7th INTERNATIONAL SYMPOSIUM ON ACUTE PROMYELOCYTIC LEUKEMIA

PML and *RARA* mutations in relapsed Acute Promyelocytic Leukemia

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Rome, September 25, 2017

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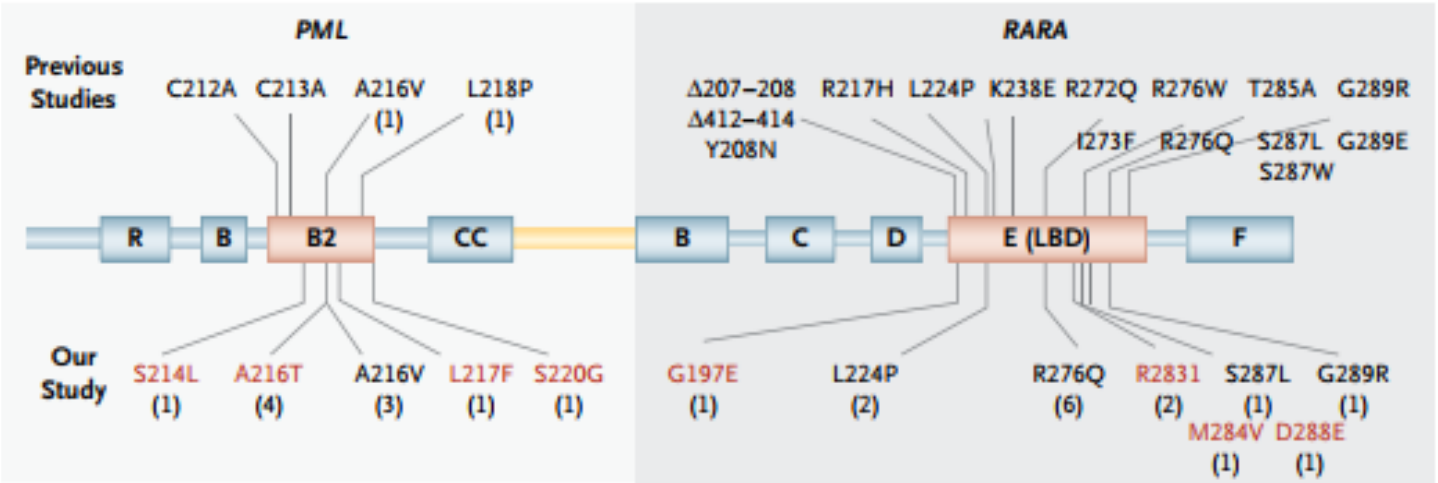
PML and *RARA* mutations associated to therapy-resistance in APL

