Actualités dans la prise en charge de la LLC

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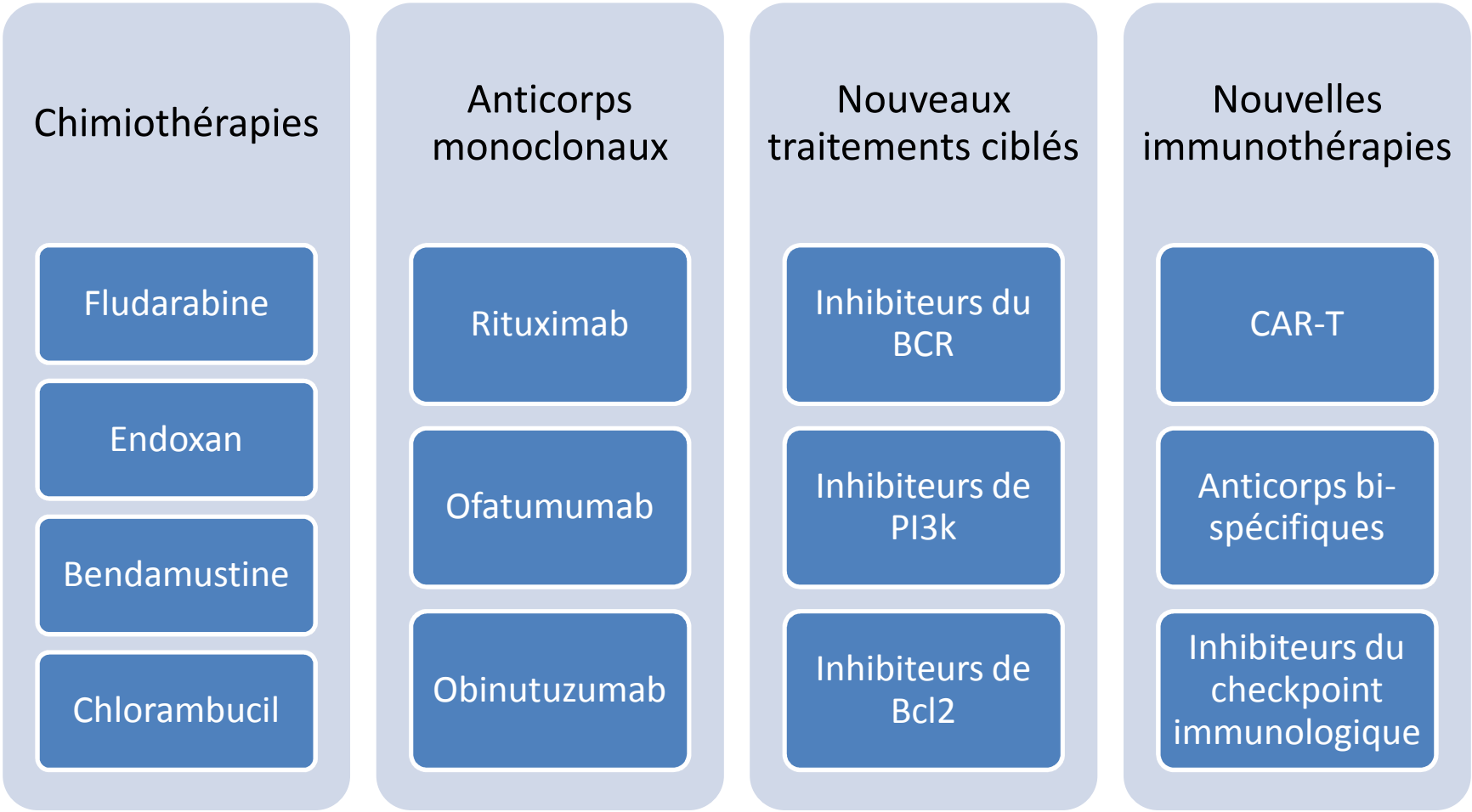
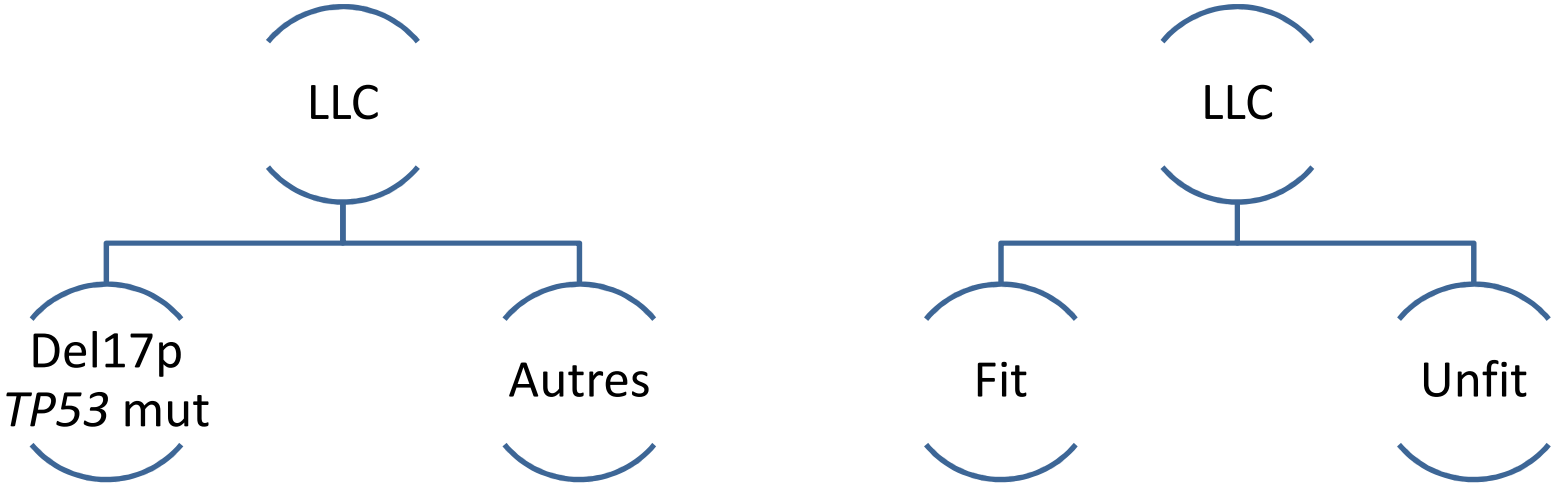
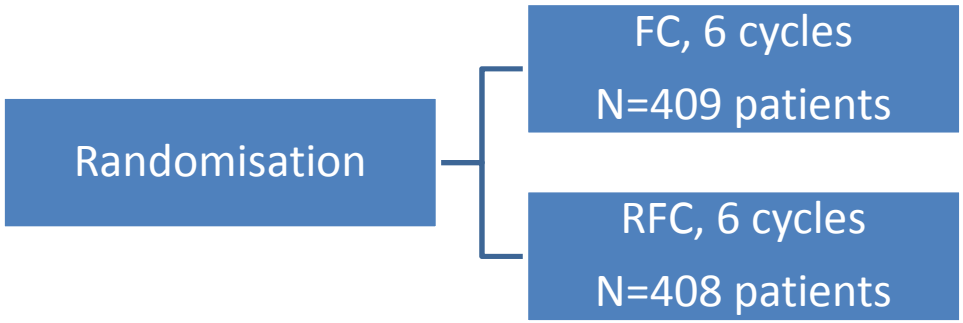
Le nouveau paysage de la LLC (1)



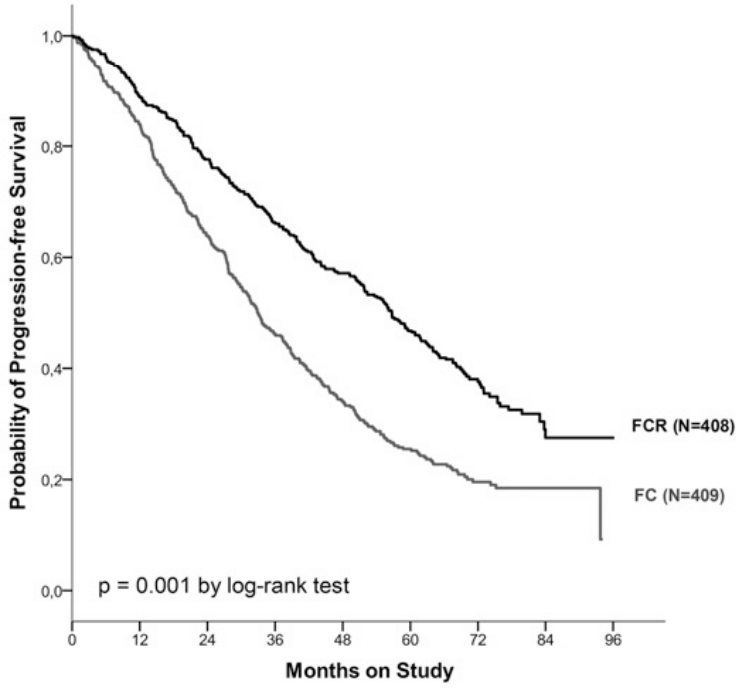
Le nouveau paysage de la LLC (2)

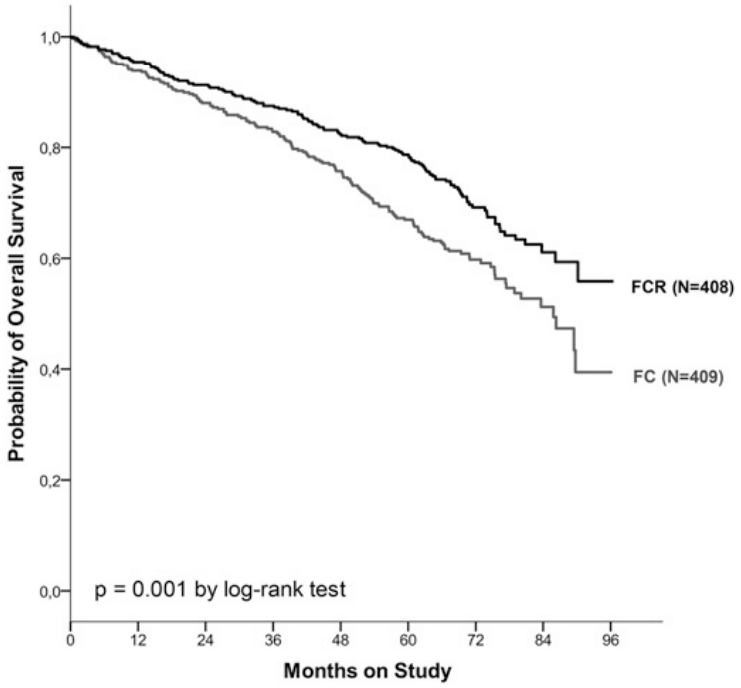


CLL8 : efficacité à long terme



Age médian : 61 ans
Age > 75 ans : 10%
CIRS médian : 1
Follow-up médian : 5.9 ans





