HBsAg-positive patients and Rituximab treatment

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ECCMID 2013 - Berlin

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Disclosures

- Board, workshop participations or meeting invitations: Gilead, Bristol-Myers Squibb, Schering-Plough / MSD, Roche, Janssen, Mayoli-Spindler

- Sub-investigator in HCV or HBV trials: Bristol-Myers Squibb, Gilead, Roche, Schering-Plough / MSD, Boehringer Ingelheim, Tibotec, Vertex, Janssen

Mr M…

- Male, 55 years old
- Born in Paris
- No particular previous disease
- Multiple adenopathies and splenomegaly
- Biopsy of an intra-abdominal adenopathy (TDM guided)

➔ Lymphoma (diffuse large B-cell non-Hodgkin's lymphoma; stage IB - modified Ann Arbor staging system)

➔ Chemotherapy including Rituximab programmed (CHOP-R)

QUESTION 1

Recommendations

Screening for HBV before immunosuppression

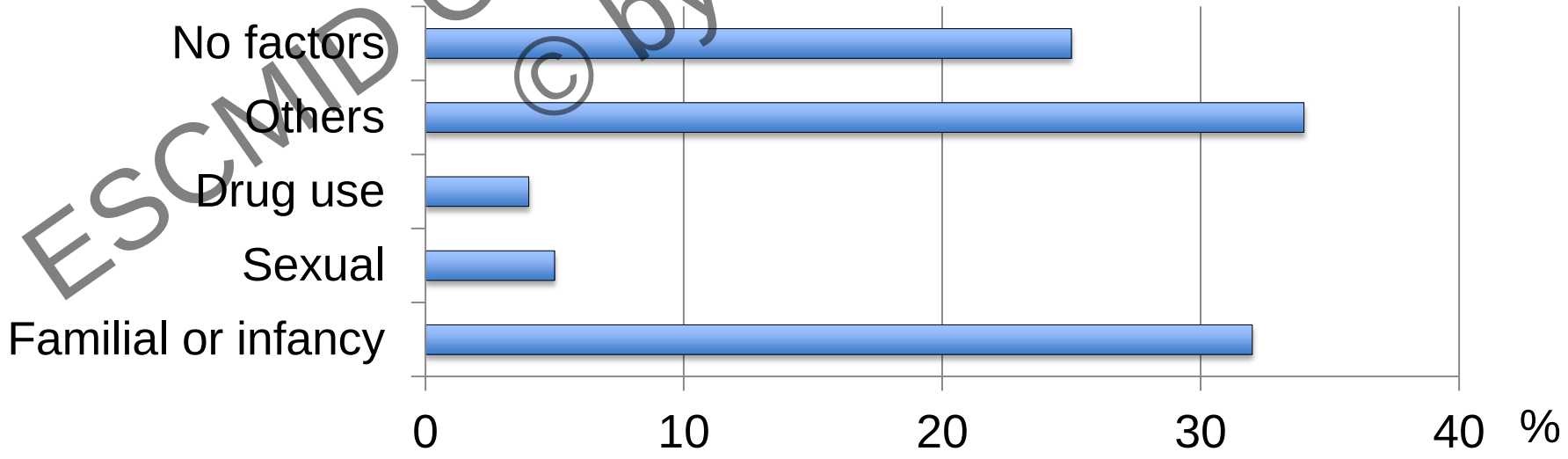
Center for Diseases Control[1] Institute of Medicine[2] European Association for the Study of Liver Diseases[3]	All patients
National Comprehensive Cancer Network[4]	If intensive immunosuppression
American Association for the Study of Liver Diseases[5]	High risk for HBV
American Society of Clinical Oncology[6]	High risk for HBV or highly immunosuppresive therapy (Rituximab, stem-cell transplantation…)

[1]Weinbaum et al. MMWR Recomm Rep 2008
[2]Colvin & Mitchell (eds). Institute of Medicine 2010
[3]EASL – Clinical Practice Guidelines. J Hepatol 2012
[4]www.nccn.org/professionals/physician_gls/pdf/infections.pdf
[5]Lok & McMahon. AASLD Practice Guidelines. Hepatology 2009
[6]Artz et al. J Clin Oncol 2010

Screening high risk patients for HBV?