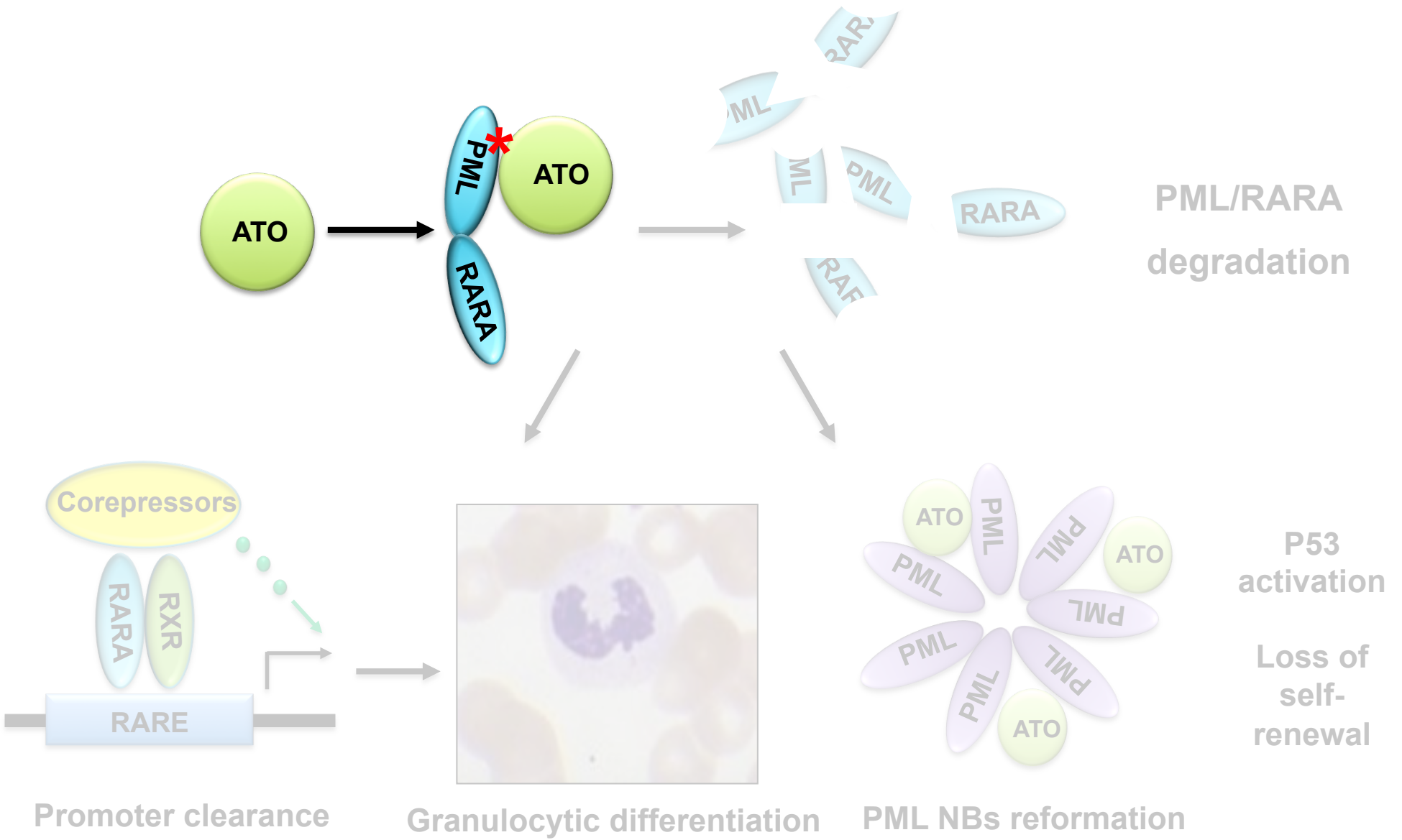
- *PML* mutations within the B2 domain of *PML/RARA* confer ATO resistance
- ATRA resistance is associated to mutations in the ligand-binding domain of the *RARA* moiety of *PML/RARA*
- Mutations in *PML* and *RARA* genes have been described in up to 47% of relapsed APL patients

Goto E., *et al*, Blood 2011; Zhu H.H., *et al*, NEJM 2014; Chendamarai E., *et al*, Plos One 2015; Lou Y., *et al*, Ann Hematol 2015; Iaccarino L., *et al*, BJH 2016