CLL8 : analyse de sous-groupe

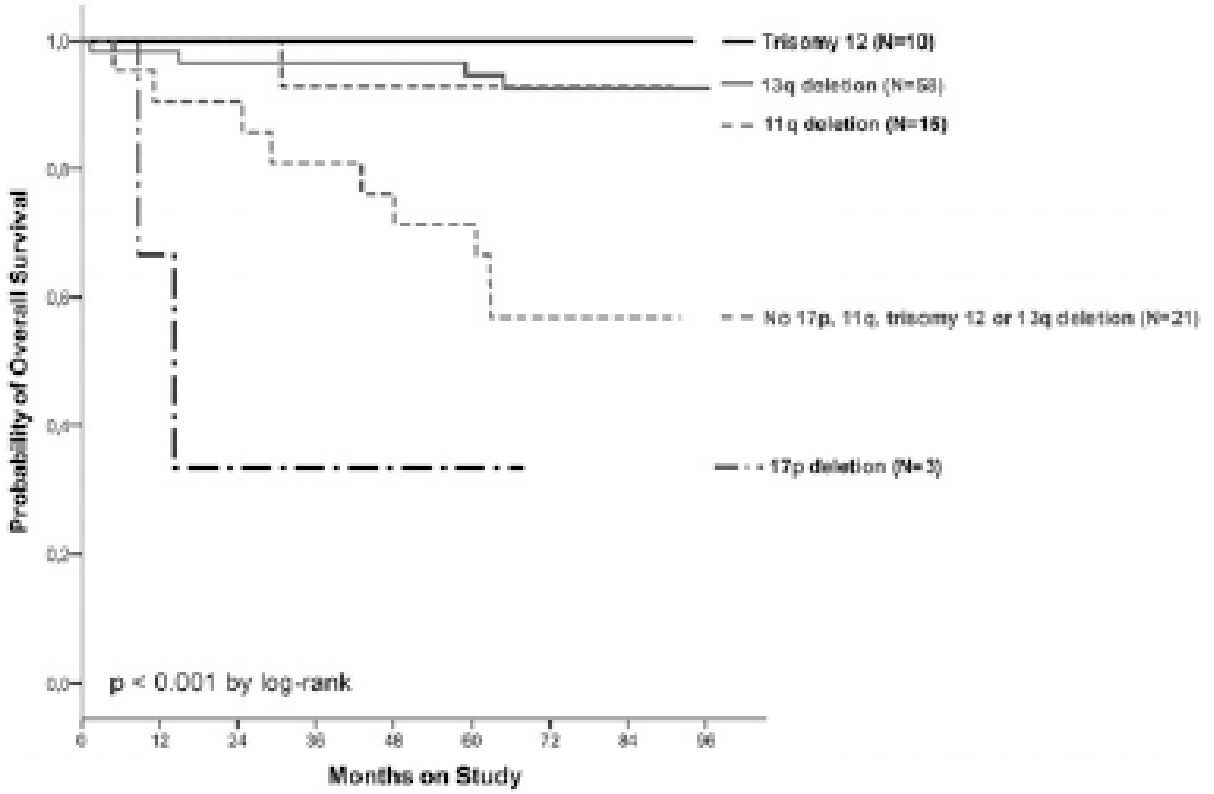
PFS				
All patients (N = 817)	46.8	25.5	0.59 (0.50-0.69)	<.001
Age				
<65 years (N = 572)	48.3	25.2	0.57 (0.47-0.70)	<.001
≥65 years (N = 245)	43.2	26.1	0.63 (0.47-0.85)	.003
Binet stage				
A (N = 40)	60.2	28.9	0.44 (0.18-1.12)	.084
B (N = 522)	47.7	25.4	0.55 (0.46-0.68)	<.001
C (N = 252)	43.0	25.3	0.71 (0.53-0.95)	.023
Sex				
Female (N = 210)	58.8	33.1	0.58 (0.40-0.83)	.003
Male (N = 607)	42.6	23.0	0.59 (0.49-0.72)	<.001
Cytogenetic abnormalities				
17p deletion (N = 51)	15.3	0.0	0.47 (0.25-0.90)	.023
11q deletion (N = 142)	31.4	11.4	0.47 (0.32-0.68)	<.001
Trisomy 12 (N = 61)	61.6	23.7	0.41 (0.20-0.81)	.01
Normal (N = 138)	42.0	37.6	0.83 (0.54-1.26)	.365
13q deletion (N = 224)	63.3	31.0	0.44 (0.31-0.62)	<.001
***IGHV* mutational status**				
UNM (N = 392)	33.1	19.4	0.65 (0.52-0.82)	<.001
MUT (N = 230)	66.6	36.2	0.47 (0.33-0.68)	<.001
***NOTCH1* mutation**				
Wild type (N = 560)	48.0	25.3	0.55 (0.45-0.68)	<.001
Mutated (N = 62)	26.7	25.8	1.01 (0.57-1.78)	.974
***SF3B1* mutation**				
Wild-type (N = 507)	49.1	27.8	0.60 (0.48-0.74)	<.001
Mutated (N = 114)	31.3	14.9	0.53 (0.35-0.80)	.003

OS				
All patients (N = 817)	78.7	66.9	0.68 (0.54-0.89)	.001
Age				
<65 years (N = 572)	80.9	69.2	0.63 (0.47-0.84)	.002
≥65 years (N = 245)	73.9	61.6	0.81 (0.54-1.20)	.288
Binet stage				
A (N = 40)	94.4	66.0	0.11 (0.01-0.84)	.034
B (N = 522)	82.1	66.8	0.59 (0.44-0.80)	.001
C (N = 252)	69.0	67.3	1.02 (0.68-1.53)	.918
Sex				
Female (N = 210)	81.3	64.5	0.56 (0.34-0.93)	.003
Male (N = 607)	77.8	67.8	0.71 (0.55-0.93)	<.001
Cytogenetic abnormalities				
17p deletion (N = 51)	36.0	18.2	0.64 (0.32-1.25)	.19
11q deletion (N = 142)	85.8	55.1	0.35 (0.20-0.61)	<.001
Trisomy 12 (N = 61)	91.5	77.4	0.54 (0.19-1.55)	.251
Normal (N = 138)	74.0	81.2	1.31 (0.73-2.35)	.370
13q deletion (N = 224)	87.1	73.1	0.49 (0.28-0.84)	.01

CLL8 : analyse multivariée

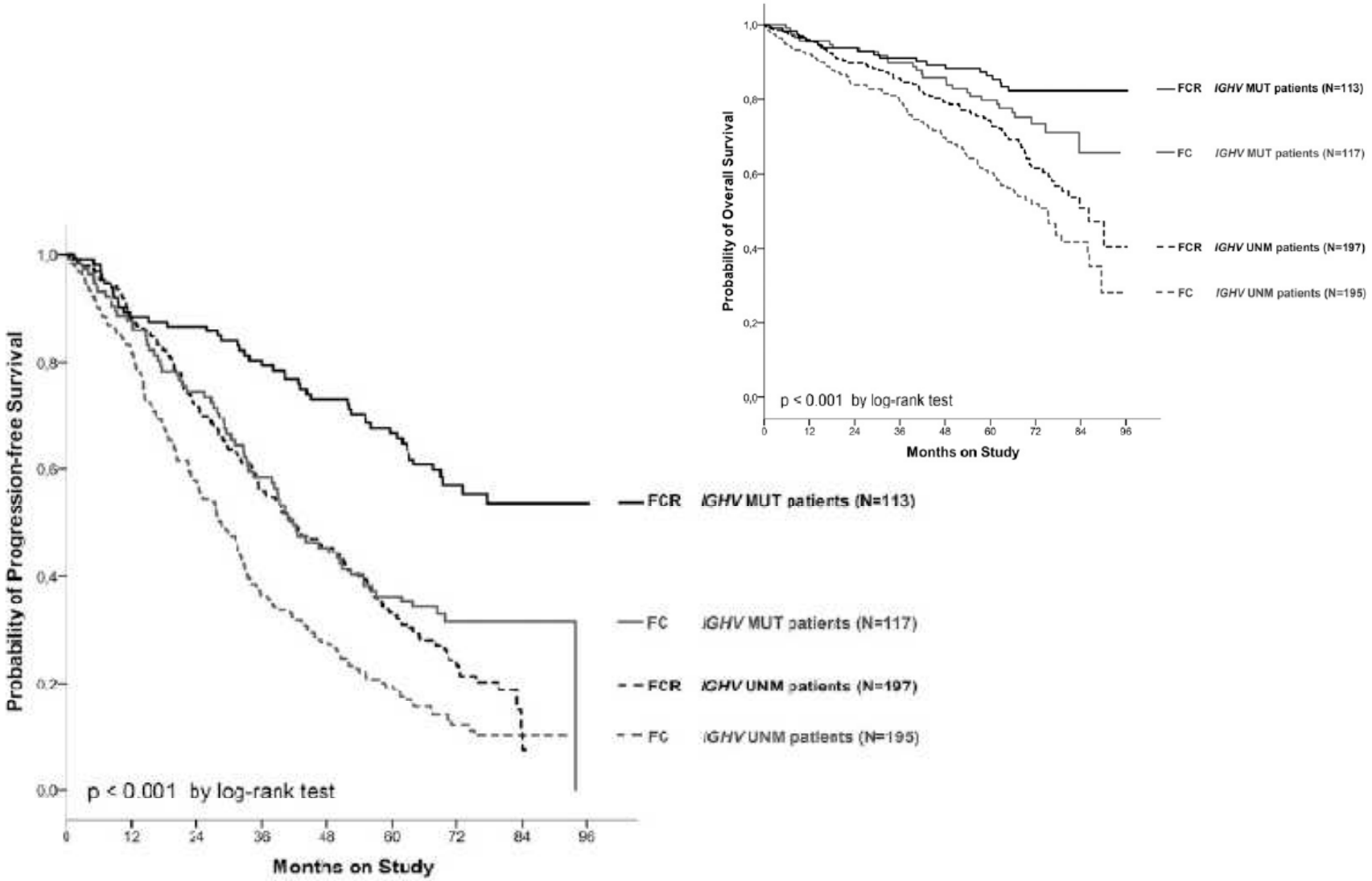
Characteristic	Adverse factor	HR	95% CI	*P* value
PFS (N = 500; 348 [42.6%] events)				
Study treatment	FC	1.976	1.59-2.45	<.001
Serum thymidine kinase level	≥10 U/L	1.362	1.10-1.77	.020
IGHV mutational status	UNM	1.719	1.33-2.23	<.001
Cytogenetic subgroup	Del(11q)	1.546	1.22-1.97	<.001
Cytogenetic subgroup	Del(17p)	2.916	1.78-4.78	<.001
TP53 mutational status	Mutated	2.123	1.40-3.22	<.001
SF3B1 mutational status	Mutated	1.346	1.04-1.75	.026
OS (N = 500; 173 [21.2%] events)				
Study treatment	FC	1.538	1.14-2.08	.006
Age	≥65 y	1.423	1.04-1.20	.018
ECOG	>0	1.622	1.20-2.21	.002
Serum β_2- microglobulin level	≥3.5 mg/L	1.473	1.07-2.03	.014
Serum thymidine kinase level	≥10 U/L	1.864	1.20-2.90	.003
IGHV mutational status	UNM	2.059	1.39-3.05	<.001
Cytogenetic subgroup	Del(17p)	2.715	1.60-4.60	<.001
TP53 mutational status	Mutated	3.014	1.89-4.80	<.001

CLL8 : Impact de la cytogénétique



N=107 patients mutés

CLL8 : statut mutationnel



CLL8 : tolérance à long terme

	Total		FC		FCR	
Long-term safety	**Cases N (%)**	**Patients N (%)**	**Cases N (%)**	**Patients N (%)**	**Cases N (%)**	**Patients N (%)**
Total patients (safety population), N		800		396		404
Total cases [N (%)] and patients [N (%)] with ≥1 SPM	136 (100)	122 (15)	77 (57)	69 (17)	59 (43)	53 (13)
Secondary malignancies						
Richter's transformation	38 (28)	38 (5)	25 (33)	25 (6)	13 (22)	13 (3)
Solid tumors	55 (40)	52 (7)	29 (38)	28 (7)	26 (44)	24 (6)
Lung	18/55 (33)	18 (2)	13/29 (45)	13 (3)	5/26 (20)	5 (1)
Prostate	8/55 (15)	8 (1)	2/29 (7)	2 (1)	6/26 (23)	6 (2)
Renal/bladder	7/55 (13)	6 (1)	3/29 (10)	3 (1)	4/26 (15)	3 (1)
Colorectal	2/55 (4)	2 (<1)	0/29 (0)	0 (0)	2/26 (8)	2 (<1)
Melanoma	8/55 (15)	8 (1)	3/29 (10)	3 (1)	5/26 (20)	5 (1)
Breast	3/55 (6)	3 (<1)	1/29 (3)	1 (<1)	2/26 (8)	2 (<1)
Pancreatic	2/55 (4)	2 (<1)	1/29 (3)	1 (<1)	1/26 (4)	1 (<1)
Ovarian/uterine/cervical	1/55 (2)	1 (<1)	0/29 (0)	0 (0)	1/26 (4)	1 (<1)
Liver/gall bladder	1/55 (2)	1 (<1)	1/29 (3)	1 (<1)	0/26 (0)	0 (0)
Thyroid	2/55 (4)	2 (<1)	2/29 (7)	2 (1)	0/26 (0)	0 (0)
Pharyngeal/laryngeal	1/55 (2)	1 (<1)	1/29 (3)	1 (<1)	0/26 (0)	0 (0)
Other	2/55 (4)	2 (<1)	2/29 (7)	2 (1)	0/26 (0)	0 (0)
Hematologic neoplasia	24 (18)	23 (3)	11 (14)	11 (3)	13 (22)	12 (3)
AML/MDS	14/24 (58)	13 (2)	7/11 (64)	7 (2)	7/13 (54)	6 (2)
Indolent B-non-Hodgkin lymphoma	3/24 (13)	3 (<1)	1/11 (9)	1 (<1)	2/13 (16)	2 (<1)
Aggressive B-non-Hodgkin lymphoma	2/24 (8)	2 (<1)	1/11 (9)	1 (<1)	1/13 (8)	1 (<1)
ALL	1/24 (4)	1 (<1)	0/11 (0)	0 (0)	1/13 (8)	1 (<1)
CML	1/24 (4)	1 (<1)	0/11 (0)	0 (0)	1/13 (8)	1 (<1)
Other	3/24 (13)	3 (<1)	2/11 (18)	2 (<1)	1/13 (8)	1 (<1)
Basalioma, squamous cell	19 (14)	17 (2)	12 (16)	11 (3)	7 (12)	6 (2)
Prolonged neutropenia						
2 months after end of treatment		101 (13)		34 (9)		67 (17)
12 months after end of treatment		30 (4)		14 (4)		16 (4)

Quel prise en charge pour les patients « fragiles » ?

- Quelle(s) définition(s) ?
  - Echelle CIRS
  - Echelles gériatriques
  - Fonction rénale
- Quelle(s) chimiothérapie(s) ?
- Quel(s) anticorps monoclonal(aux) ?
- Quel(s) traitement(s) ciblé(s) ?