- French survey for risk factors in HBsAg + patients and followed in reference centers (Jan 2008 – Aug 2009)
- Naïve of treatment at first referral (n=1,016)
  - Born in moderate-high endemic countries 78%
  - Born in low endemic countries 22%

Identified risk factors in HBsAg + patients born in low endemic countries



Larsen et al. BEHweb 2010

Recommendations
European Association for the Study of Liver Diseases (EASL)

"… all candidates for chemotherapy or immunosuppressive therapy should be screened for HBsAg and antiHBc prior to initiation of treatment (A1)"

Grading of evidence: A

- High quality (further research is very unlikely to change our confidence in the estimate of effect)

Grading of recommendation: 1

- Strong recommendation warranted (factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost)

EASL – Clinical Practice Guidelines. J Hepatol 2012

HBV screening in clinical practice
Prior chemotherapy

Retrospective study at the MD Anderson (January 2004 to September 2007

↓

10,729 new patients who received chemotherapy and fulfilled inclusion criteria

↓

1,787 (17%) underwent HBsAg and/or antiHBc screening
- 20% with HBV risk factors
- 71% treated with Rituximab

- Prevalence of HBsAg + 1.5% and isolated antiHBc + 7.4%
- Factors associated with HBV screening (multivariate analysis):
  - ✓ History of HBV infection
  - ✓ Hematologic malignancy
  - ✓ Rituximab treatment

Hwang et al. J Clin Oncol 2012

HBV screening in clinical practice
Prior immunosuppressive therapy

- Cross-sectional survey of members of the French National Society of Internal Medicine (Jan 2011)
- Do you performed a screening for HBV in patients receiving or prior receiving (n=290)?
  - Corticosteroids 44%
  - Immunosuppressive (except biotherapy) 67%
  - Biotherapy (Rituximab, antiTNFalpha…) 76%
  - No detection 19%

Terrier et al. Rev Med Interne 2012

In practice: HBV screening

- Recommendations for HBV screening highlights the need for HBV screening prior initiating chemotherapy, immunosuppressive or immunomodulatory agents, especially in patients receiving Rituximab
- Screening on high risk factor for HBV is insufficient
- Published surveys highlights also the need for improving the education of physicians regarding the risk of HBV reactivation

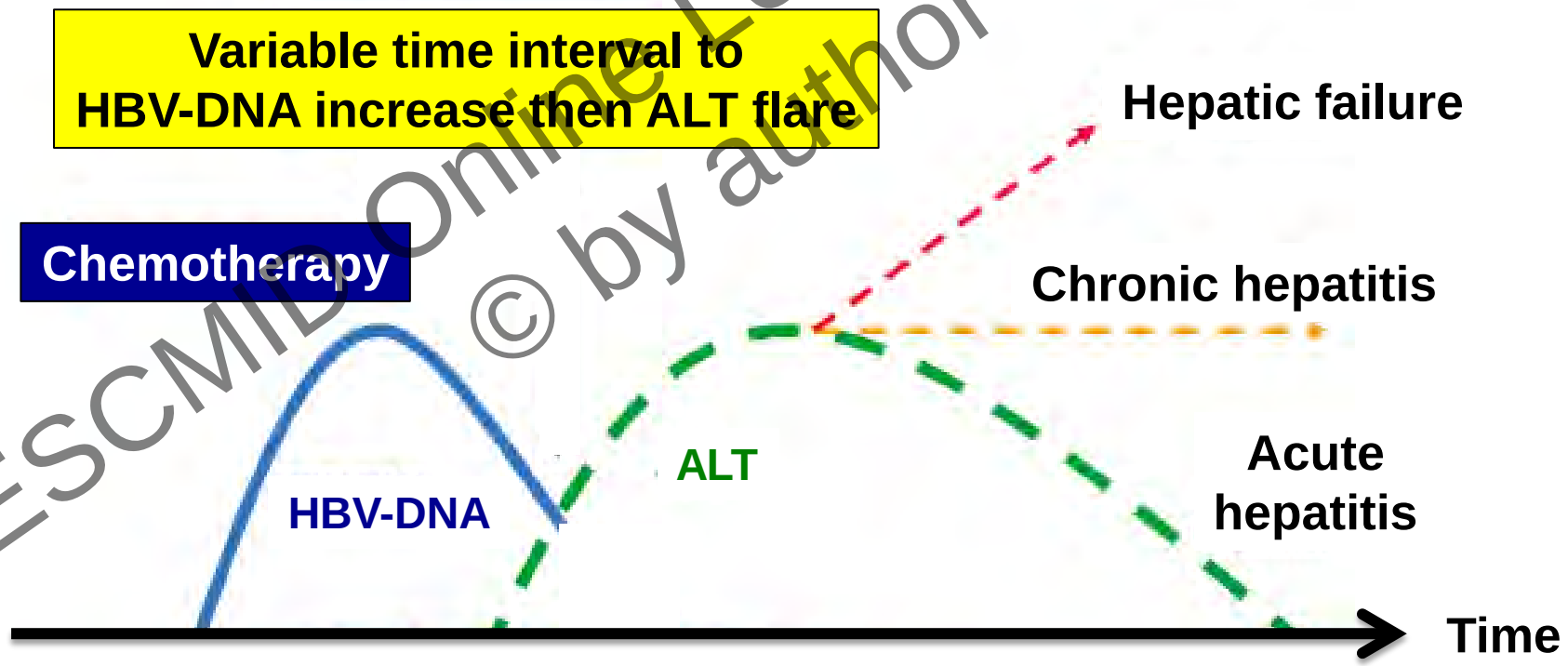
Mr M. (con't)