Zhu H.H., *et al*, NEJM 2014

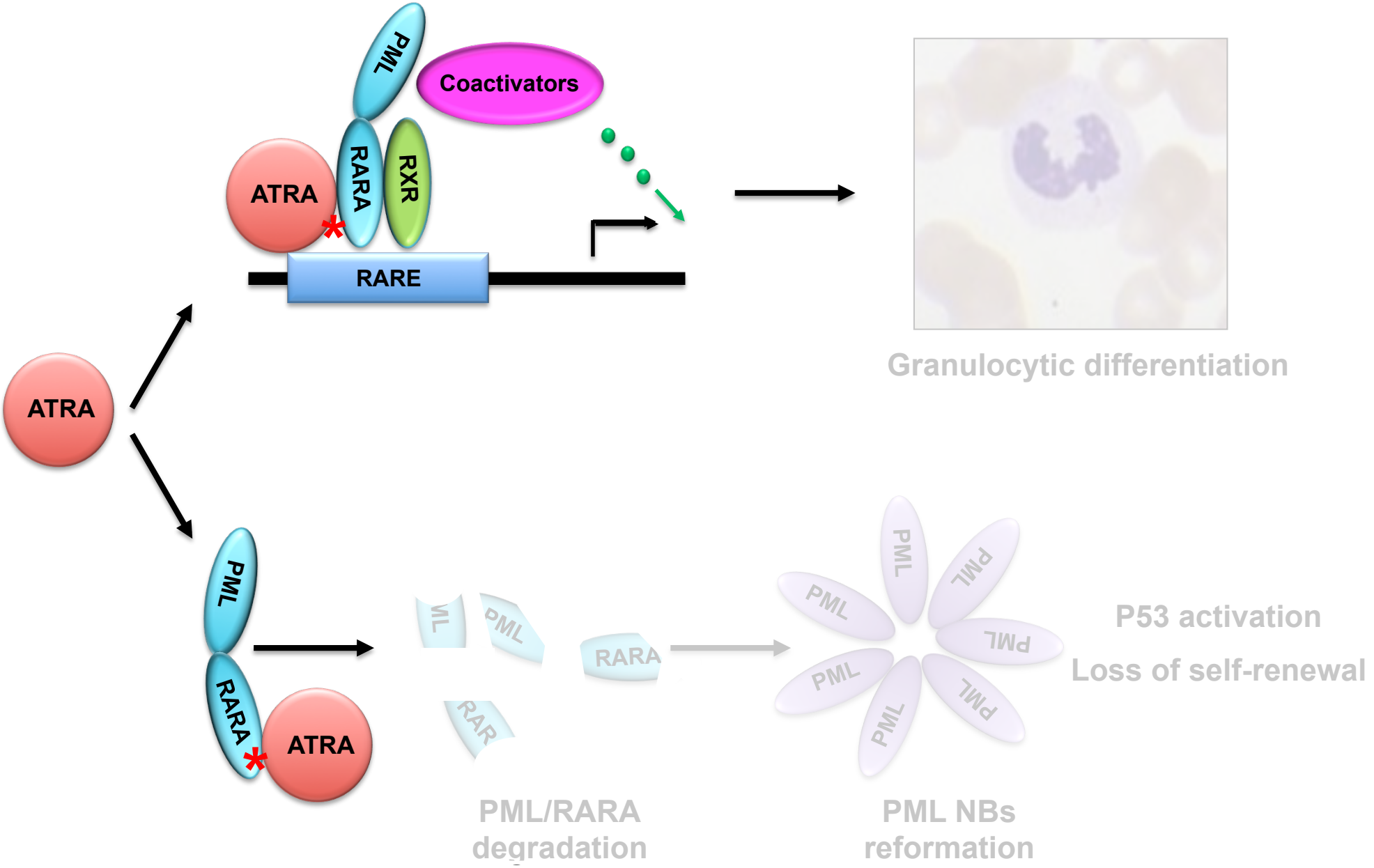
PML mutations in APL



* **mutations**

Jeanne M, *et al.*, Cancer Cell 2010

RARA mutations in APL



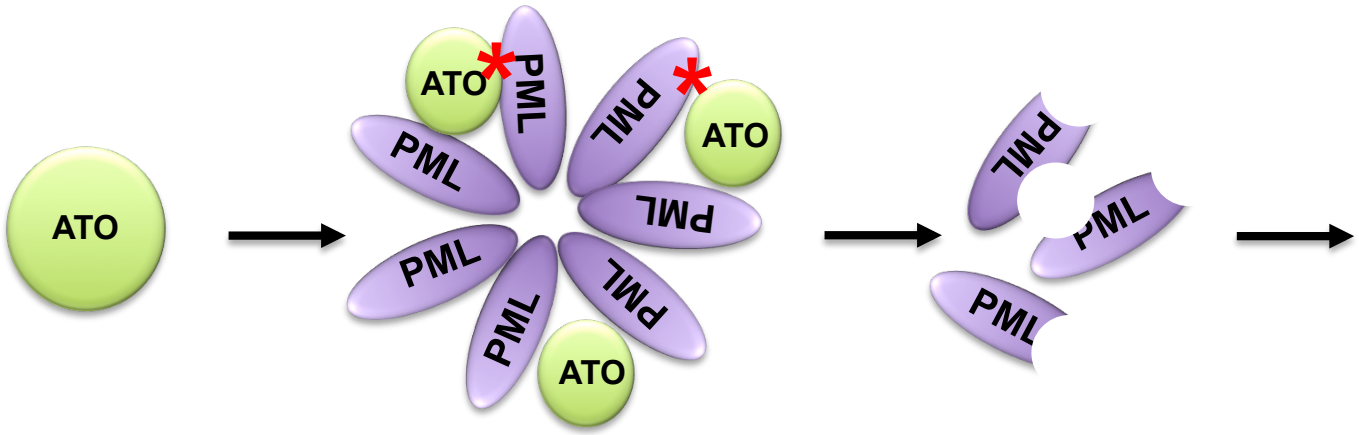
Ablain J., *et al*, Nat Med 2014

* **mutations**

PML and *RARA* mutations associated to therapy-resistance in APL

- Mutations in the **normal *PML*** allele have been proposed as additional mechanism associated with ATO resistance
- Two refractory APL cases with ***PML* A216V** mutation reported