CLL10

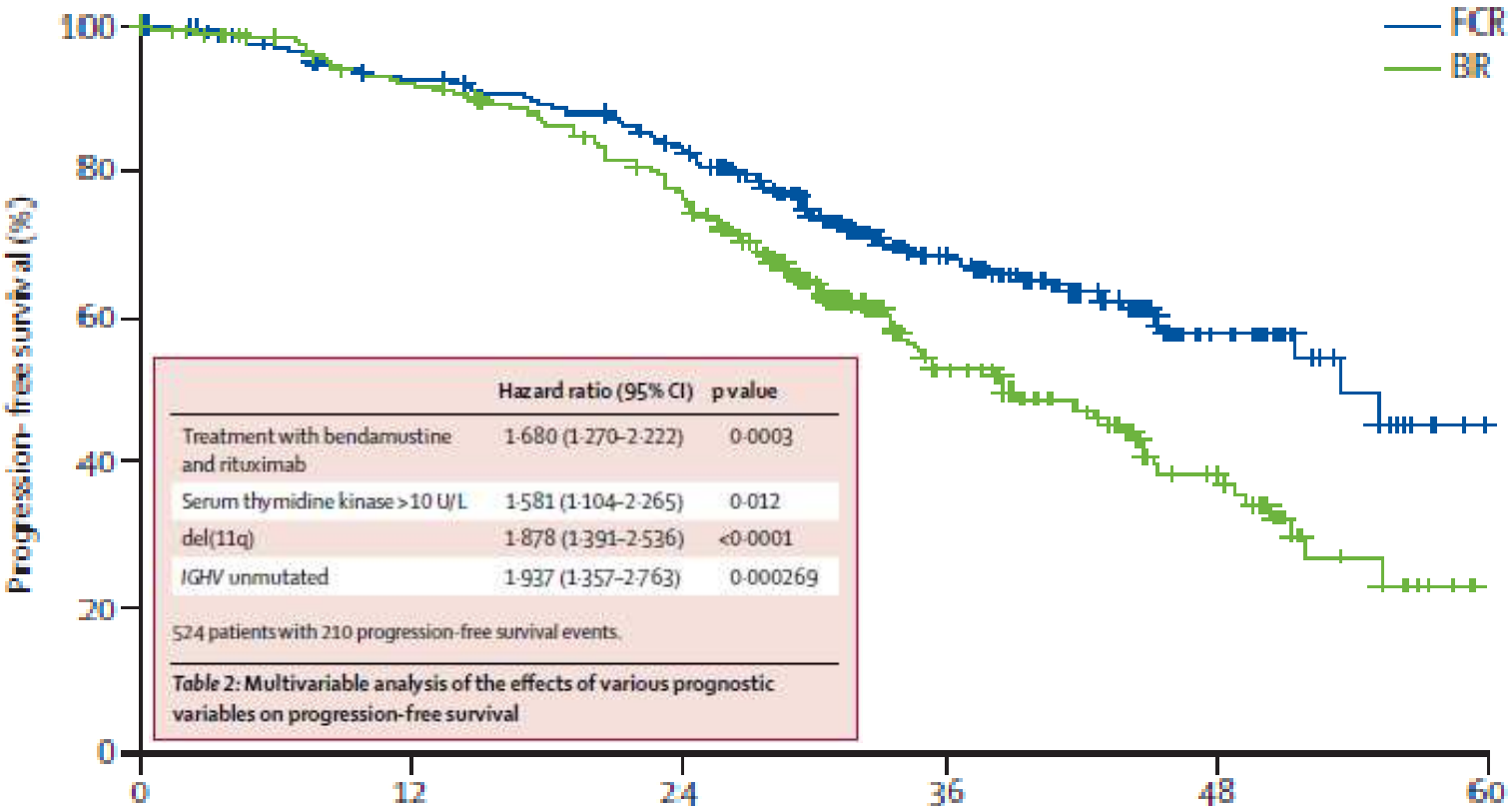
	Fludarabine, cyclophosphamide, and rituximab (n=282)	Bendamustine and rituximab (n=279)
Age (years)	62·1 (55·0–67·0)	61·0 (54·0–69·0)
>65 years	86 (30%)	108 (39%)
>70 years	28 (10%)	51 (18%)
Sex		
Male	201 (71%)	207 (74%)
Female	81 (29%)	72 (26%)
Median time from diagnosis to study entry (months)	21·6 (4·0–52·6)	24·6 (6·2–50·1)
Binet stage		
A	63 (22%)	62 (22%)
B	105 (37%)	107 (38%)
C	114 (41%)	110 (39%)
Rai stage		
0	7/221 (3%)	11/224 (5%)
I	29/221 (13%)	32/224 (14%)
II	86/221 (39%)	84/224 (37%)
III	44/221 (20%)	34/224 (15%)
IV	55/221 (25%)	65/224 (29%)
ECOG performance status		
0	180/281 (64%)	177/276 (64%)
1	95/281 (34%)	98/276 (36%)
2	6/281 (2%)	1/276 (<1%)
B-symptoms present	116 (41%)	113 (41%)
Median CIRS	2·0 (1·0–3·0)	2·0 (0–3·0)
Total CIRS ≤3	240 (85%)	234 (84%)
Number of involved CIRS categories ≤1	163 (58%)	149 (53%)
Median creatinine clearance (mL/min)	87·0 (71·7–106·9)	86·4 (72·6–101·6)
Thymidine kinase >10 U/L	198/272 (73%)	196/270 (73%)
β_2-microglobulin >3·5 mg/L	84/272 (31%)	103/270 (38%)
Cytogenetic abnormalities		
del(11q)	68 (24%)	63 (23%)
12q+	33 (12%)	32 (11%)
del(13q)	155 (55%)	147 (53%)
Unmutated *IGHV*	152/275 (55%)	183/270 (68%)

Patients plutôt « fit »
85% avec un CIRS<4
Fonction rénale normale
Age médian : 62 ans

	FC-R	B-R
Neutropénie grade 3-4	85%	55%
Thrombopénie grade 3-4	21%	14%
Infection grade 3-5	40%	30%
Grade 5	5%	5%

Majoration de la toxicité si âge > 65 ans

CLL10 : PFS



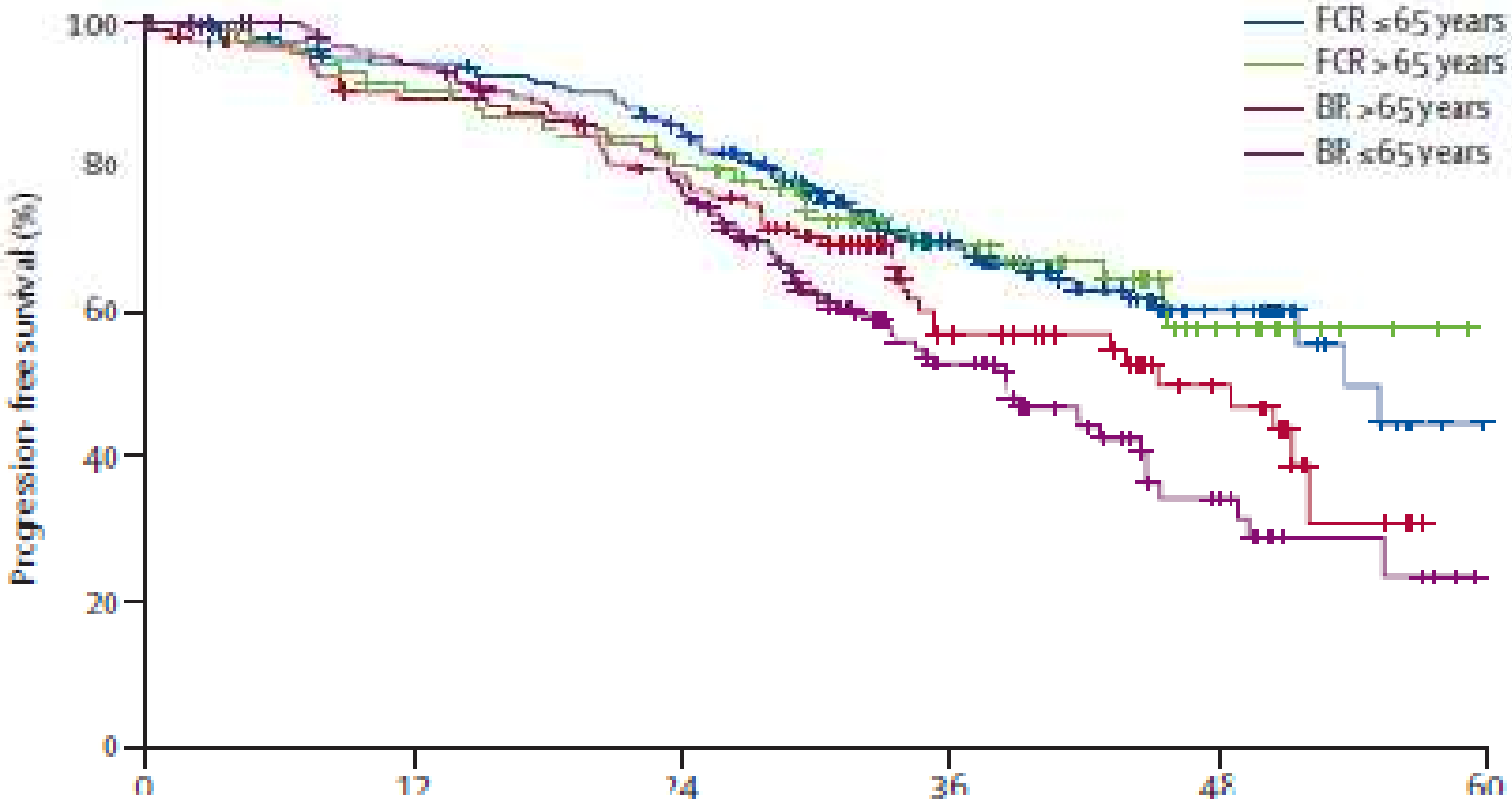
	Hazard ratio (95% CI)	p value
Treatment with bendamustine and rituximab	1·680 (1·270–2·222)	0·0003
Serum thymidine kinase >10 U/L	1·581 (1·104–2·265)	0·012
del(11q)	1·878 (1·391–2·536)	<0·0001
IGHV unmutated	1·937 (1·357–2·763)	0·000269

524 patients with 210 progression-free survival events.

Table 2: Multivariable analysis of the effects of various prognostic variables on progression-free survival

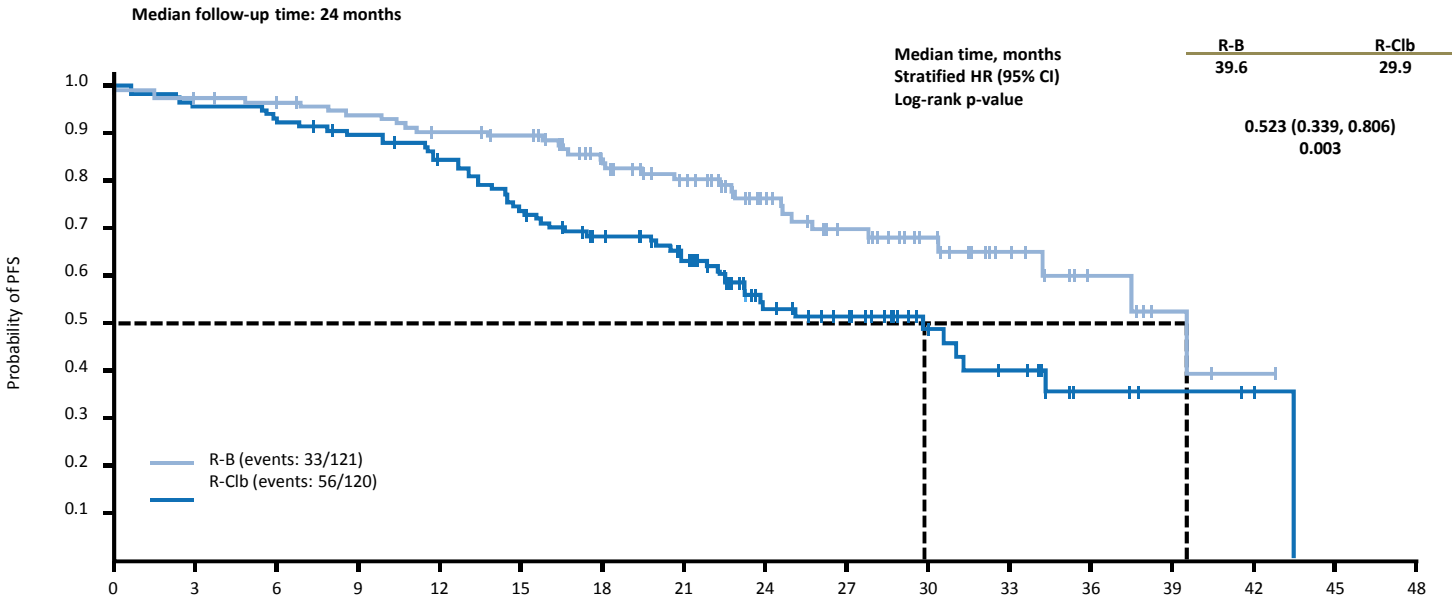
Pas de différence de survie globale

CLL10 : impact de l'âge



Mable : B ou CLB ?

