Protocole européen ALLTogether (A2G)

Cytogenetique

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A novel integrated cytogenetic and genomic classification refines risk stratification in pediatric acute lymphoblastic leukemia

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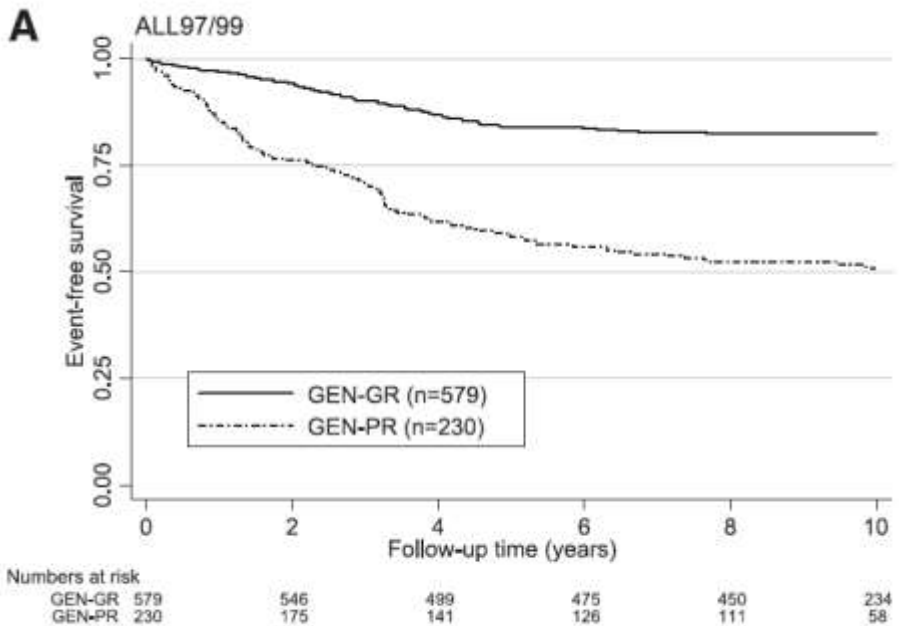
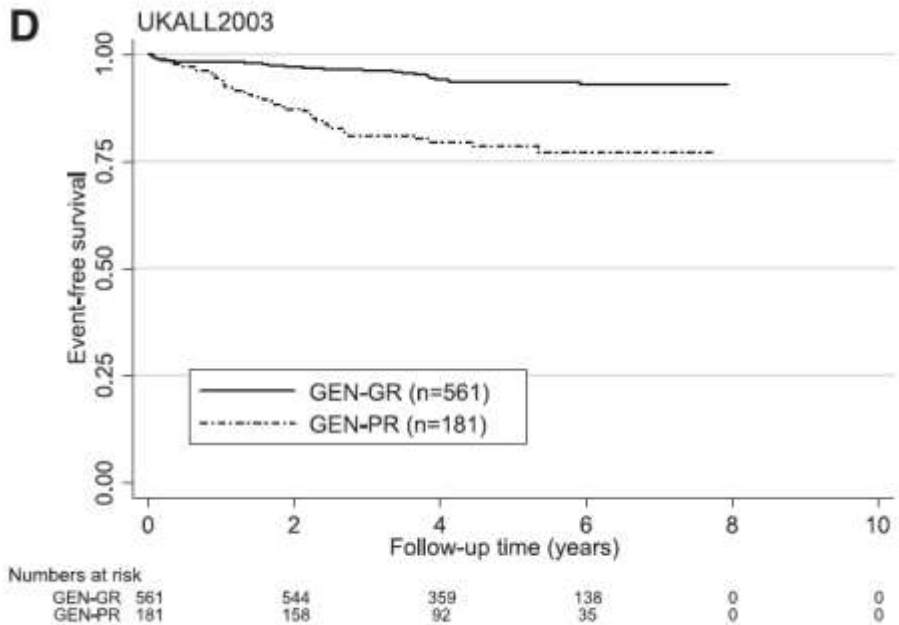
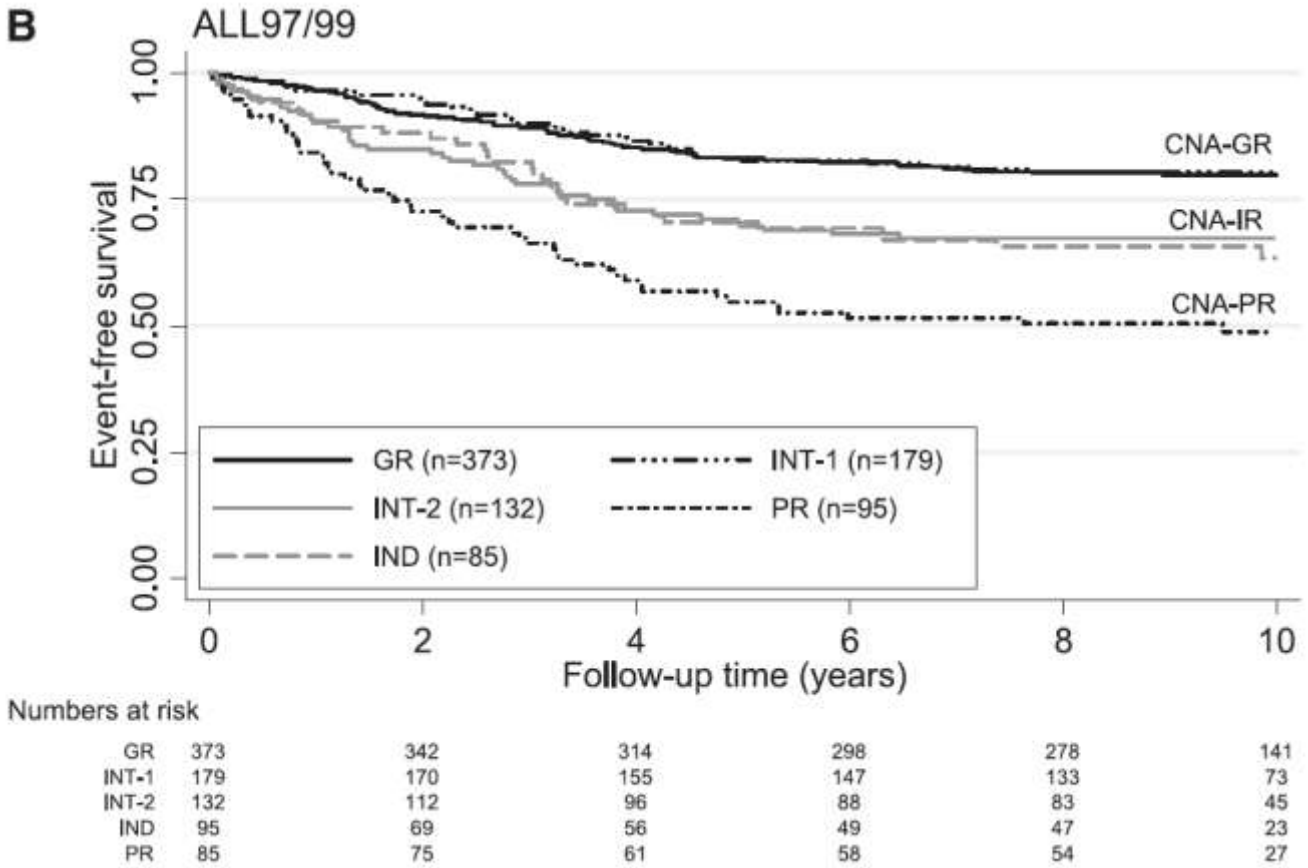