Lehmann-Che et al, *NEJM* 2014; Iaccarino et al, *BJH* 2016



P53 activation

Loss of self-renewal

Jeanne M., *et al*, Cancer Cell 2010

* **mutations**

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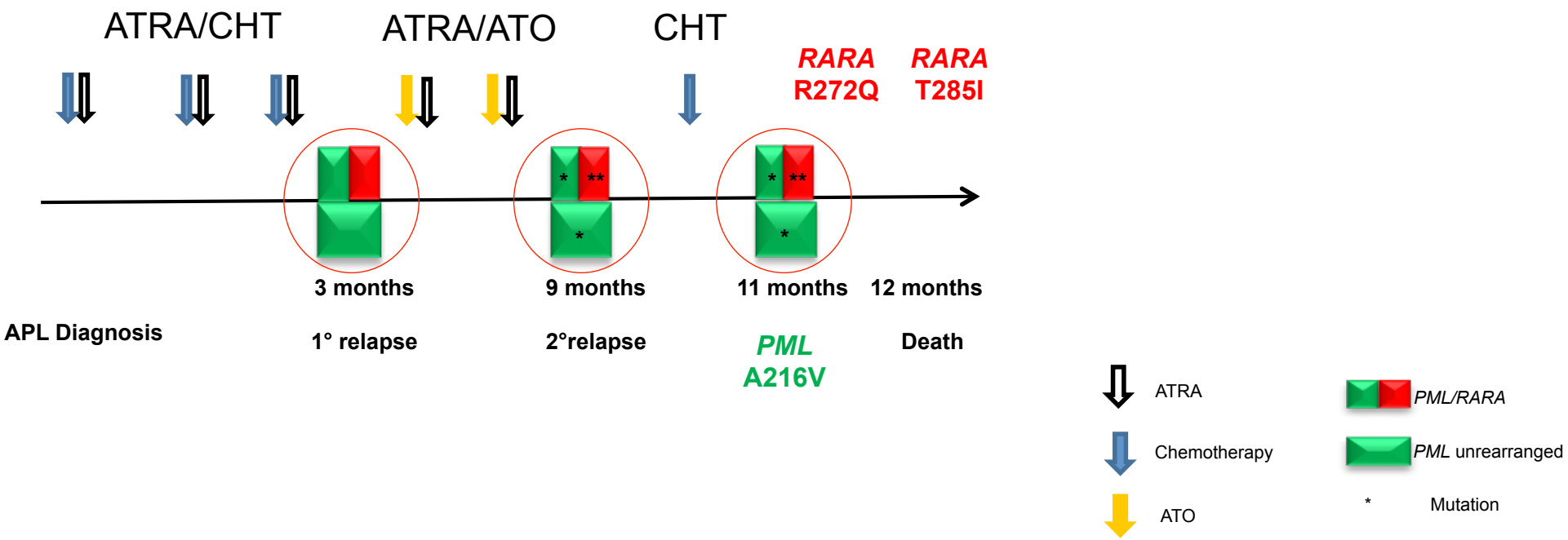