- HBV screening: HBsAg +, antiHBs -, antiHBc +
- No identified risk factor

- Screening proposed to sexual contacts and family

QUESTION 2

HBV reactivation



HBV reactivation

AgHBs + patients receiving chemotherapy

Liver consequences (meta-analysis)

	Frequency	Range
Reactivation	46 %	24 – 88 %
Hepatitis	33 %	24 – 88 %
Liver decompensation	13 %	5 – 33 %
Liver-related death	5 %	0 – 33 %

Loomba et al. Ann Intern Med 2008

HBV reactivation

AgHBs + patients receiving chemotherapy

Tumor consequences (meta-analysis)

	Number of studies	Frequency
Premature stop of chemotherapy	6	39 %
Cancer-related death	4	35 %

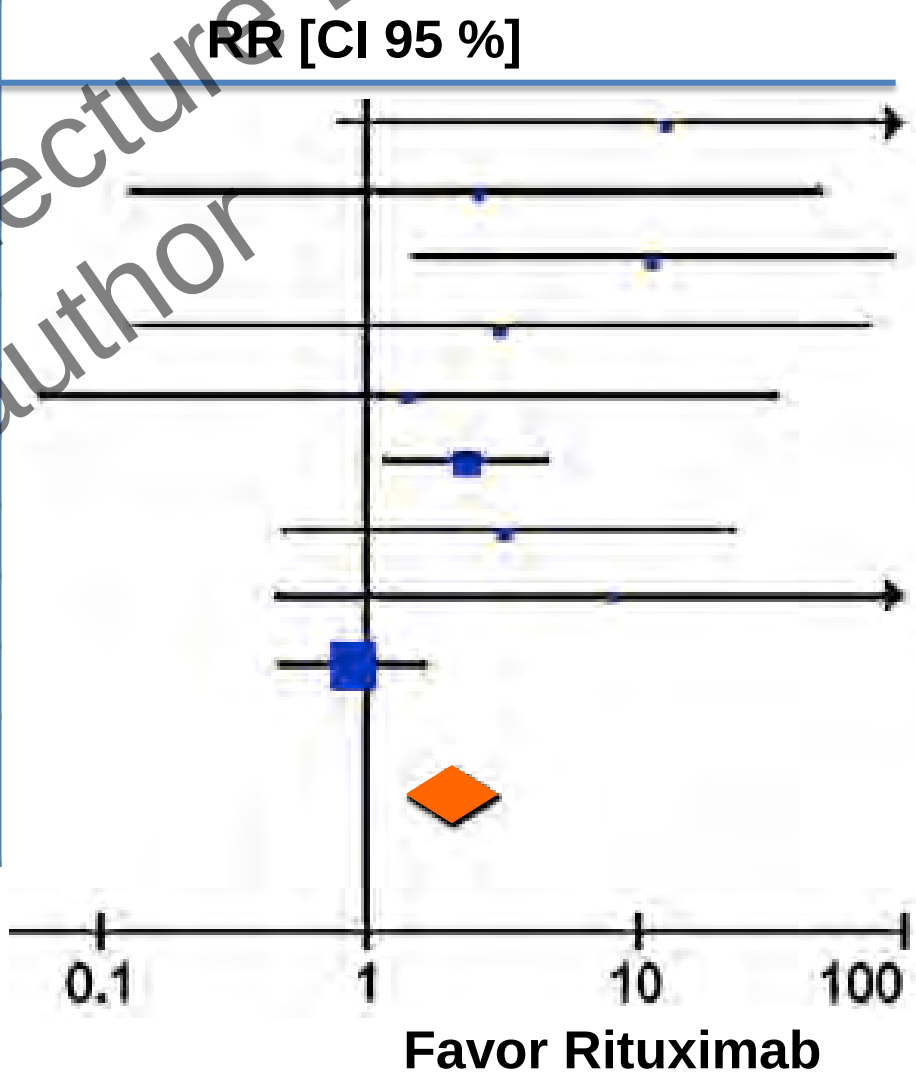
↗ liver-related complication and ↗ liver-related death
↘ chemotherapy efficiency and ↗ cancer-related death

