OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

REAL LIFE CON TAGRAXOFUSP NELLA TERAPIA DELLA BPDCN: L'ESPERIENZA DELL'EAP EUROPEO

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Preliminary Results from an Observational Multicenter Study of Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm Treated with Tagraxofusp in the European Expanded Access Program

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Modified from Deconinck et al., Preliminary Results from an Observational Multicenter Study of Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm Treated with Tagraxofusp in the European Expanded Access Program; Poster presentation #3623, ASH 2022

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INTRODUCTION (I)

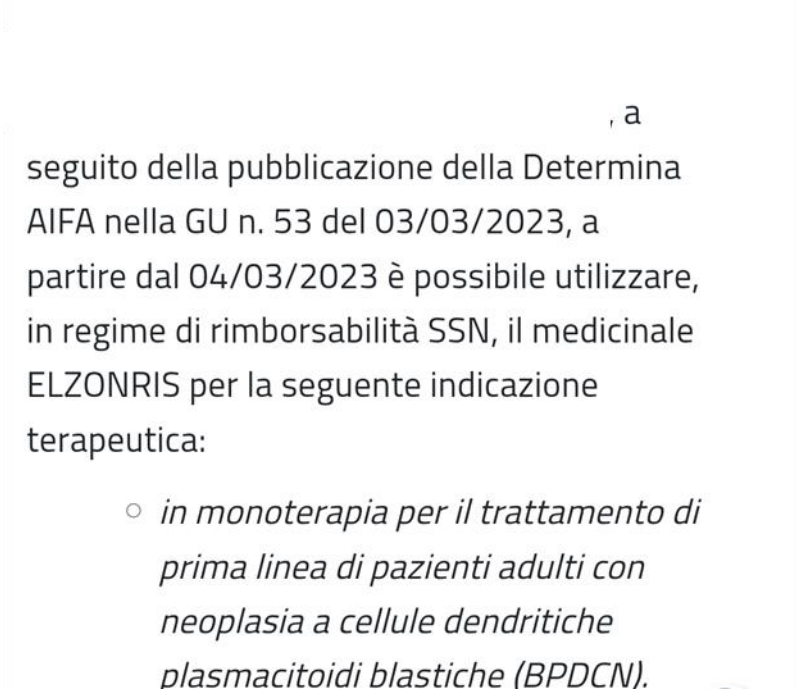
- Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive myeloid malignancy with poor prognosis and a median overall survival (OS) of ~1 year[1]
- It is derived from plasmacytoid dendritic cell precursors expressing CD123, the interleukin-3 receptor alpha (IL-3Rα), which is overexpressed in all cases of BPDCN[2,3]
- Tagraxofusp (TAG), a first-in-class CD123-directed therapy, is composed of a recombinant human IL-3 fused to a truncated diphtheria toxin payload[4]

- In the pivotal 0114 BPDCN study (NCT02113982), treatment with TAG 12 mcg/kg demonstrated a well-characterized and manageable safety profile, and resulted in an overall response rate (ORR) of 75% in first-line (1L) and 58% in relapsed/refractory (R/R) patients[5]
  - In 1L patients, complete response (CR) + clinical CR (CRc; CR with residual skin abnormality not indicative of active disease) rate was 57%, with 51% of these patients bridging to hematopoietic stem cell transplant (HSCT). Median duration of CR + CRc was 25 months after 3 years of follow-up
  - In R/R patients, CR + CRc rate was 16% and 5% of patients bridged to HSCT

1L, first line; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CR, complete response; CRc, clinical CR; EMA, European Medicines Agency; FDA, Food and Drug Administration; HSCT, hematopoietic stem cell transplant; IL-3Rα, interleukin-3 receptor alpha; ORR, overall response rate; R/R, relapsed/refractory; TAG, tagraxofusp.
Modified from Deconinck et al., Preliminary Results from an Observational Multicenter Study of Patients with Blastic Plasmacytoid Dendritic Cell Neoplasm Treated with Tagraxofusp in the European Expanded Access Program; Poster presentation #3623, ASH 2022

INTRODUCTION (I)

- TAG was approved by the EMA (01/2021) as monotherapy for the 1L treatment of adult patients with BPDCN and by the US FDA (12/2018) for treatment of BPDCN (1L and R/R) in adult and pediatric patients 2 years and older[6,7]