Iaccarino L., *et al*, BJH 2016

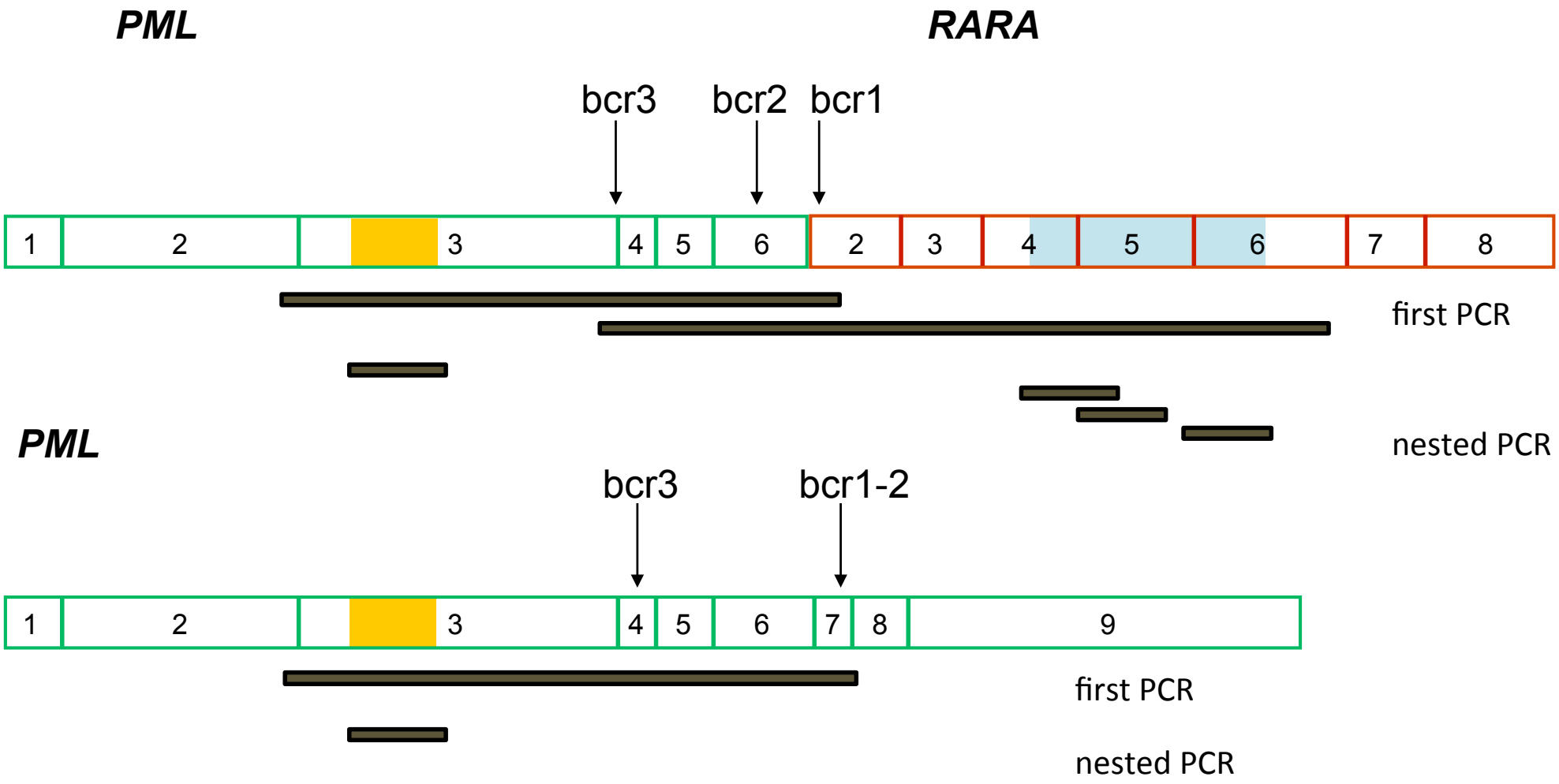
Aims of the study

- Design a sensitive NGS assay for detection of *PML* and *RARA* mutations predictive of treatment resistance in APL patients

- Investigate the time of onset of the mutations

PML/RARA mutational analysis by NGS

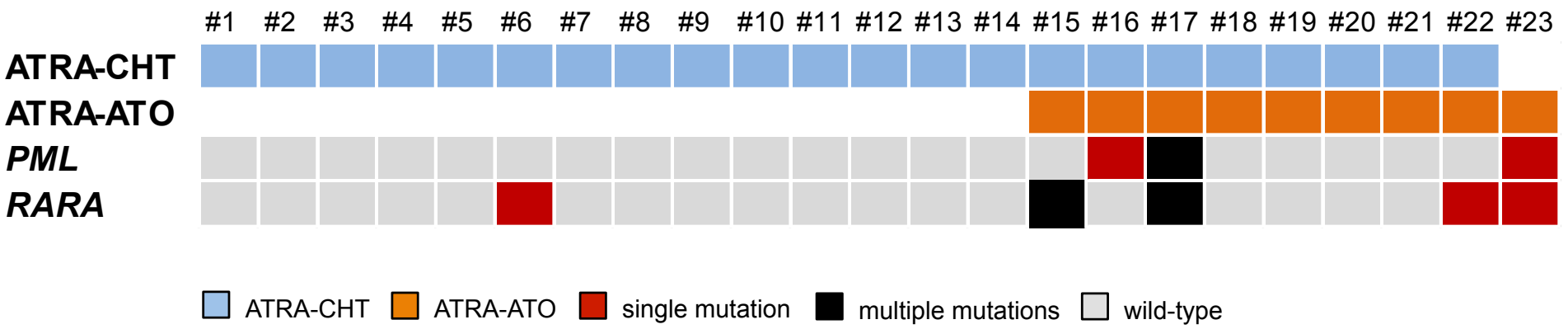
- **23** APL patients relapsing after ATRA-CHT (n=14) and/or ATRA-ATO (n=9)