Loomba et al. Ann Intern Med 2008

Rituximab in HBsAg + patients

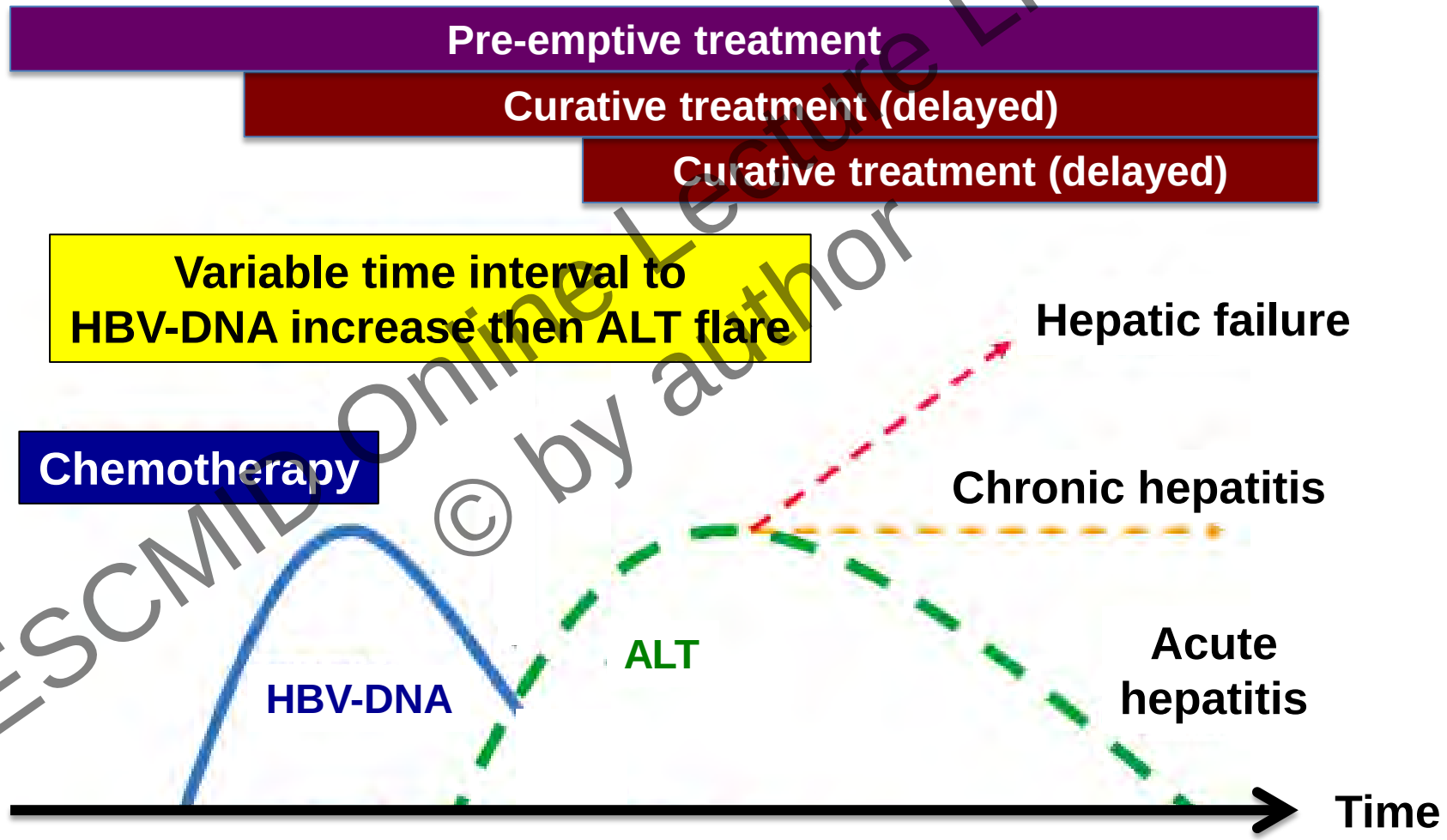
Risk of reactivation / control chemotherapy