A Unique CNA combinations

IKZF1	*CDKN2A/B*	PAR1	*BTG1*	*EBF1*	*PAX5*	*ETV6*	*RB1*
0	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0
0	1	0	0	0	0	0	0
0	1	0	0	0	1	0	0
..	..	..	..	..	..	..	..

B



Numbers at risk

GR	373	342	314	298	278	141
INT-1	179	170	155	147	133	73
INT-2	132	112	96	88	83	45
IND	95	69	56	49	47	23
PR	85	75	61	58	54	27

Moorman AV et al, Blood, 124(9),1434-1444, 2014

GEN-GR

CYTO-GR

or CNA group A w/o CYTO-HR

Good risk genetic abnormalities

Good risk cytogenetic abnormalities
- *ETV6-RUNX1*/t(12;21)(p13;q22)
- High Hyperdiploidy (51-65 chromosomes)

Good risk copy number alteration profiles
- No deletion of *IKZF1, CDKN2A/B, PAR1, BTG1, EBF1, PAX5, ETV6* or *RB1*
- Isolated deletions of *ETV6, PAX5 or BTG1*
- *ETV6* deletions with a single additional deletion of *BTG1, PAX5 or CDKN2A/B*

GEN-PR

CYTO-HR

or CNA group B w/o CYTO-GR

Poor risk genetic abnormalities

High risk cytogenetic subgroups
- t(9;22)(q34;q11)/*BCR-ABL1*
- *MLL*/11q23 translocation
- Near haploidy (<30 chromosomes)
- Low hypodiploidy / near triploidy (30-39 / 60-78 chromosomes)
- Intrachromosomal amplification of chromosome 21 (iAMP21)
- t(17;19)(q23;p13)/*TCF3-HLF*