Coverage (mean): *PML*: 33886X *per* base

RARA: 26051X *per* base

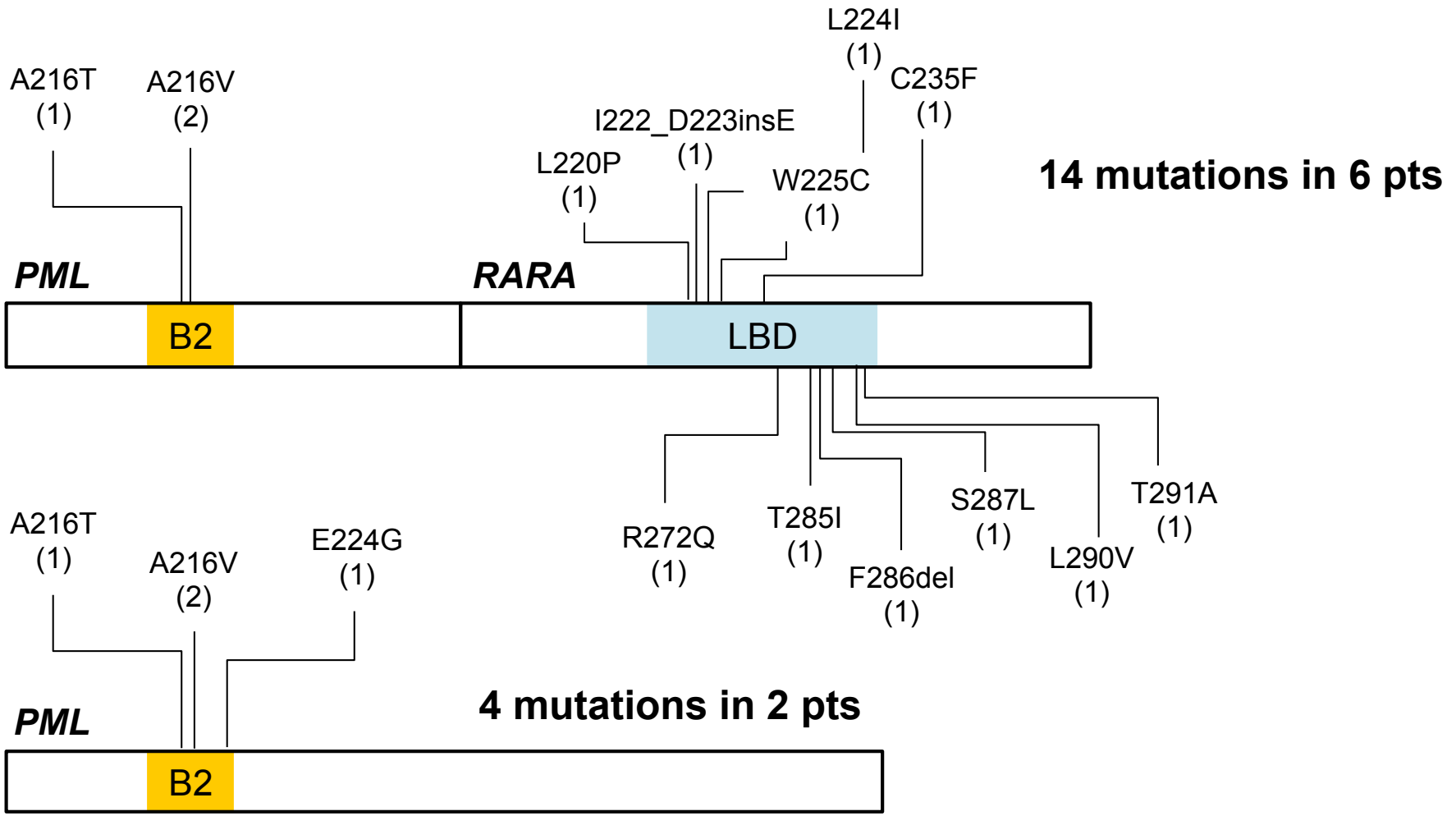
Results: mutational profile of *PML* and *RARA* at relapse