- Augmentation globale de la toxicité (hématologique et extra-hématologique) avec la bendamustine



- Pas de différence de survie globale

CLL11

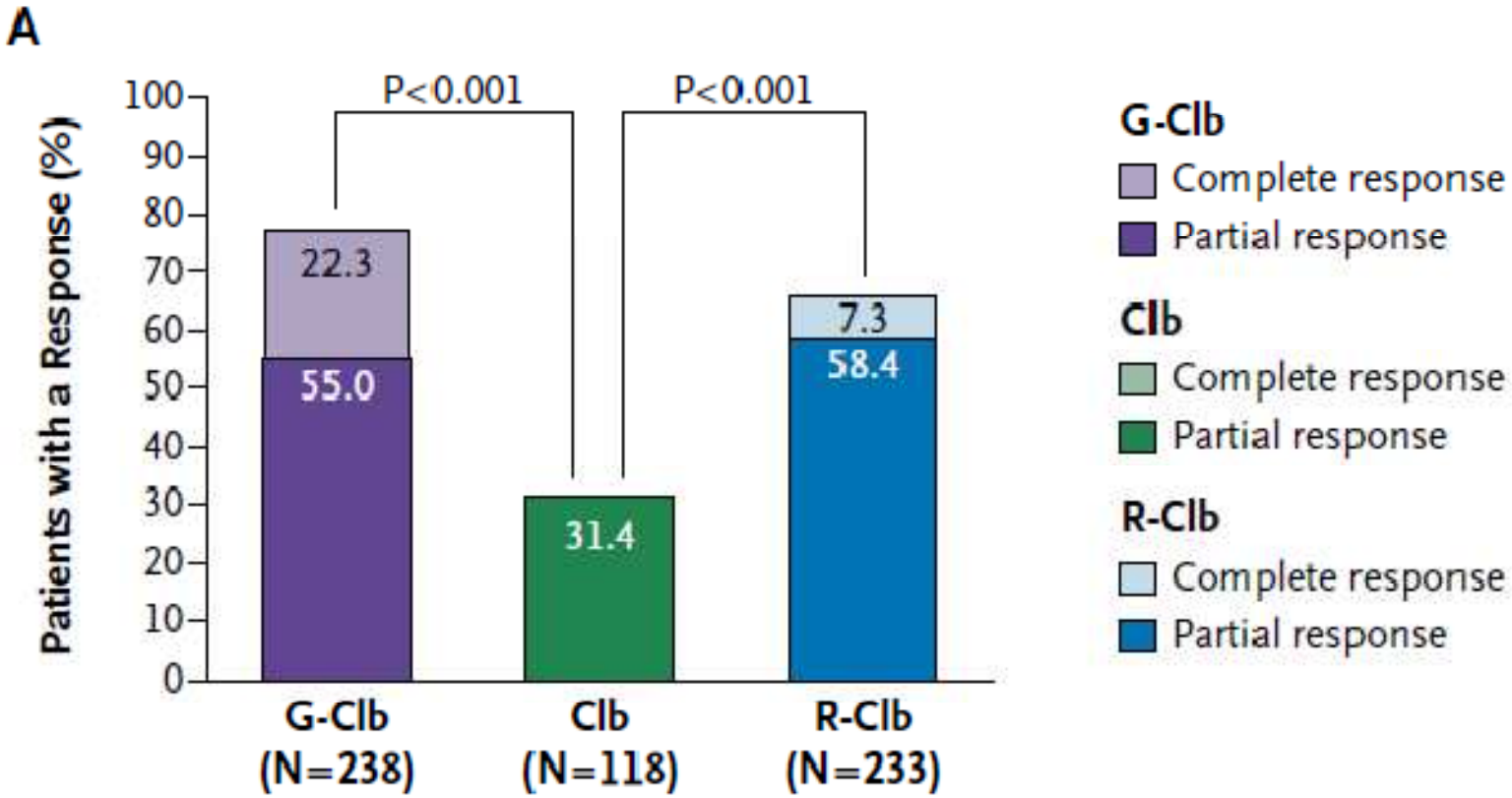
Critères d'inclusion : CIRS > 6 ou clairance de la créatinine 30-70 mL/min

Characteristic	Obinutuzumab–Chlorambucil vs. Chlorambucil Alone		Rituximab–Chlorambucil vs. Chlorambucil Alone		Obinutuzumab–Chlorambucil vs. Rituximab–Chlorambucil	
	Obinutuzumab–Chlorambucil (N=238)	Chlorambucil Alone (N=118)	Rituximab–Chlorambucil (N=233)	Chlorambucil Alone (N=118)	Obinutuzumab–Chlorambucil (N=333)	Rituximab–Chlorambucil (N=330)
Age — yr						
Median	74	72	73	72	74	73
Range	39–88	43–87	40–90	43–87	39–89	40–90
Cumulative Illness Rating Scale†						
Score — median (range)	8 (1–20)	8 (0–18)	8 (0–18)	8 (0–18)	8 (0–22)	8 (0–18)
Median calculated creatinine clearance — ml/min	61.4	63.8	61.8	63.8	62.5	62.6
Binet stage — no. (%)						
A	55 (23)	24 (20)	49 (21)	24 (20)	74 (22)	74 (22)
B	98 (41)	50 (42)	100 (43)	50 (42)	142 (43)	135 (41)
C	85 (36)	44 (37)	84 (36)	44 (37)	117 (35)	121 (37)
Unmutated *IGHV* — no./total no. (%)	129/210 (61)	58/99 (59)	126/204 (62)	58/100 (58)	188/305 (62)	182/298 (61)
del(17p) on FISH — no./total no. (%)	16/203 (8)	10/96 (10)	9/196 (5)	10/97 (10)	22/295 (7)	20/287 (7)

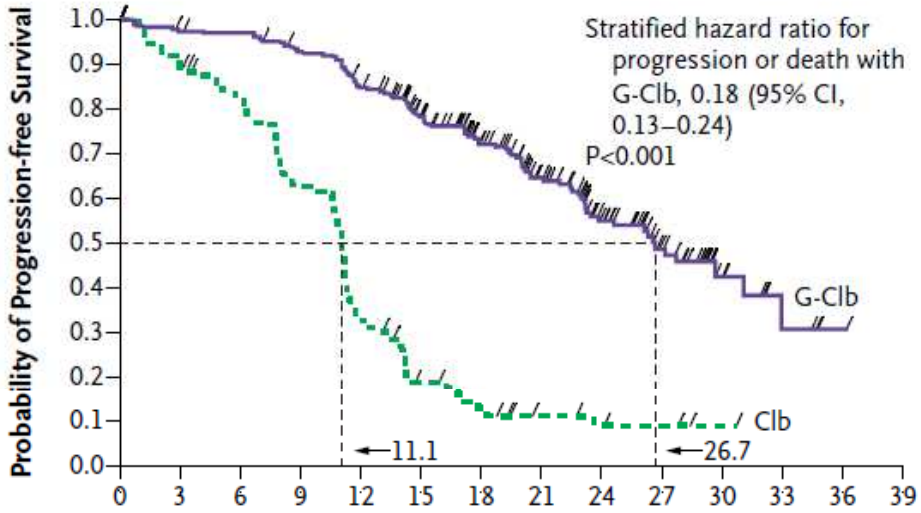
CLL11 : tolérance

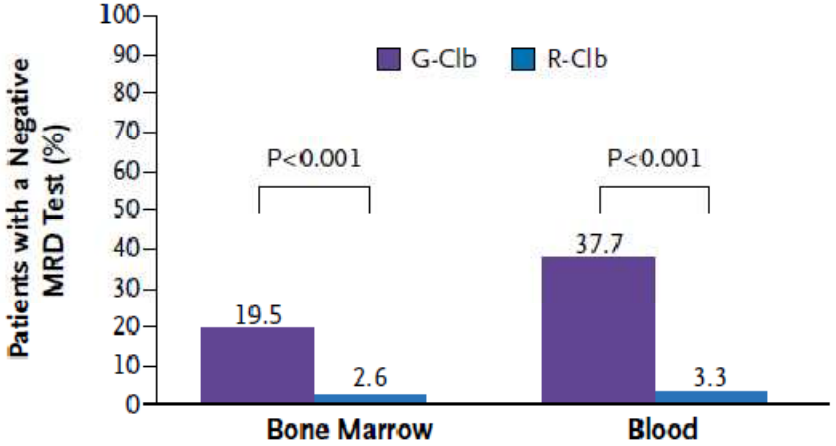
Event	Obinutuzumab–Chlorambucil vs. Chlorambucil Alone		Rituximab–Chlorambucil vs. Chlorambucil Alone		Obinutuzumab–Chlorambucil vs. Rituximab–Chlorambucil	
	Obinutuzumab–Chlorambucil (N=241)	Chlorambucil Alone (N=116)	Rituximab–Chlorambucil (N=225)	Chlorambucil Alone (N=116)	Obinutuzumab–Chlorambucil (N=336)	Rituximab–Chlorambucil (N=321)
	number of patients (percent)					
Any event	175 (73)	58 (50)	125 (56)	58 (50)	235 (70)	177 (55)
Infusion-related reactions	51 (21)	—	9 (4)	—	67 (20)	12 (4)
Neutropenia	84 (35)	18 (16)	60 (27)	18 (16)	111 (33)	91 (28)
Anemia	11 (5)	5 (4)	10 (4)	5 (4)	14 (4)	12 (4)
Thrombocytopenia	27 (11)	5 (4)	8 (4)	5 (4)	35 (10)	10 (3)
Leukopenia	13 (5)	0	3 (1)	0	15 (4)	3 (1)
Infections	27 (11)	16 (14)	30 (13)	16 (14)	40 (12)	44 (14)
Pneumonia	8 (3)	4 (3)	11 (5)	4 (3)	13 (4)	17 (5)
Febrile neutropenia	4 (2)	5 (4)	4 (2)	5 (4)	8 (2)	4 (1)