, a seguito della pubblicazione della Determina AIFA nella GU n. 53 del 03/03/2023, a partire dal 04/03/2023 è possibile utilizzare, in regime di rimborsabilità SSN, il medicinale ELZONRIS per la seguente indicazione terapeutica:

- *in monoterapia per il trattamento di prima linea di pazienti adulti con neoplasia a cellule dendritiche plasmacitoidi blastiche (BPDCN).*

INTRODUCTION (II)

Figure 1. Tagraxofusp – CD123-Directed Therapy

- In August 2019, an expanded access program (EAP) was established in Europe to
  - Provide adult patients with BPDCN access to TAG prior to its approval by the EMA
  - Gather experience on the safety and efficacy of TAG in real-world practice
- This is the preliminary analysis as of September 15, 2022, including 40 adult patients with BPDCN treated with TAG in the European EAP

BPDCN, blastic plasmacytoid dendritic cell neoplasm; EAP, expanded access program; EMA, European Medicines Agency; IL-3Rα, interleukin-3 receptor alpha; TAG, tagraxofusp.
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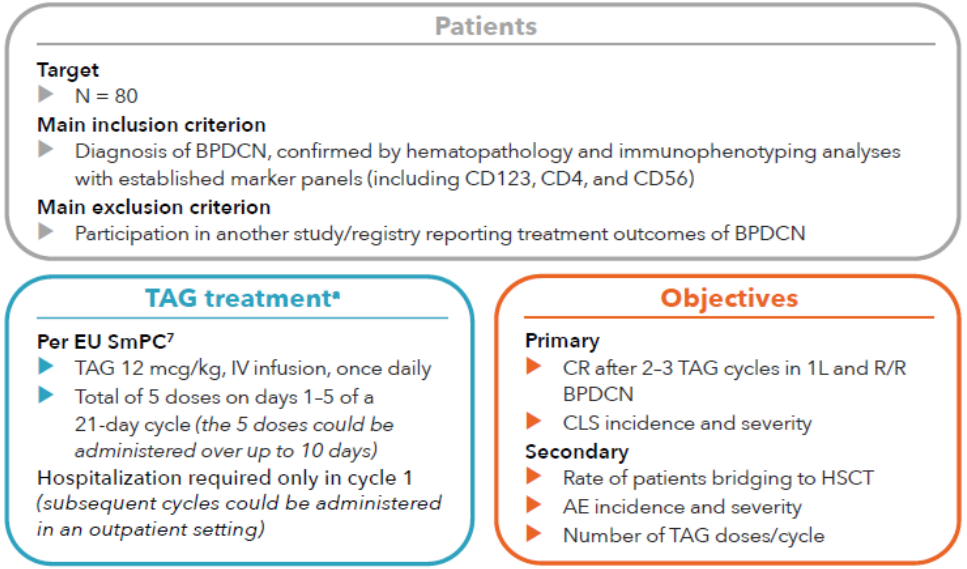
METHODS

- The EAP is a non-interventional, retrospective, observational, multicenter, single-arm study in patients with 1L and R/R BPDCN treated with TAG in a real-world setting (**Figure 2**)

Figure 2. EAP Study Design



[a]Patients were informed on TAG treatment by the physician who signed the supply form. Prior to TAG administration, physicians, nurses, and pharmacists were trained on dosing, administration, storing, and serious AE reporting.

- This is the preliminary analysis as of September 15, 2022, including 40 adult patients with BPDCN treated with TAG in the European EAP

1L, first-line; AE, adverse event; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CLS, capillary leak syndrome; CR, complete response; EAP, expanded access program; HSCT, hematopoietic stem cell transplant; IV, intravenous; R/R, relapsed or refractory; SmPC, summary of product characteristics; TAG, tagraxofusp.

