen only	7 (13)

Synergistic targeting of JAK-2 cells by IFN-α and Arsenic

In vivo tests on animals (mice with PV):

Addition of arsenic to IFN therapy

- improved reduction o blood cells
- Spleen size reduction
- Allelic burden

New treatmentment options
Phase 1/ 2 trials

- **Alisertib** selective inhibitor of Aurora Kinase
- **Pemigatinib** -inhibitor of FGFR1,2 i 3
- **LCL161**- Smac mimetic
- **Imetelstat**- telomerase inhibitor
- **PRM-151** recombinant human pentraxin that inhibits fibrosis