Study of subgroup	RR
Yeo et al. 2009	13.00
Fukushima et al. 2009	2.58
Hui et al. 2006	11.53
Ji et al. 2010	3.14
Koo et al. 2010	1.40
Luo et al. 2010	2.29
Targhetta et al. 2008	3.31
Tsutsumi et al. 2009	7.96
Wang et al. 2008	0.88
Total	**2.14 [1.42 – 3.22]**



Dong et al. J Clin Virol 2013

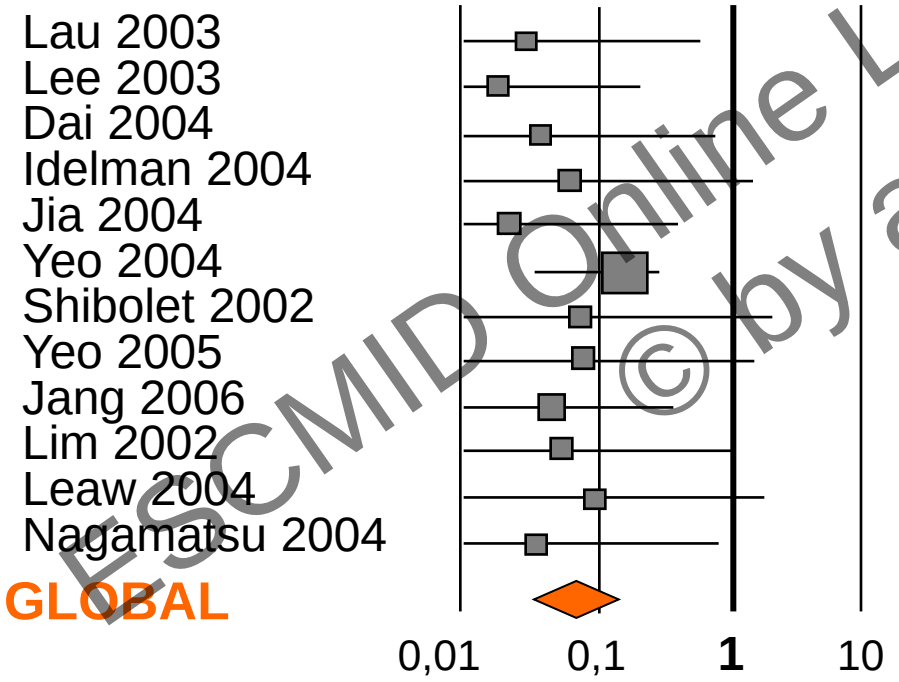
HBV reactivation



HBV reactivation

Beneficial effect of Lamivudine

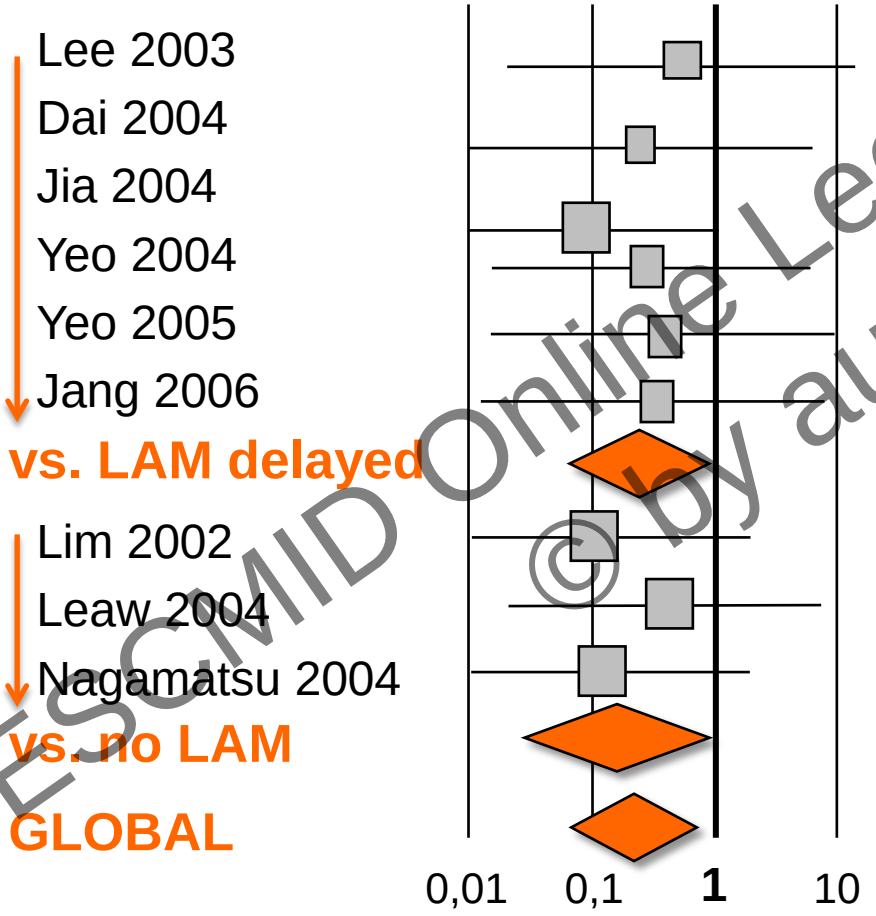
Meta-analysis



Loomba et al. Ann Intern Med 2008

HBV reactivation - Liver-related death

Beneficial effect of Lamivudine



	Odds ratio (CI 95%)	p
Lee 2003	0.56 (0.21-15.0)	0.733
Dai 2004	0.25 (0.01-6.8)	0.408
Jia 2004	0.086 (0.01-1.1)	0.058
Yeo 2004	0.26 (0.01-4.8)	0.366
Yeo 2005	0.41 (0.02-11)	0.597
Jang 2006	0.33 (0.013-8.4)	0.505
vs. LAM delayed	**0.25 (0.071-0.85)**	**0.027**
Lim 2002	0.08 (0.004-1.6)	0.096
Leaw 2004	0.38 (0.02-7.4)	0.526
Nagamatsu 2004	0.11 (0.005-2.5)	0.166
vs. no LAM	**0.15 (0.026-0.87)**	**0.034**
GLOBAL	**0.21 (0.076-0.57)**	**0.002**

Loomba et al. Ann Intern Med 2008

HBV reactivation

Beneficial effect of pre-emptive Lamivudine

Tumor consequences (meta-analysis)

	Lamivudine	Controls
Premature stop of chemotherapy	17 %*	39 %
Cancer-related death	26 %*	35 %
All cause of death	18 %*	36 %

*: $p < 0.05$ vs. controls

Loomba et al. Ann Intern Med 2008

In practice: HBV reactivation and pre-emptive treatment

- HBV reactivation is responsible for an increase in liver-related and cancer-related mortality
- Pre-emptive treatment with Lamivudine decreases HBV reactivation, liver decompensation, liver-related and cancer-related mortality
- Pre-emptive treatment with Lamivudine is superior to delayed treatment

Mr M. (con't)

- HBV screening: HBsAg +, antiHBs -, antiHBc +
- No identified risk factor

- HBV-DNA < 10 mUI/ml, HBeAg -, antiHBe +
- HIV, HCV and HDV serology negative
- ALT, prothrombin time and albumin: normal
- Liver stiffness (FibroScan®): 5.3 kPa (IQR 1.1)
- Liver imagery (TDM): normal

- ➢ Probably asymptomatic HBV carrier
- ➢ No co-infection
- ➢ Pre-emptive treatment before chemotherapy