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RESULTS (I): PATIENTS CHARACTERISTICS

Patients

- Preliminary analysis of data from 40 patients with BPDCN (**Table 1**)
  - 1L, n = 22 (55%)
  - R/R, n = 18 (45%)
- Male
  - 1L, 86%
  - R/R, 89%
- Skin involvement
  - 1L, 77%
  - R/R, 67%
- Countries
  - France (n = 15), Germany (n = 9), Italy (n = 8), Switzerland (n = 6), Austria (n = 1), and Spain (n = 1)

Table 1. Baseline Demographic and Disease Characteristics

Parameter	1L (n = 22)	R/R (n = 18)
Median age, years (range)	**68** (21-82)	**66** (29-83)
Disease presentation at initial diagnosis, n (%)		
Skin involvement[a]	**17** (77)	**12** (67)
Single lesion[b]	**3** (15)	**1** (7)
Multiple lesions[b]	**13** (65)	**10** (71)
Lymph node involvement	**12** (55)	**11** (61)
Single	**2** (9)	**0**
Multiple	**10** (46)	**11** (61)
Spleen involvement	**8** (36)	**4** (22)
CNS involvement[c]	**3** (10)	**4** (22)
Previous lines of therapy, n (%)		
0	**22** (100)	**0**
1	**0**	**12** (67)
2	**0**	**5** (28)
3	**0**	**1** (6)
Time to TAG start,[d,e] months, median (range)	**1.5** (0.4-9.0)	**7.5** (1.0-27.3)

[a]Unknown for 1 patient each in the 1L and R/R groups. [b]Includes only patients with computerized tomography or positron emission tomography scans performed. [c]Not evaluated in 1 patient each in the 1L and R/R groups. [d]Missing for 1 patient each in the 1L and R/R groups. [e]Time from the date of diagnosis to the start of TAG therapy.

1L, first-line; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CNS, central nervous system; R/R, relapsed or refractory; TAG, tagraxofusp.

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Results (II): RESPONSE AND HSCT

Efficacy

- Best response (**Table 2**)
  - ORR
    - 1L, 88% (15/17)
    - R/R, 67% (10/15)
  - CR rate
    - 1L, 71% (12/17)
    - R/R, 40% (6/15)
- Bridged to allogeneic HSCT (**Table 2**)
  - 1L, 10/22 (45%)
  - R/R, 7/18 (39%)

Table 2. Objective Response and HSCT

Parameter	1L (n = 22)	R/R (n = 18)
Patients with ≥1 tumor assessment, n (%)	**17** (77)	**15** (83)
Best overall response,[a] n (%) [95% CI]		
ORR	**15** (88) [63.6–98.5]	**10** (67) [38.4–88.2]
CR	**12** (71) [44.0–89.7]	**6** (40) [16.3–67.7]
PR	**3** (18) [3.8–43.4]	**4** (27) [7.8–55.1]
SD	**1** (6)	**2** (13)
PD	**1** (6)	**3** (20)
Median response duration, months, (95% CI) [range]	**8.8** (3.2–NR) [0.3–14.1[b]]	**5.6** (3.0–NR) [1.4–19.2[b]]
Patients who received HSCT, n (%) [95% CI]	**10** (45) [24.4–67.8]	**7** (39) [17.3–64.3]
In CR prior to HSCT, n (%)	**7** (70)	**5** (71)
In PR prior to HSCT, n (%)	**3** (30)	**2** (29)

[a]Based on all tumor assessments regardless of the cycle in which they were obtained. [b]Last observation censored.

1L, first-line; CI, confidence interval; CR, complete response; HSCT, hematopoietic stem cell transplant; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed or refractory; SD, stable disease; TAG, tagraxofusp.