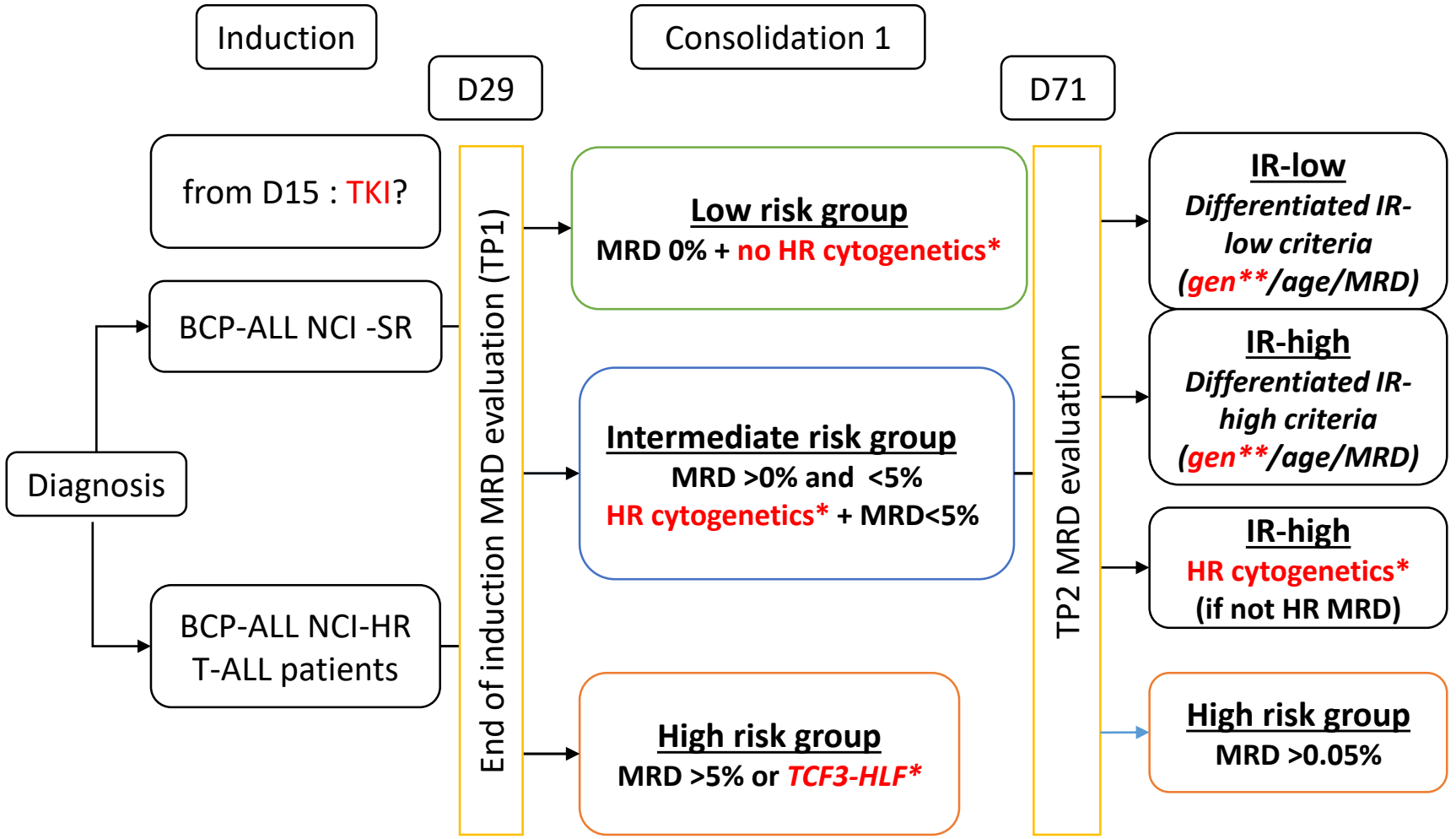
Intermediate and poor risk copy number alteration profiles
- Any deletion of *IKZF1, PAR1, EBF1* or *RB1*
- All other copy number alteration profiles not mentioned above.

Patients are classified hierarchically with cytogenetic abnormalities taking precedence over copy number alteration profiles.

Definition of novel genetic risk groups for pediatric BCP-ALL.

Moorman AV et al, Blood, 124(9),1434-1444, 2014

Overview of the risk stratification algorithm for the ALLtogether trial



High risk cytogenetics** : ***KMT2A/MLL **gene fusions, near haploidy, low hypodiploidy, iAMP21,t(17;19)/*TCF3-HLF*** **and *ABL*-class rearrangements affecting *ABL1, ABL2, PDGFRB* and *CSF1R*** (except *BCR-ABL1* which are excluded from the study)

*** gen : genetics* including primary good risk *cytogenetics* abnormalities (HeH, ETV6-RUNX1) and *CNA* (Copy Number Alterations) such as *IKZF1* deletion***

ALLTogether and Cytogenetics : conclusion

- Démarrage en France prévu en octobre 2021
- LAL de 1 à 18 ans
- Cytogénétique obligatoire au diagnostic
- Diagnostic de LAL B autre avant J8 (15% des LAL B)
- Diagnostic de LAL B de type ABL-class (indication d'Imatinib) :
  - avant J15 par FISH en local (subvention demandée par Pr André Baruchel) :

    3 sondes de type séparation : ABL1, ABL2, PDGFRB/CSF1R
  - Confirmation (précision) par RNA-seq (Dr Aurélie Caye/ Pr Hélène Cavé)
- Responsables en France :
  - pour la Cytogénétique : Dr Wendy Cuccuini / Dr Marina Lafage
  - pour la Biologie : Pr Hélène Cavé
  - pour la Clinique : Pr Yves Bertrand / Pr André Baruchel