- 6/23 patients (**26%**) had at least one mutation in *PML* and *RARA* genes

- **No mutations** detectable at initial **diagnosis** in 3 of 6 available samples

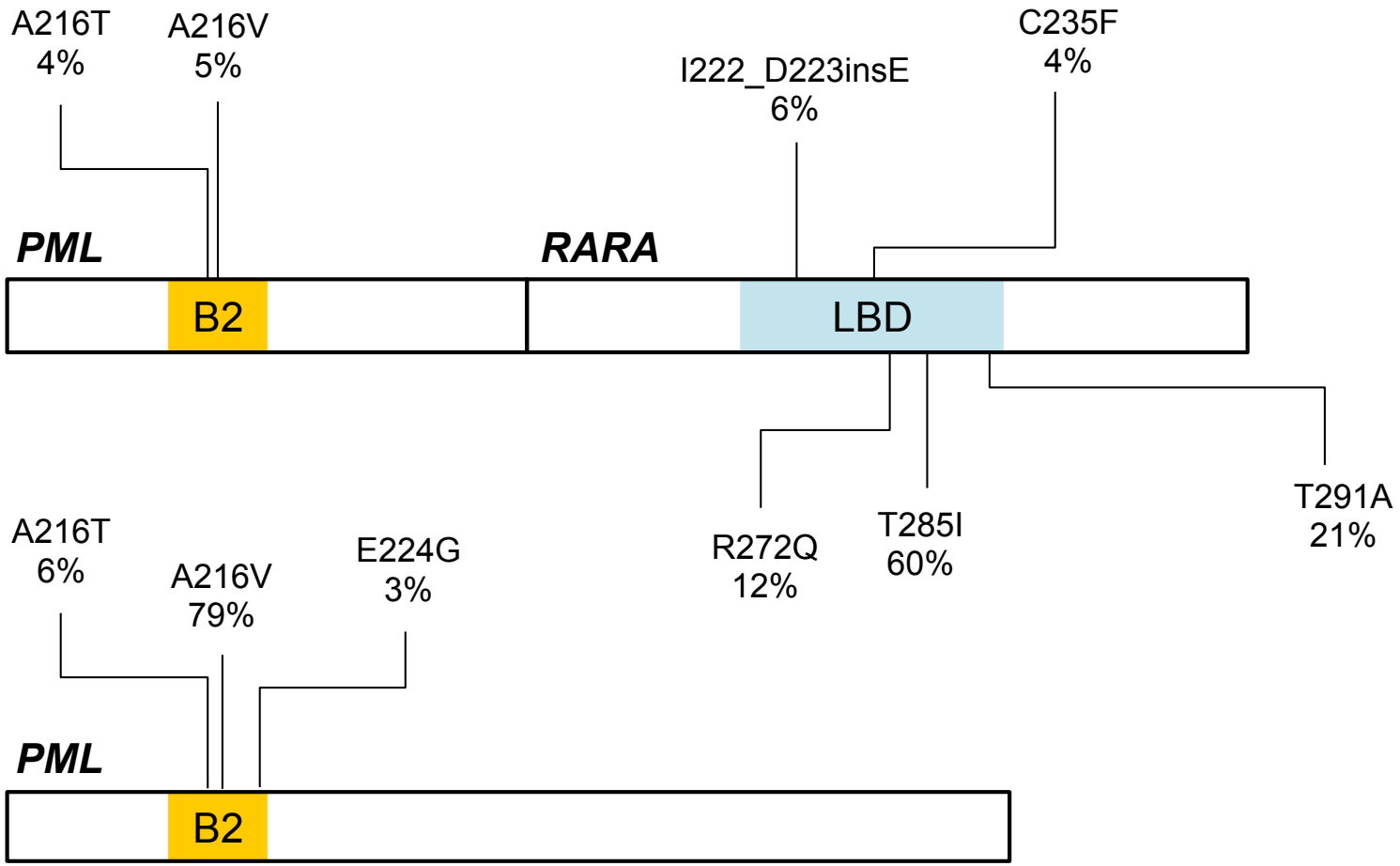
Results: location of mutations in *PML* and *RARA*