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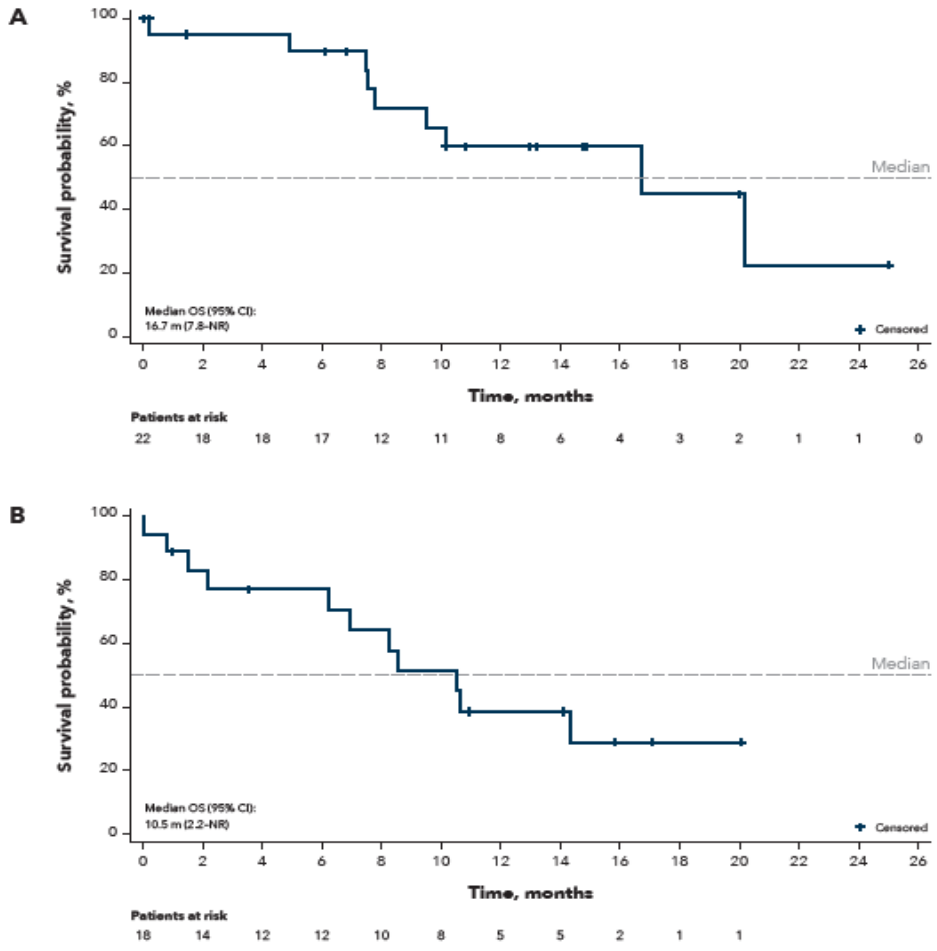
RESULTS (III)

Efficacy

- Median follow-up time
  - 1L, 10.1 months
  - R/R, 8.4 months
- Median OS
  - 1L (n = 22), 16.7 months (**Figure 3A**)
  - R/R (n = 18), 10.5 months (**Figure 3B**)

Figure 3. Overall Survival by Line of Treatment in 1L (A) and R/R (B) Patients[a]



[a]Overall survival is the period from tagraxofusp start date to death from any cause.

1L, first-line; NR, not reached; OS, overall survival; R/R, relapsed or refractory

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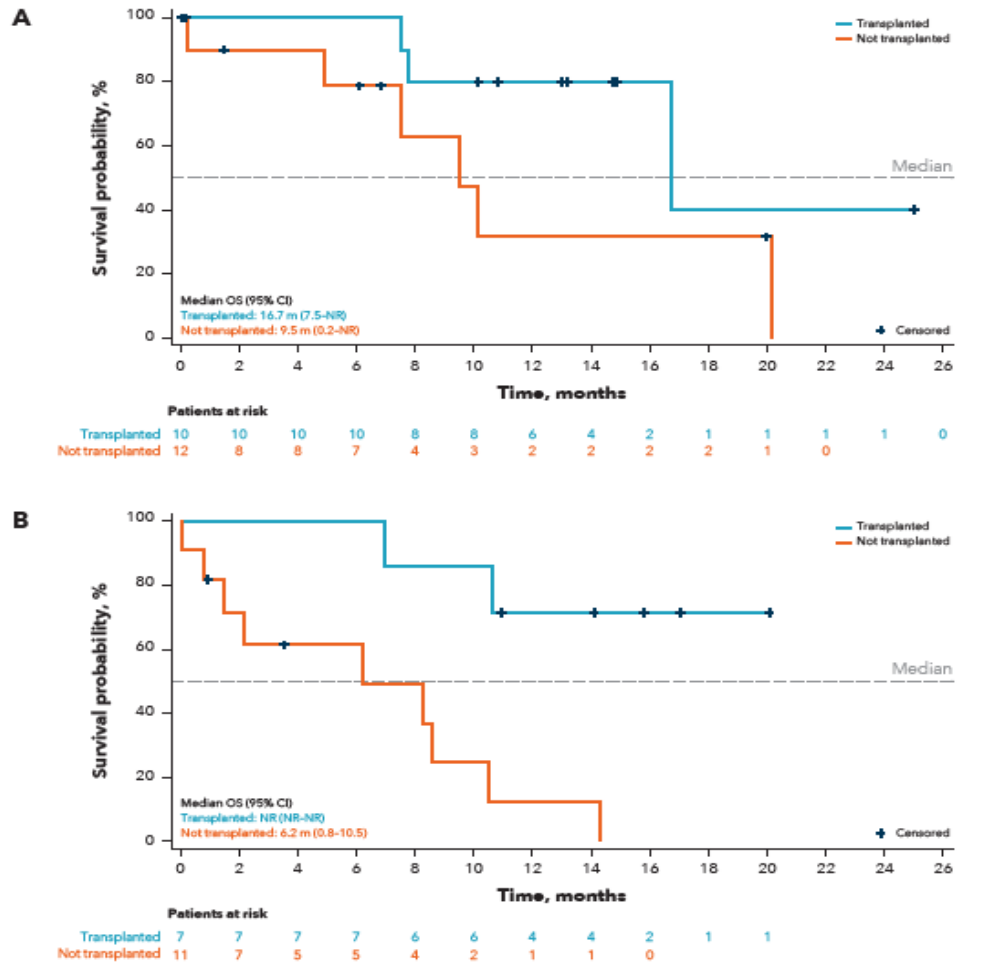
RESULTS (IV)