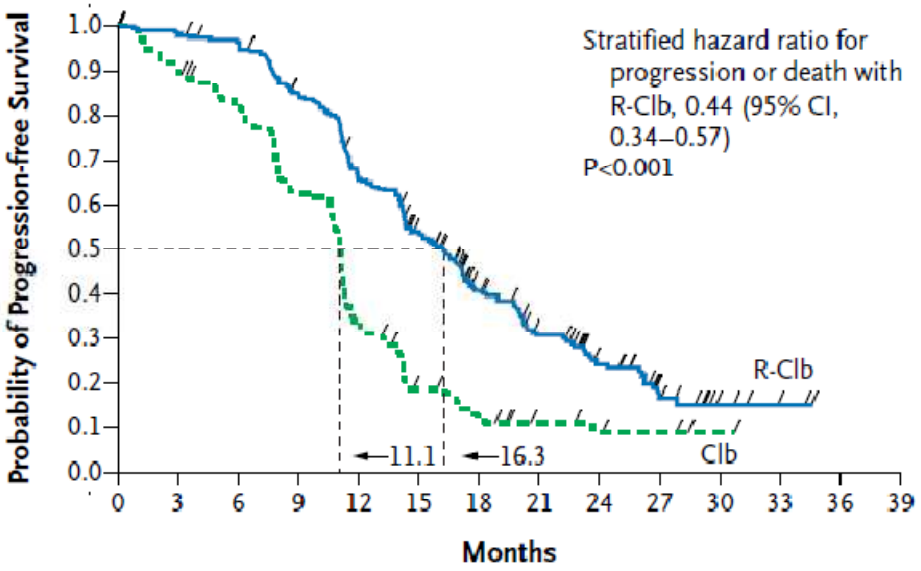
CLL11 : réponse

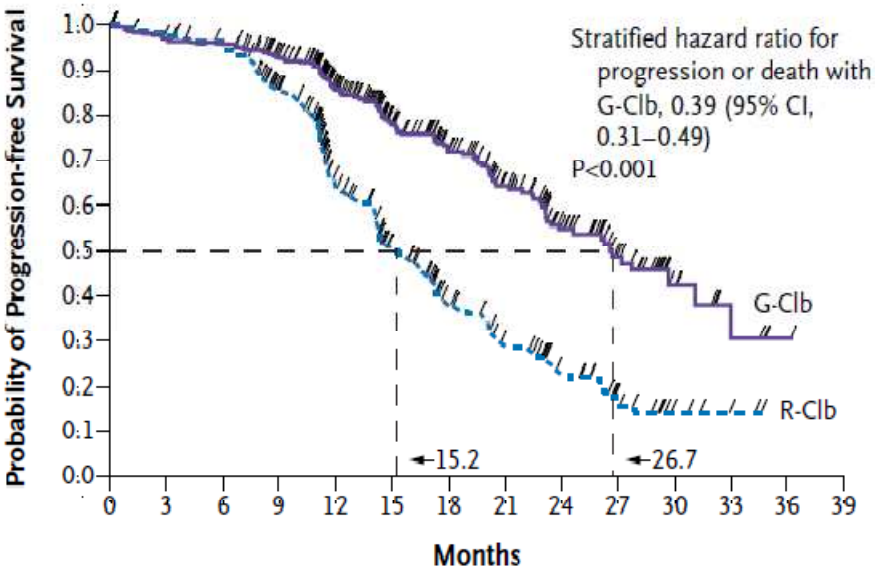


CLL11 : PFS

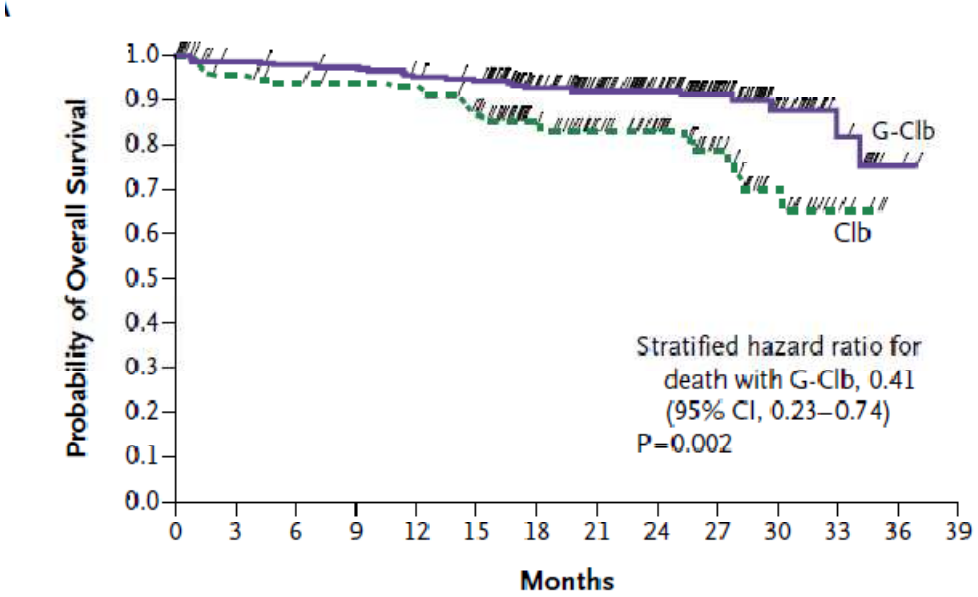

Probability of Progression-free Survival
Stratified hazard ratio for progression or death with G-Clb, 0.18 (95% CI, 0.13–0.24)
P<0.001
G-Clb
Clb
11.1
26.7

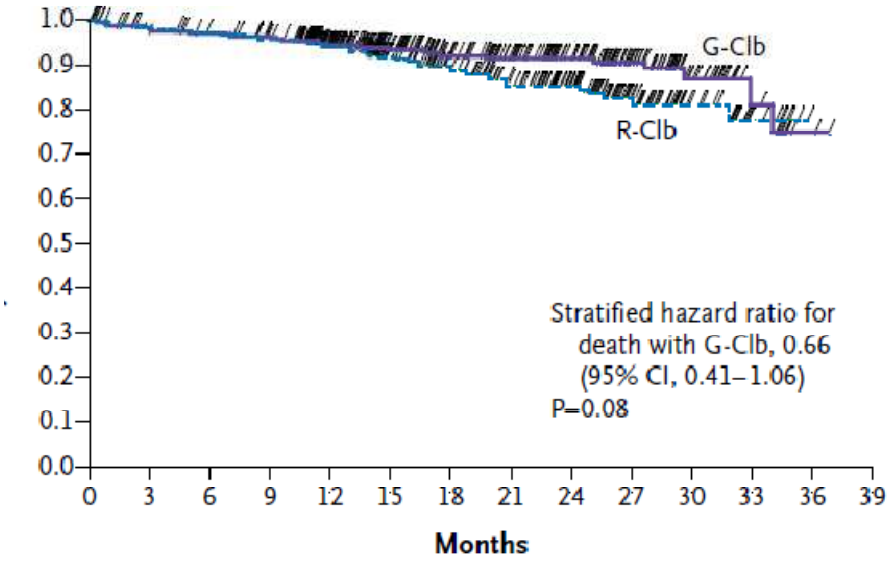

Patients with a Negative MRD Test (%)
G-Clb
R-Clb
P<0.001
P<0.001
19.5
2.6
37.7
3.3
Bone Marrow
Blood


Probability of Progression-free Survival
Stratified hazard ratio for progression or death with R-Clb, 0.44 (95% CI, 0.34–0.57)
P<0.001
R-Clb
Clb
11.1
16.3
Months


Probability of Progression-free Survival
Stratified hazard ratio for progression or death with G-Clb, 0.39 (95% CI, 0.31–0.49)
P<0.001
G-Clb
R-Clb
15.2
26.7
Months

CLL11 : OS





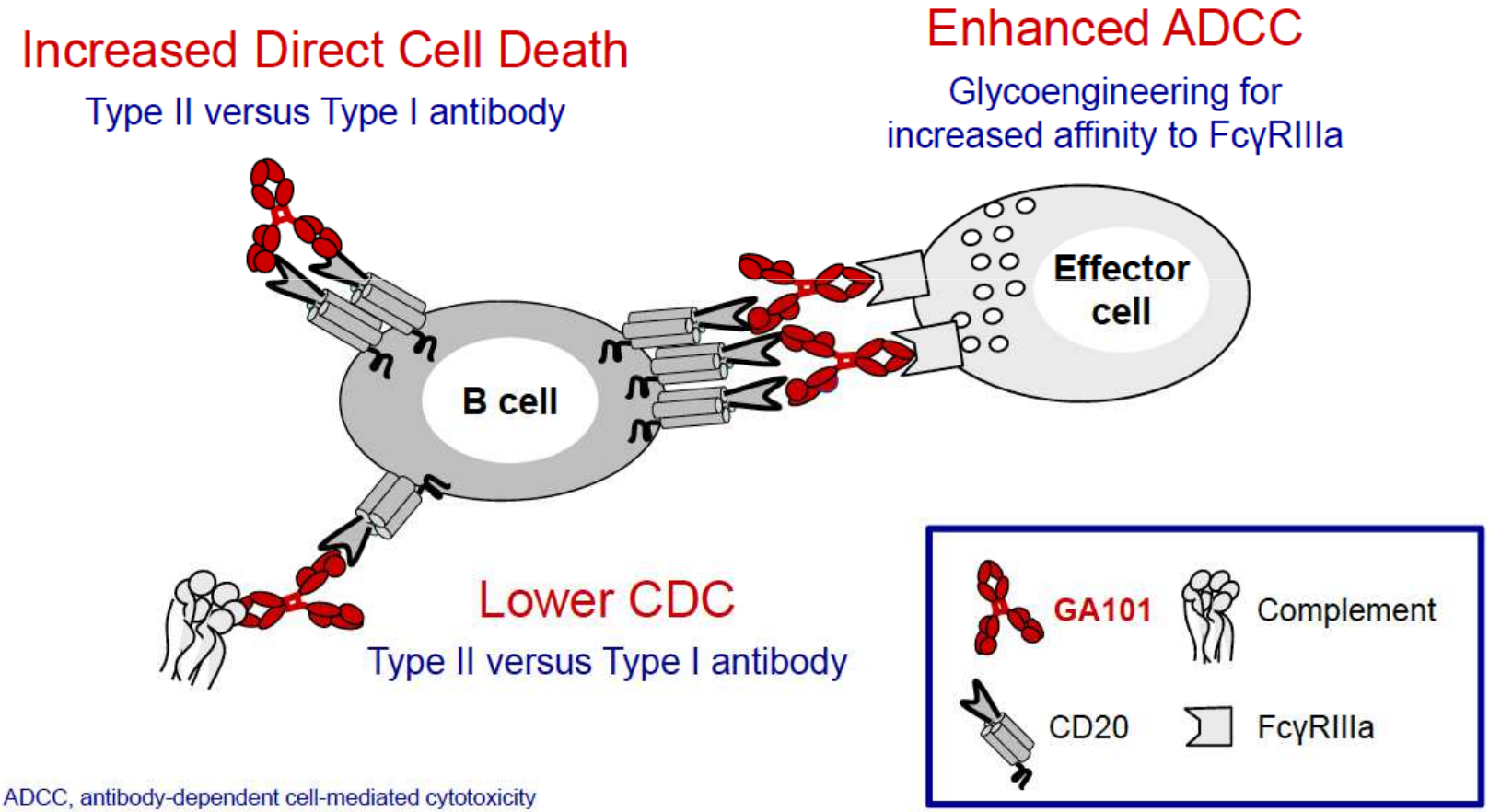
No. at Risk

G-Clb	238	226	223	221	215	211	170	144	115	71	34	14	2	0
Clb	118	109	105	103	102	94	70	56	44	29	15	5	0	0

Risk

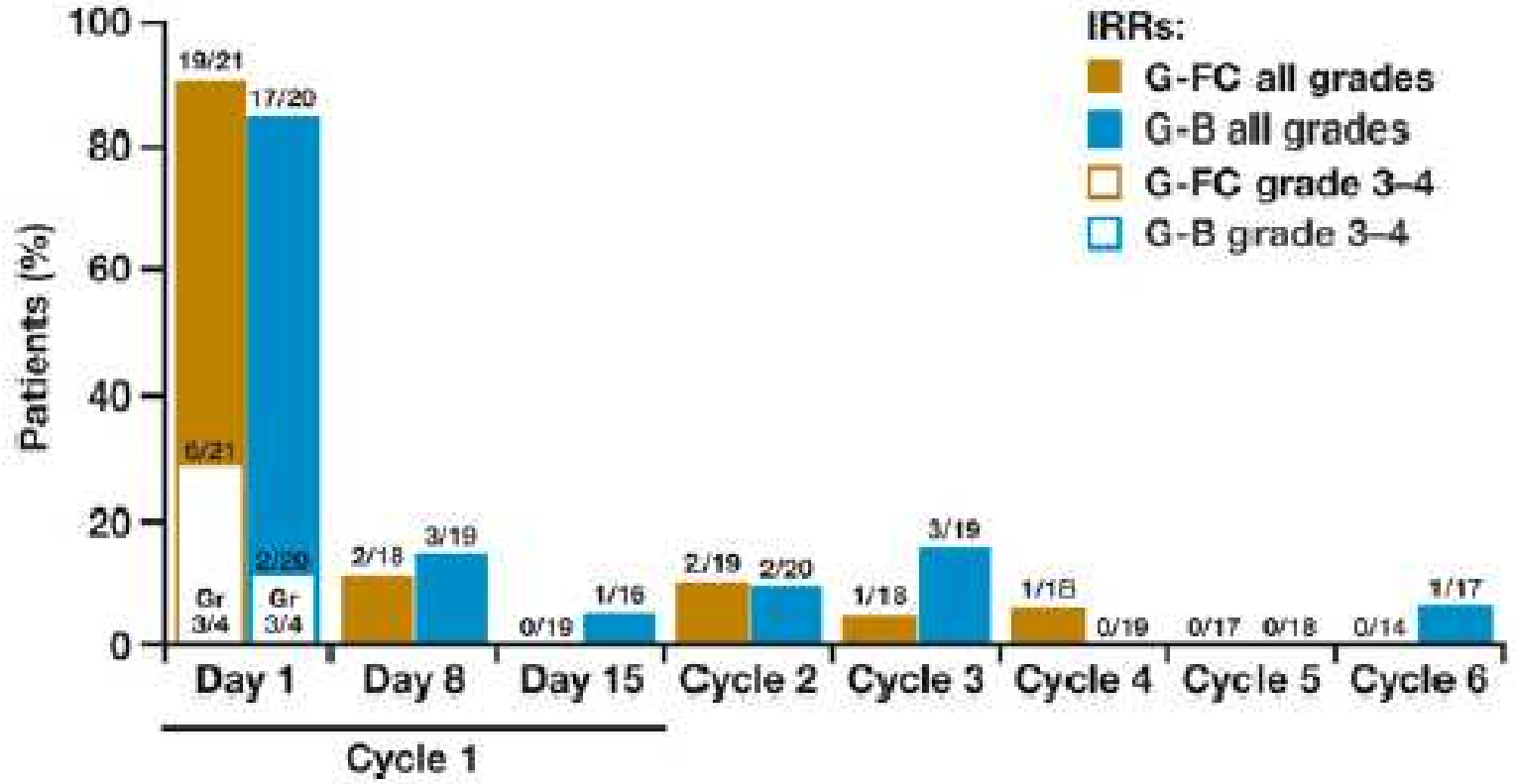
	333	316	310	303	261	214	170	144	115	71	34	14	2	0
	330	320	314	305	255	203	169	138	105	61	27	8	0	0

Obinutuzumab



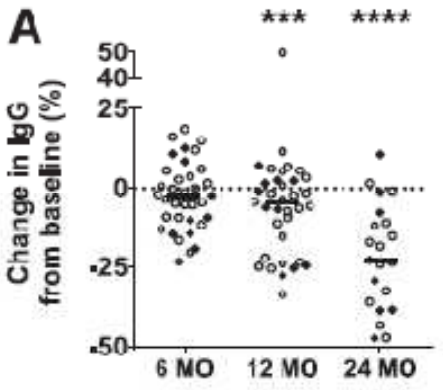
ADCC, antibody-dependent cell-mediated cytotoxicity
CDC, complement-dependent cytotoxicity
Mössner E, *et al. Blood* 2010; 115:4393–4402