3% ≤ **VAF** ≤ 100%

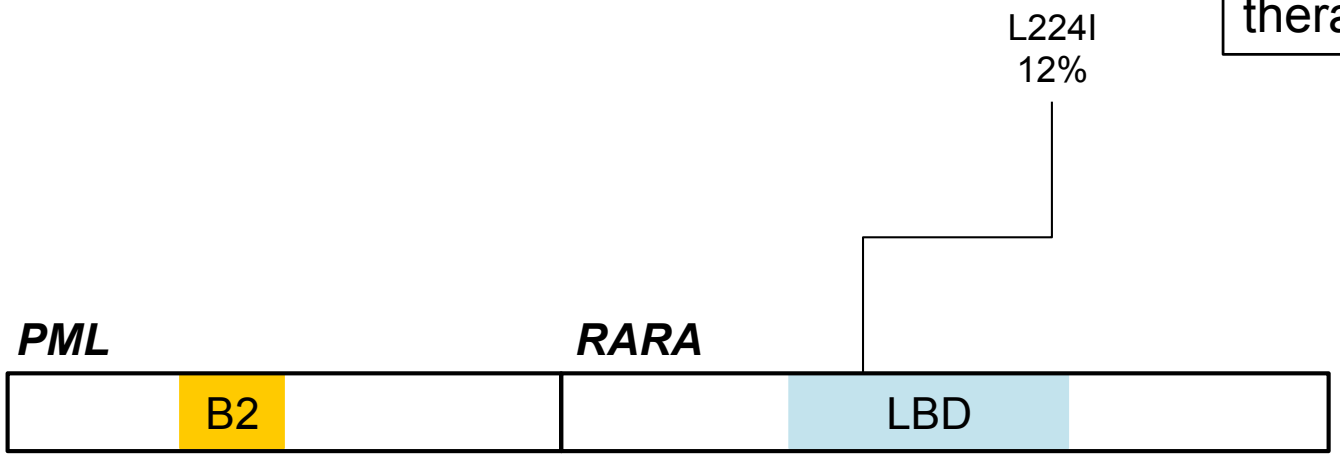
UPN 17

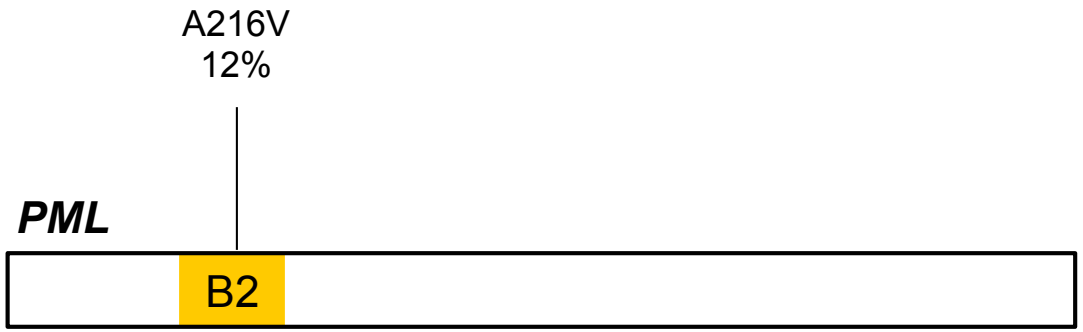
therapy-related APL with multiple relapses after ATRA-CHT and ATRA-ATO



UPN 23

de novo APL relapsed after ATRA-ATO as first-line therapy





Conclusions

- High prevalence of *PML* and *RARA* mutations in relapsed APL
- A sensitive method for *PML* and *RARA* mutational analysis is required to early detect resistant clones
- Screening of *PML* and *RARA* mutations may help to identify ATRA and/or ATO-resistant APL patients candidates to alternative treatment strategies

Acknowledgements

Tiziana Ottone

Mariadomenica Divona

Laura Cicconi

Serena Lavorgna

Valentina Alfonso

Claudia Ciardi

Syed Khizer Hasan

Adriano Venditti

Sergio Amadori

William Arcese

Maria Teresa Voso

Francesco Lo-Coco

Roberto Cairoli, Niguarda Hospital, Milan

Monica Bocchia, University of Siena

Annette Fasan

Constance Regina Bär

Torsten Haferlach

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Fondazione Umberto Veronesi PER IL PROGRESSO DELLE SCIENZE

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