Efficacy

- Median OS in 1L (**Figure 4A**)
  - Transplanted (n = 10), 16.7 months
  - Not transplanted (n = 12), 9.5 months
- Median OS in R/R (**Figure 4B**)
  - Transplanted (n = 7), not reached
  - Not transplanted (n = 11), 6.2 months

Figure 4. Overall Survival by Transplant Status in 1L (A) and R/R (B) Patients[a]



[a]Overall survival is the period from tagraxofusp start date to death from any cause.

1L, first-line; NR, not reached; OS, overall survival; R/R, relapsed or refractory

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RESULTS (V): NON CLS AES

Safety

- Median number of TAG cycles
  - 1L, 3 (range, 1–8)
  - R/R, 2 (range, 1–5)
- TAG-related grade 3/4 AEs or SAEs (**Table 3**)
  - Overall, the most frequent (in ≥10% of patients) were thrombocytopenia (23%), anemia (18%), and neutropenia (13%)
  - 1L, n = 8 (36%). The most frequent AE was thrombocytopenia (23%)
  - R/R, n = 8 (44%). The most frequent AE was anemia (28%)
- All grade 3/4 AEs and SAEs occurred only during cycle 1

Table 3. Grade 3/4 AEs or SAEs Related to TAG in ≥10% of Patients in Either Group

AE, n (%)	1L (n = 22)	R/R (n = 18)
Nonhematologic grade 3/4 AEs or SAEs		
Hepatic cytolysis[a]	**1** (5)	**2** (11)
Tumor lysis syndrome	**0**	**2** (11)
Increased AST	**3** (14)	**0**
Pneumonia	**0**	**2** (11)
Hematologic grade 3/4 AEs		
Thrombocytopenia	**5** (23)	**4** (22)
Anemia	**2** (9)	**5** (28)
Neutropenia	**3** (14)	**2** (11)
Pancytopenia	**0**	**2** (11)

[a]Definitions collected retrospectively from the clinical dossier.

1L, first-line; AE, adverse event; AST, aspartate aminotransferase; R/R, relapsed/refractory; SAE, severe AE; TAG, tagraxofusp.

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RESULTS (VI): CLS EVENTS

Safety

- Mean albumin level prior to TAG therapy
  - 1L, 3.8 g/dL
  - R/R, 3.7 g/dL
- A summary of capillary leak syndrome (CLS) events as reported by the investigator is shown in **Table 4**
  - Symptoms associated with CLS events were weight gain, edema, hypotension, and hypoalbuminemia
- In the 1L setting, 9/22 patients had a total of 12 events
  - 8 of the 12 events occurred in cycle 1
- In the R/R setting, 11/18 patients had a total of 13 events
  - 11 of the 13 events occurred in cycle 1
- The majority of CLS events were grade 1/2; no grade 5 events occurred
- CLS was managed by TAG dose interruption and intravenous albumin supplementation +/- steroid administration
- All CLS events resolved