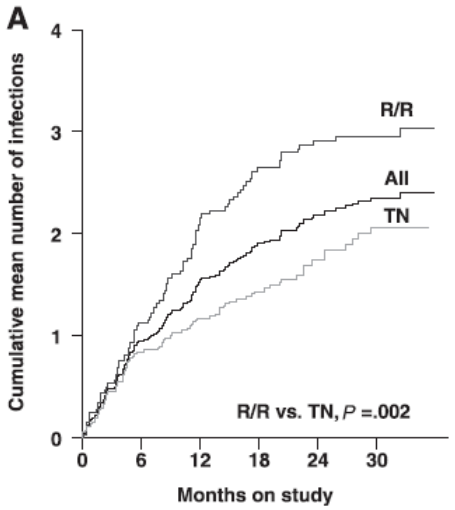
Obinutuzumab : effet 1ère perfusion



Ibrutinib (1)

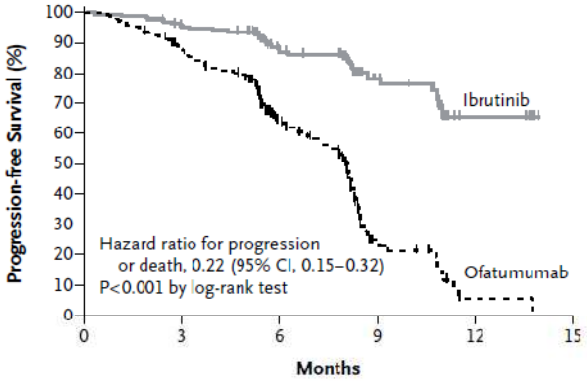
- Fibrillation atriale : 5-8%
  - Augmente avec l'exposition → 15% à 2 ans ?
  - Problème liés à la prise en charge
    - Poursuite du traitement ?
    - Anticoagulation ?
- Saignement
  - Très fréquent
  - Forme grave 1-5%
- Diarrhée
- Infection
  - Dosage immunoglobulines
  - Pneumocystose
  - Aspergillose et autres maladie fongiques
  - LEMP

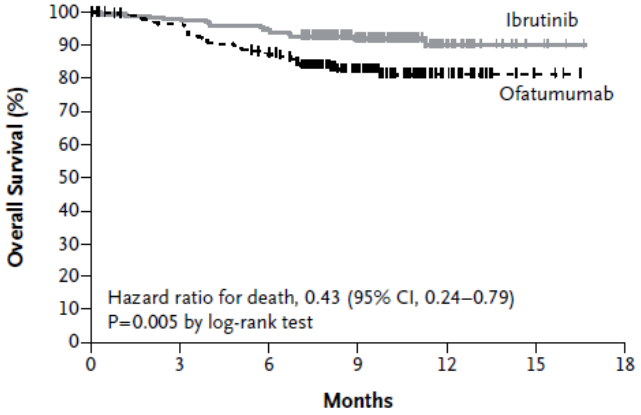




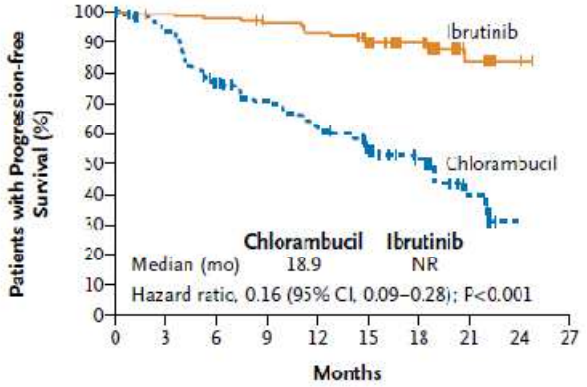
Ibrutinib (2)

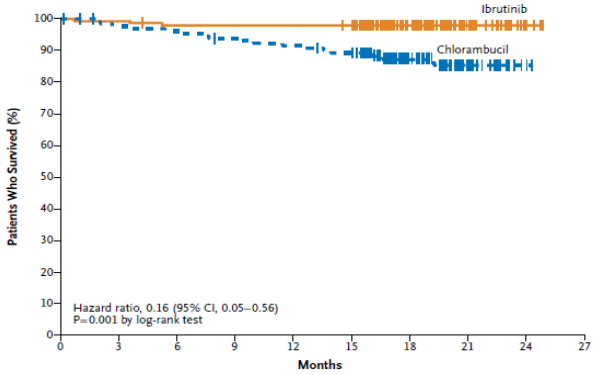
Rechute
Ofatumumab versus Ibrutinib



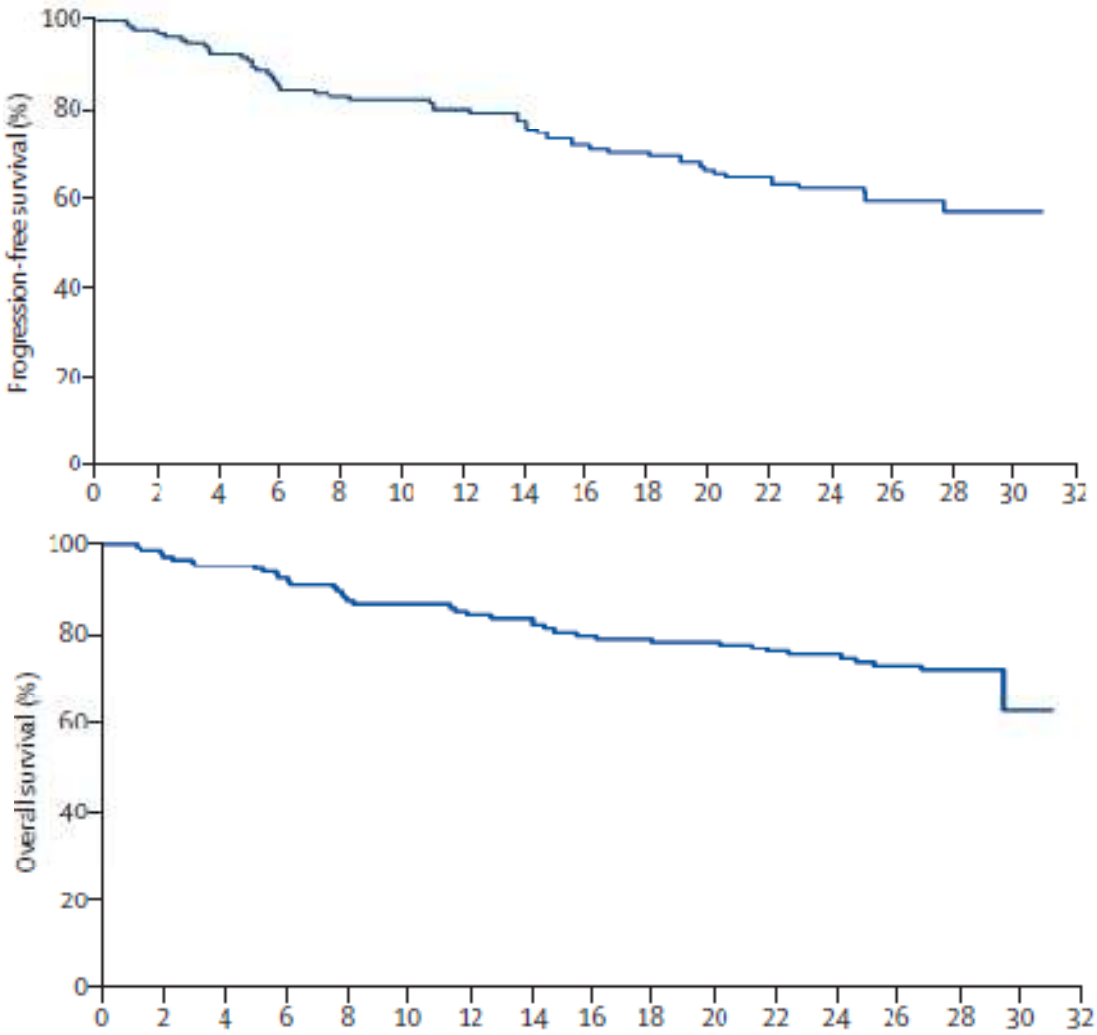


Première ligne
Chlorambucil versus Ibrutinib





Ibrutinib : patients del17p/p53mut



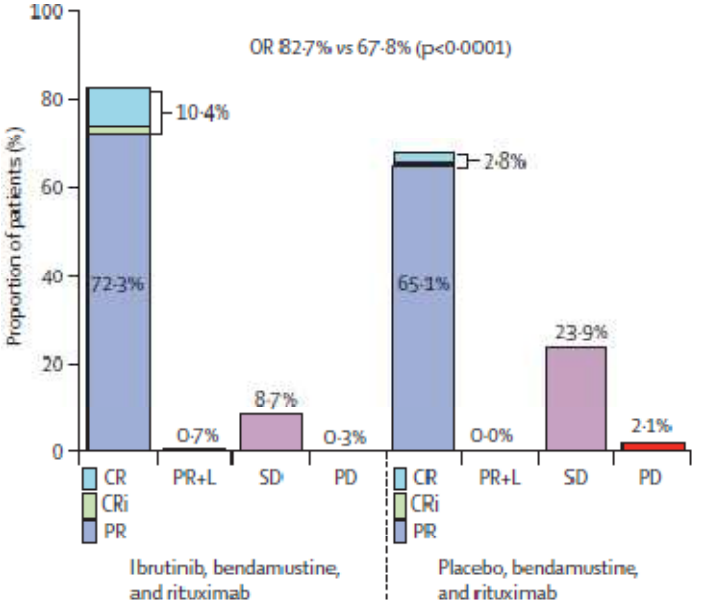
Combinaisons

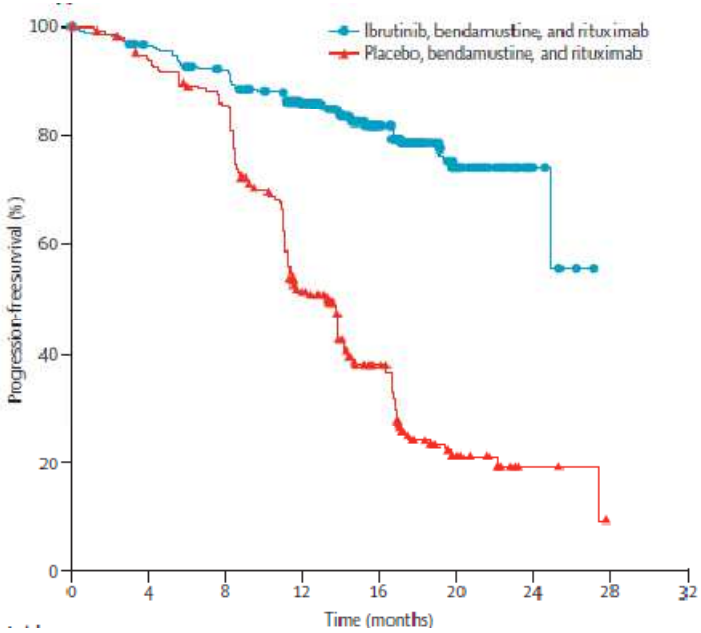
- B-R versus B-R ibrutinib
- Pas de différence de toxicité :
  - infectieuse
  - hématologique

	Ibrutinib, bendamustine, and rituximab (n=287)	Placebo, bendamustine, and rituximab (n=287)
Any grade bleeding	89 (31%)	42 (15%)
Grade 1–2 bleeding events		
Haematoma	23 (8%)	3 (1%)
Contusion	22 (8%)	9 (3%)
Epistaxis	17 (6%)	9 (3%)
Ecchymosis	9 (3%)	2 (1%)
Petechiae	8 (3%)	1 (<1%)
Major haemorrhage*	11 (4%)	5 (2%)

Data are n (%). *Major haemorrhage includes grade ≥3 haemorrhage, central nervous system haemorrhage, and serious bleeding events of any grade.