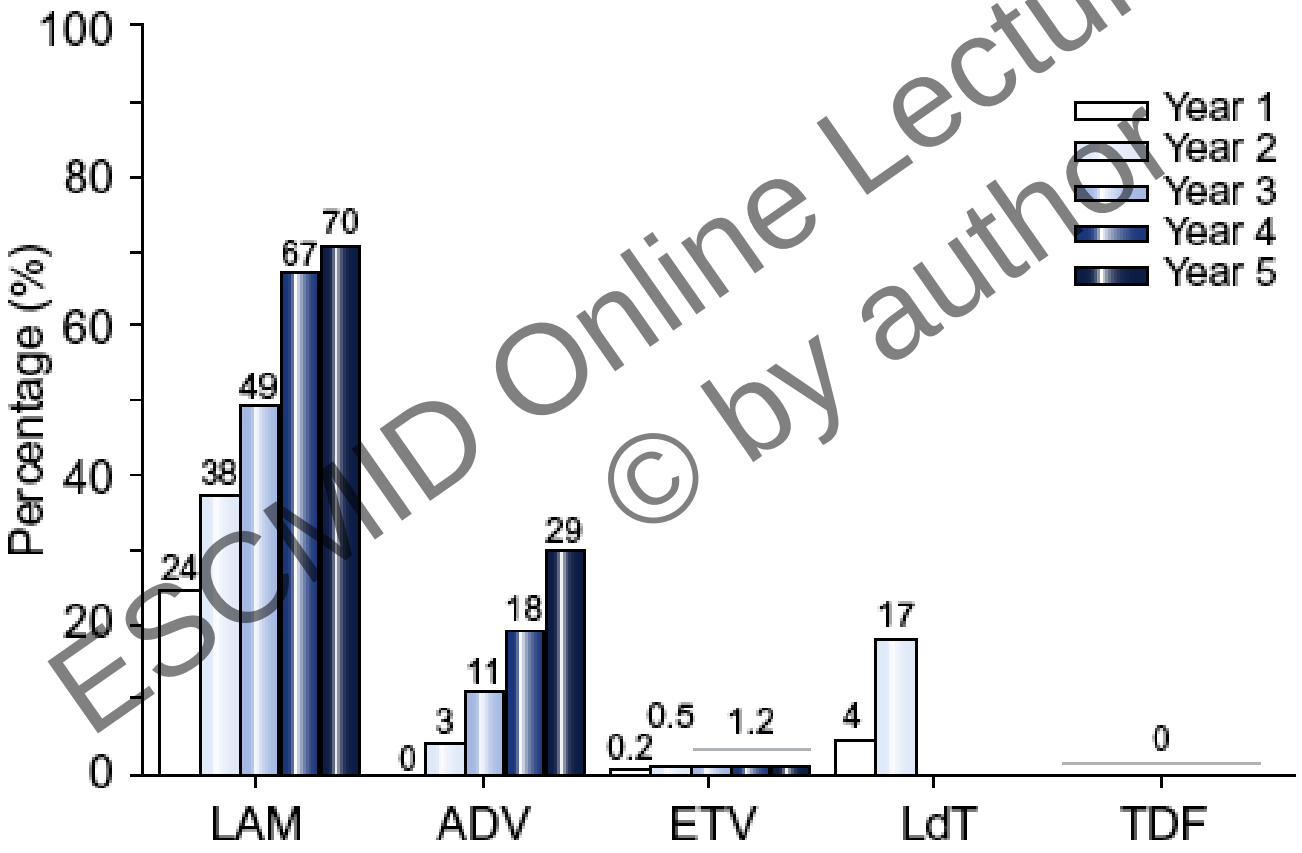
QUESTION 3

Which treatment for Mr M.?

- 2nd generation analogues (Entecavir or Tenofovir) are more potent antiHBV analogues than 1st generation (Lamivudine, Adefovir or Telbivudine)
- ↘ risk of viral resistance
- ↗ cost
- No benefit of combo therapy in naïve patients

AntiHBV analogue in monotherapy

Risk of resistance in naïve patients



LAM: Lamivudine
ADV: Adefovir
ETV: Entecavir
LdT: Telbivudine
TDF: Tenofovir

EASL – Clinical Practice Guidelines. J Hepatol 2012

Recommendation

European Association for the Study of Liver Diseases (EASL)

- "…prophylactic lamivudine reduces the risk of HBV reactivation and the associated morbidity and mortality (B1).
- It is, however, recommended that patients, who have a high HBV DNA level and/or may receive a lengthy and repeated cycles of immunosuppression, should be protected with a NA with high antiviral potency and a high barrier to resistance, i.e. entecavir or tenofovir (C1)."