Table 4. Incidence of CLS Events[a] (All Cycles)

Parameter	1L (n = 22)	R/R (n = 18)
Patients who experienced CLS, n	**9**	**11**
Patients who experienced CLS on 2 occasions	**3**	**2**
Number of CLS events	**12**[b]	**13**[c]
Grade, n		
1	**1**	**0**
2	**8**	**8**
3	**3**	**4**
4	**0**	**1**
Action taken on TAG, n		
Dose reduced	**0**	**0**
Drug interrupted	**6**	**5**
Median duration, days (range)	**8** (3–172)	**5** (3–11)

[a]Symptoms associated with CLS events (as reported by the investigator): weight gain, edema, hypotension, and hypoalbuminemia. [b]Three patients had more than 1 event. [c]Two patients had more than 1 event.

1L, first-line; CLS, capillary leak syndrome; R/R, relapsed/refractory; TAG, tagraxofusp.

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AUTHOR'S Conclusions

- This preliminary analysis of real-world data with tagraxofusp (N = 40; 1L, n = 22; R/R, n = 18) as of September 15, 2022, from the ongoing European EAP confirms a positive benefit-to-risk ratio in adult patients with BPDCN
- In the real-world setting, stronger clinical efficacy with higher CR rates than in the pivotal BPDCN study were reported
  - In 1L, the ORR was 88% with a CR rate of 71%
    - 45% of patients bridged to HSCT
  - In R/R, the ORR was 67%, with a CR rate of 40%
    - 39% of patients bridged to HSCT
- The majority of CLS events were mild/moderate (grade 2/3) and no grade 5 events were reported. This demonstrates the effectiveness of adherence to CLS monitoring and management guidelines

1L, first-line; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CLS, capillary leak syndrome; CR, complete response; EAP, expanded access program; HSCT, hematopoietic stem cell transplant; ORR, overall response rate; R/R, relapsed/refractory; TAG, tagraxofusp.

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TAGRAXOFUSP IN BPDCN WITH/WITHOUT CENTRAL NERVOUS SYSTEM INVOLVEMENT AND INTRATHECAL CHEMOTHERAPY AS PRIMARY TREATMENT OR PROPHYLAXIS:

N	AGE (Y)	Symptoms of CNS+	Systemic TXT	N cycles	HSCT	CNS response to ITT	Survival after CNS+(months)	Survival after diagnosis (months)
1	64	N	TAG only	3	Y	-	-	46
2	51	Y	TAG only*	3	N	CR	10	10
3	71	Y	TAG only*	4	N	CR	12	12
4	16	N	TAG only*	4	Y	-	-	23
5	72	Y	TAG only	1	N	CR	18	18

*pt n. 2, 3, 4: TAG 1st line / subsequent 2nd line chemotherapy

TAGRAXOFUSP IN BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM WITH/WITHOUT CENTRAL NERVOUS SYSTEM INVOLVEMENT AND INTRATHECAL CHEMOTHERAPY AS PRIMARY TREATMENT OR PROPHYLAXIS: AN ITALIAN EXPERIENCE, Rivoli G et al, EHA 2022, P#530

TAGRAXOFUSP IN BPDCN WITH/WITHOUT CENTRAL NERVOUS SYSTEM INVOLVEMENT AND INTRATHECAL CHEMOTHERAPY AS PRIMARY TREATMENT OR PROPHYLAXIS:

- Data supporting the feasibility of IT chemotherapy in combination with systemic TAG therapy

- Baseline CNS involvement did not appear to impact TAG efficacy, with 2 (40%) patients achieving complete response (CR) and 3 (60%) partial response

- Two patients were bridged to HSCT

- IT chemotherapy effectively cleared disease from the CSF, with all 3 patients with baseline CNS involvement achieving CNS CR

- No unexpected safety events occurred when TAG was administered concomitantly with CNS prophylaxis or treatment

- Despite the limited number of patients analyzed, this single-center experience shows high frequency of patients with CNS+ BPDCN at the time of diagnosis and suggests that patients should be routinely checked for CNS involvement

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GRAZIE PER L'ATTENZIONE!

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