Table 3: **Bleeding-related events**



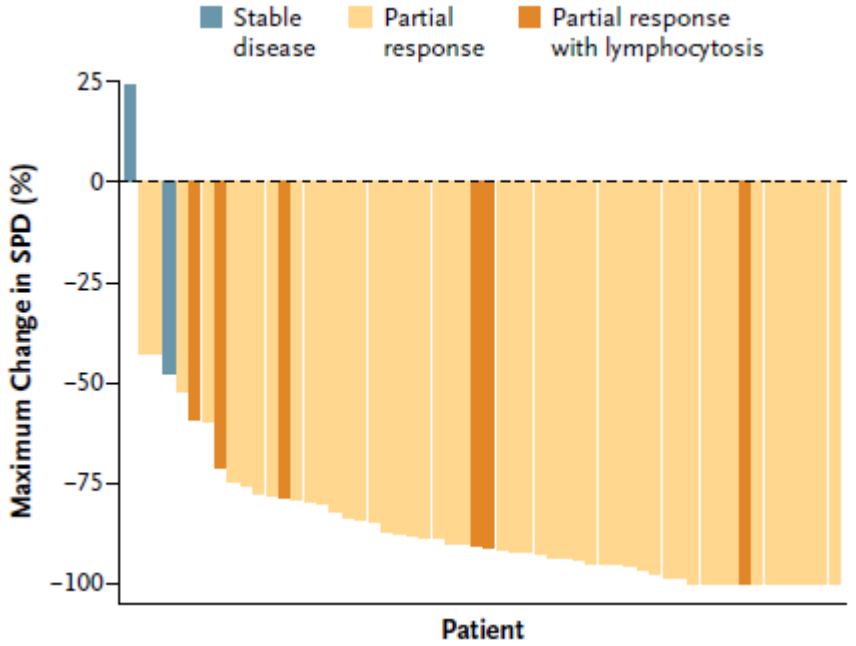


Acalabrutinib

- Inhibiteur de BTK de nouvelle génération
- Tolérance :
  - Pas de fibrillation atriale
  - Pas de saignement de grade 3-5
- Efficacité

Table 2. Adverse Events.*

Adverse Event	All Grades†	Grades 3–4
Headache	26 (43)	0
Diarrhea	24 (39)	1 (2)
Increased weight	16 (26)	1 (2)
Pyrexia	14 (23)	2 (3)
Upper respiratory tract infection	14 (23)	0
Fatigue	13 (21)	2 (3)
Peripheral edema	13 (21)	0
Hypertension	12 (20)	4 (7)
Nausea	12 (20)	0
Contusion	11 (18)	0
Arthralgia	10 (16)	1 (2)
Petechiae	10 (16)	0
Decreased weight	10 (16)	0



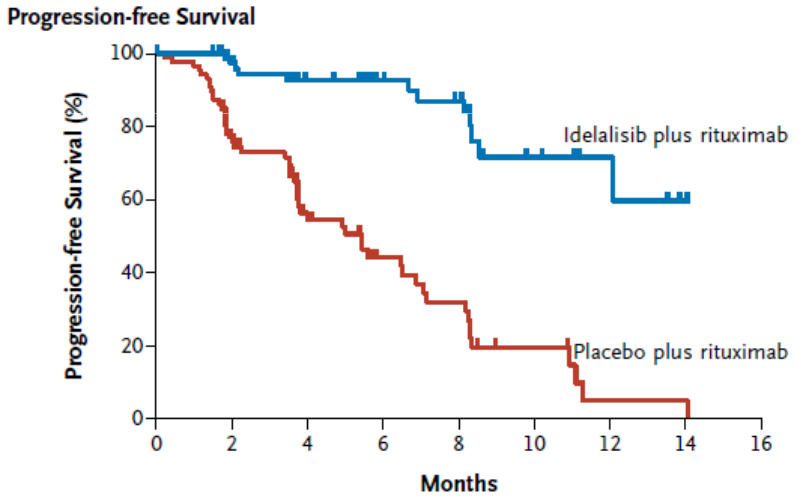
Idelalisib (1)

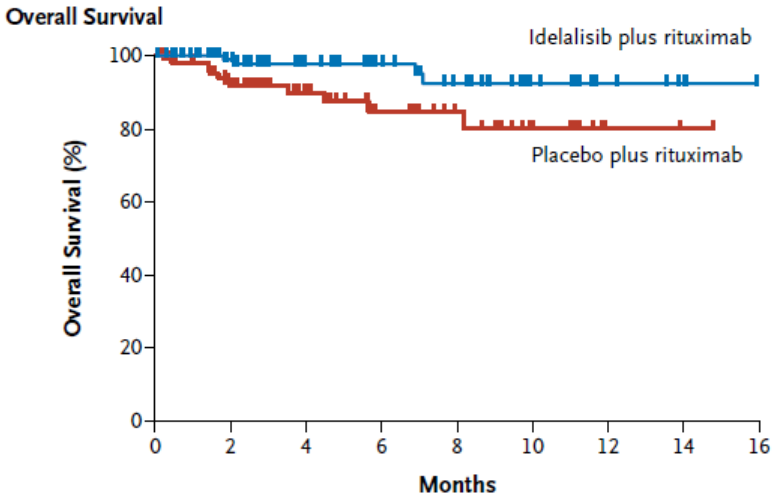
- Hématotoxicité
- Hépatotoxicité
- Diarrhée
- Pneumonie
- Cutanée
- Infection
  - CMV
  - Pneumocystose
  - Autre ?
  - Rôle direct ou indirect ?

Hematologic, n (%)		
Neutrophils, decreased	34 (53)	18 (28)
Leukocytes, decreased	19 (31)	4 (6)
Hemoglobin, decreased	15 (23)	2 (3)
Lymphocytes, decreased	13 (21)	3 (5)
Platelets, decreased	9 (14)	1 (2)
Nonhematologic, n (%)		
ALT/AST, increased	43 (67)	15 (23)
Alkaline phosphatase, increased	22 (34)	0 (0)
Sodium, decreased	19 (30)	2 (3)
Bilirubin, increased	16 (25)	0 (0)
Creatinine, increased	11 (17)	1 (2)
Potassium, decreased	10 (16)	1 (2)

	Grade	
Preferred term	**Any**	**≥3**
TEAEs, n (%)	64 (100)	49 (77)
Diarrhea and/or colitis	41 (64)	27 (42)
Only diarrhea	25 (39)	11 (17)
Only colitis	3 (5)	9 (14)
Pyrexia	27 (42)	2 (3)
Nausea	24 (38)	1 (2)
Rash*	37 (58)	8 (13)
Chills	23 (36)	0 (0)
Cough	21 (33)	1 (2)
Fatigue	20 (31)	0 (0)
Pneumonia	18 (28)	12 (19)
Dyspnea	16 (25)	4 (6)
Headache	15 (23)	0 (0)
Vomiting	14 (22)	2 (3)
Insomnia	13 (20)	0 (0)
Arthralgia	11 (17)	1 (2)
Constipation	11 (17)	0 (0)
Pruritus	11 (17)	1 (2)
Night sweats	10 (16)	0 (0)
Back pain	10 (16)	1 (2)
Urinary tract infection	10 (16)	4 (6)

Idelalisib (2)





Venetoclax (1)

- Toxicité hématologique
- Syndrome de lyse tumorale
  - Nécessité d'adaptation des modalités d'administration

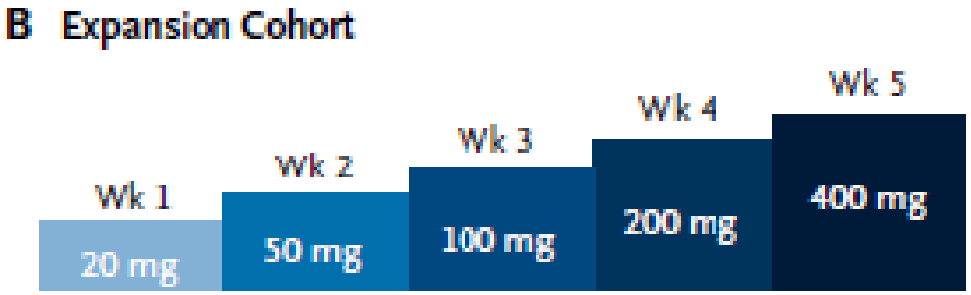
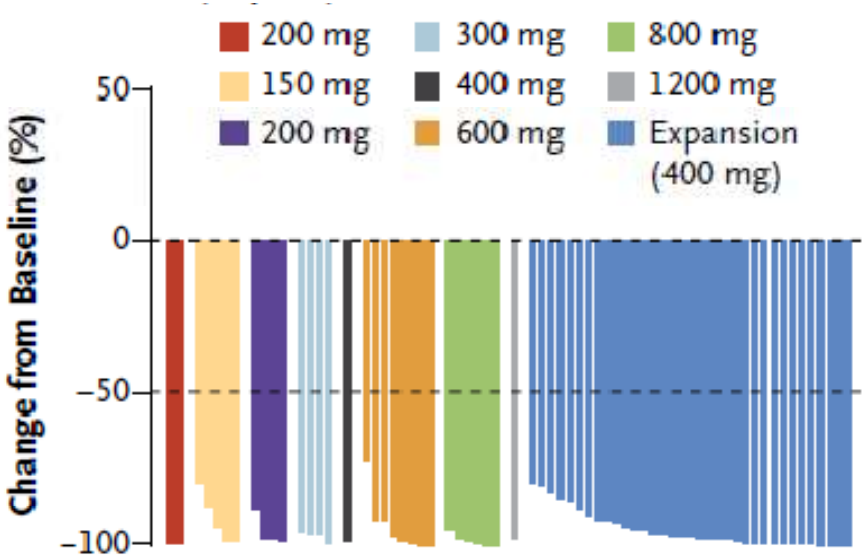
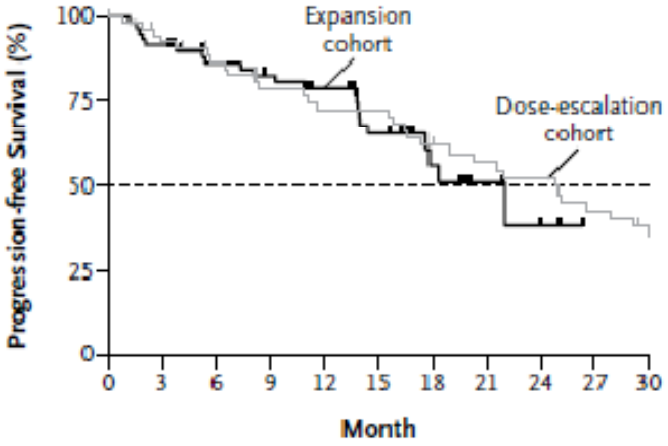


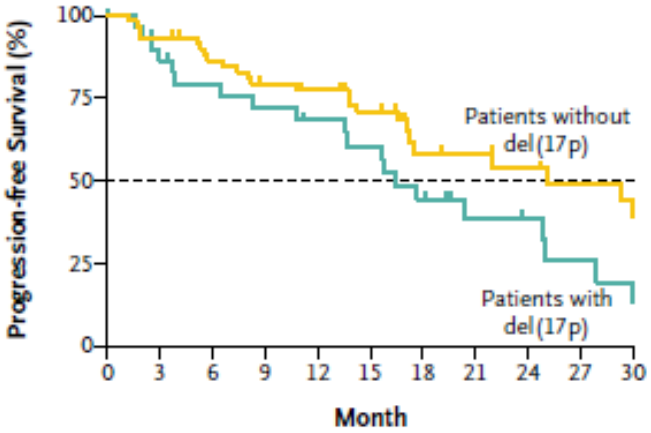
Table 2. Adverse Events and Serious Adverse Events in the 116 Study Patients.

Event	Any Grade	Grade 3 or 4
	no. of patients (%)	
Adverse event*		
Any	115 (99)	96 (83)
Diarrhea	60 (52)	2 (2)
Upper respiratory tract infection	56 (48)	1 (1)
Nausea	55 (47)	2 (2)
Neutropenia	52 (45)	48 (41)
Fatigue	46 (40)	4 (3)
Cough	35 (30)	0
Pyrexia	30 (26)	1 (1)
Anemia	29 (25)	14 (12)
Headache	28 (24)	1 (1)
Constipation	24 (21)	1 (1)
Thrombocytopenia	24 (21)	14 (12)
Arthralgia	21 (18)	1 (1)
Vomiting	21 (18)	2 (2)
Peripheral edema	18 (16)	0
Hyperglycemia	17 (15)	10 (9)
Serious adverse event†		
Any	52 (45)	
Febrile neutropenia	7 (6)	
Pneumonia	5 (4)	
Upper respiratory tract infection	4 (3)	
Immune thrombocytopenia	3 (3)	
Tumor lysis syndrome	3 (3)	
Diarrhea	2 (2)	
Fluid overload	2 (2)	
Hyperglycemia	2 (2)	
Prostate cancer	2 (2)	
Pyrexia	2 (2)	

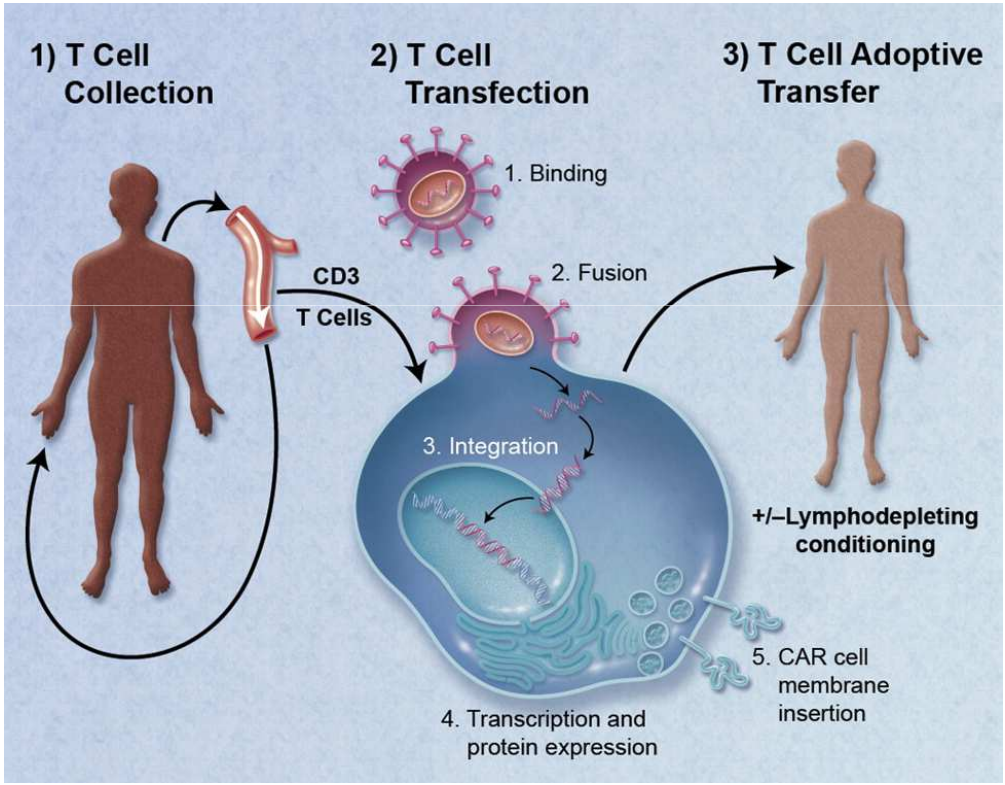
Venetoclax (2)

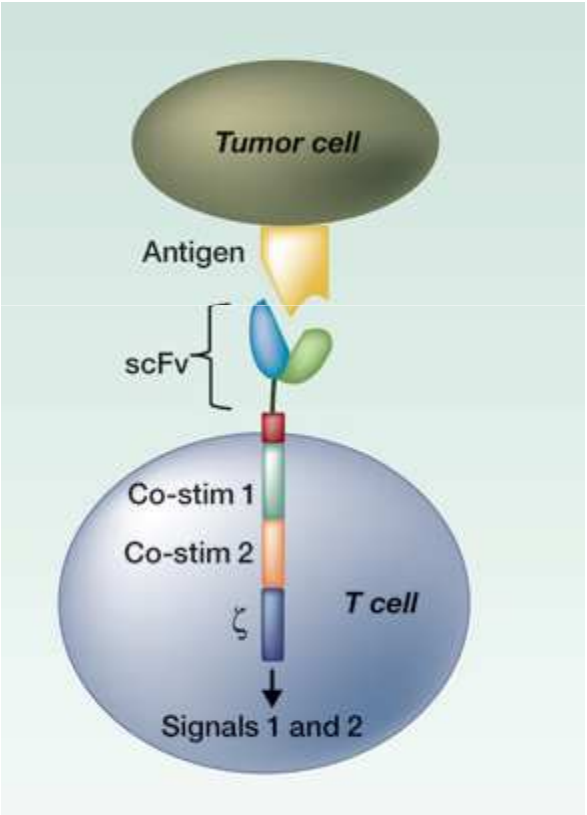




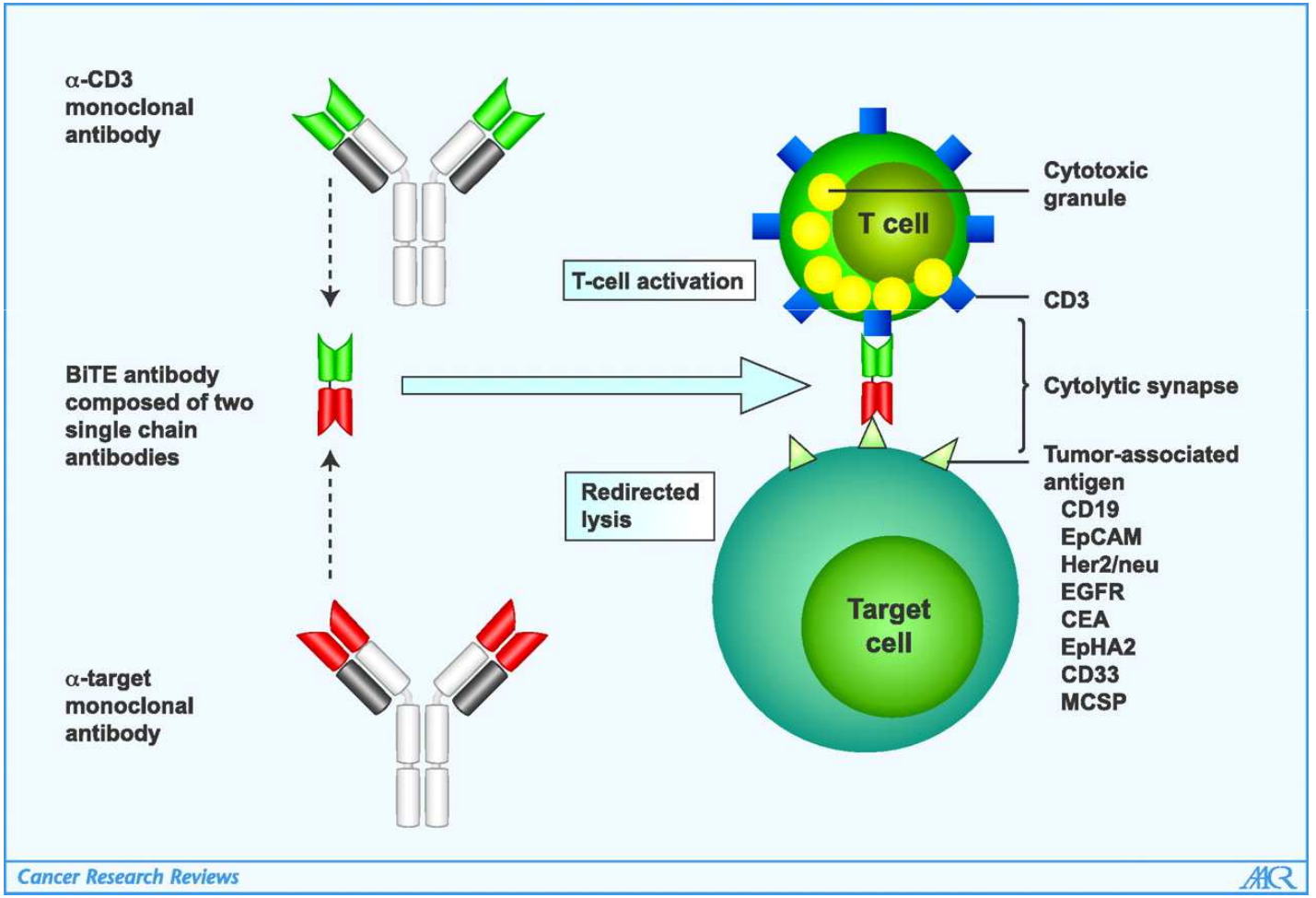


CAR-T


1) T Cell Collection
2) T Cell Transfection
3) T Cell Adoptive Transfer
1. Binding
2. Fusion
CD3
T Cells
3. Integration
+/–Lymphodepleting conditioning
5. CAR cell membrane insertion
4. Transcription and protein expression

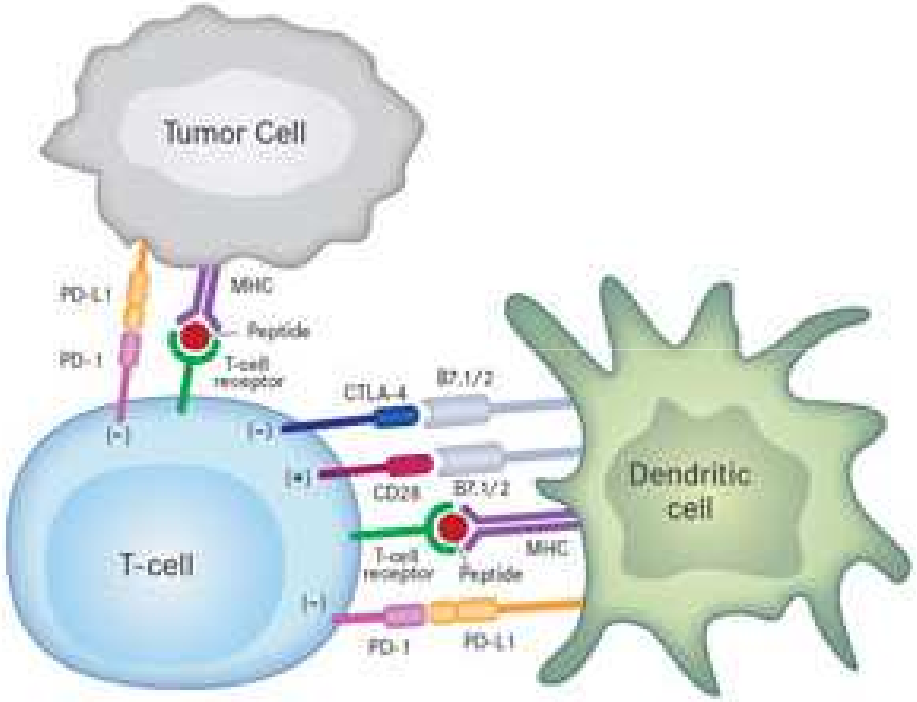

Tumor cell
Antigen
scFv
Co-stim 1
Co-stim 2
ζ
T cell
Signals 1 and 2

Anticorps bi-spécifiques

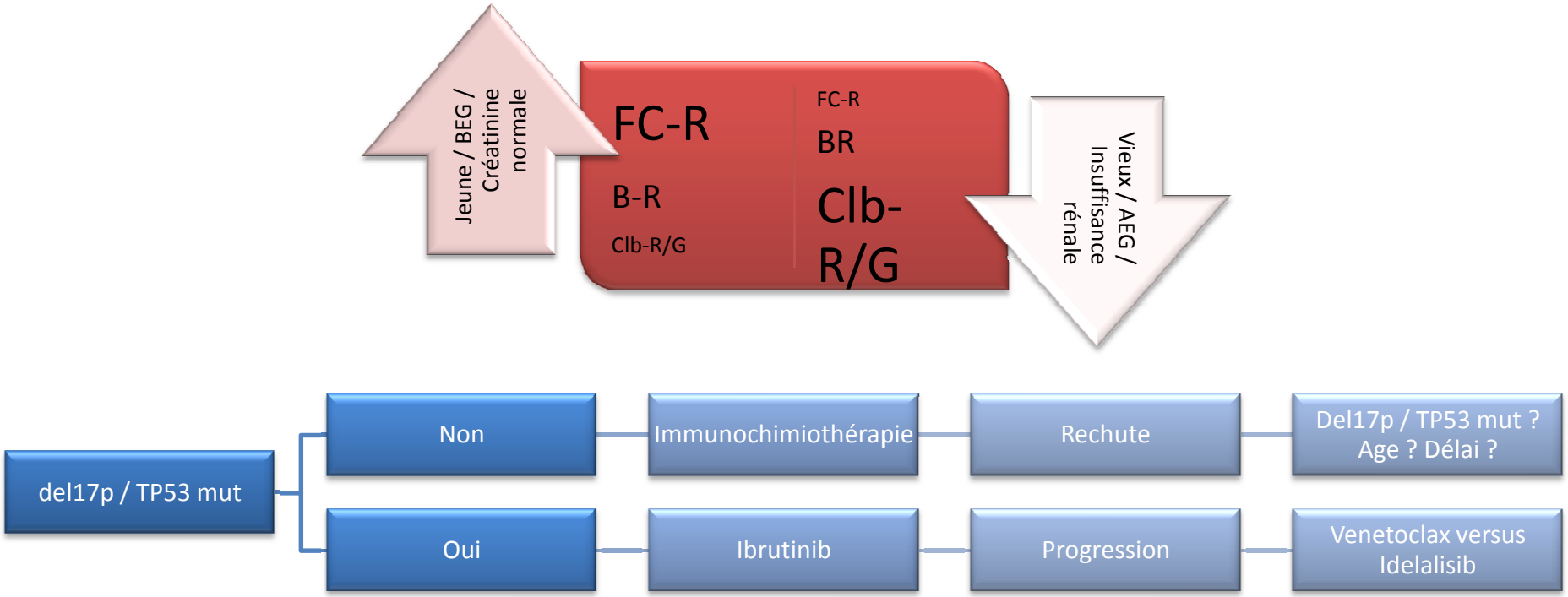


Inhibiteurs du checkpoint immunologique

- Anti-PD1, PDL1, CTLA4
- Success story : cancer solides, lymphomes, autres hémopathies
- Toxicité : induction de réactions immunologiques
  - Majorée en cas de combinaisons



Algorithme de prise en charge



De nouveaux paradigmes

- La mise en évidence d'un biomarqueur pronostic et d'un traitement conditionnel à celui-ci rend nécessaire une réorganisation des plateformes biologiques et des pratiques
- Des traitements chemo-free mais pas « side effect-free »
- Des traitements jusqu'à progression
- Des coûts