- How to be sure of the duration of immunosuppression?
- How to be sure of the same regimen during the treatment?
- In case of reactivation, the risk of hepatic failure is probably higher in case of significant liver disease

EASL – Clinical Practice Guidelines. J Hepatol 2012

1st vs. 2nd generation antiHBV analogue

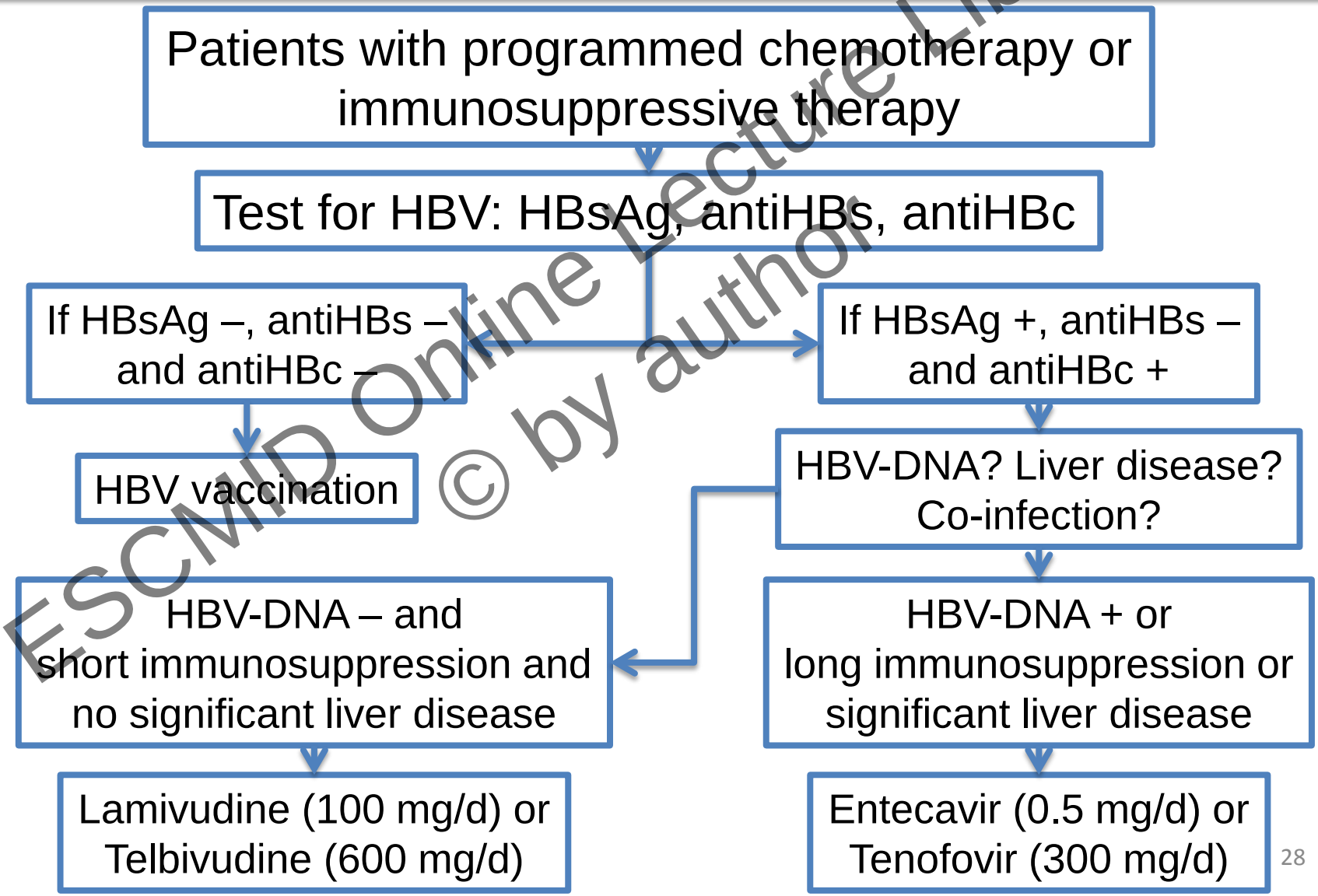
- No randomized study
- Comparative study (Jan 2007 – Feb 2008) in patients HBsAg treated for lymphoma (2/3 with Rituximab)

* p<0.05 vs. Entecavir	Lamivudine (n=89)	Entecavir (n=34)
HBV reactivation	20%	12%
HBV-related hepatitis	12%*	0
Chemotherapy disruption	20%*	6%
Mortality	1%	0

- No risk factor found in multivariate analysis

Li et al. J Viral Hepat 2011

In practice



QUESTION 4

Recommendations

European Association for the Study of Liver Diseases (EASL)

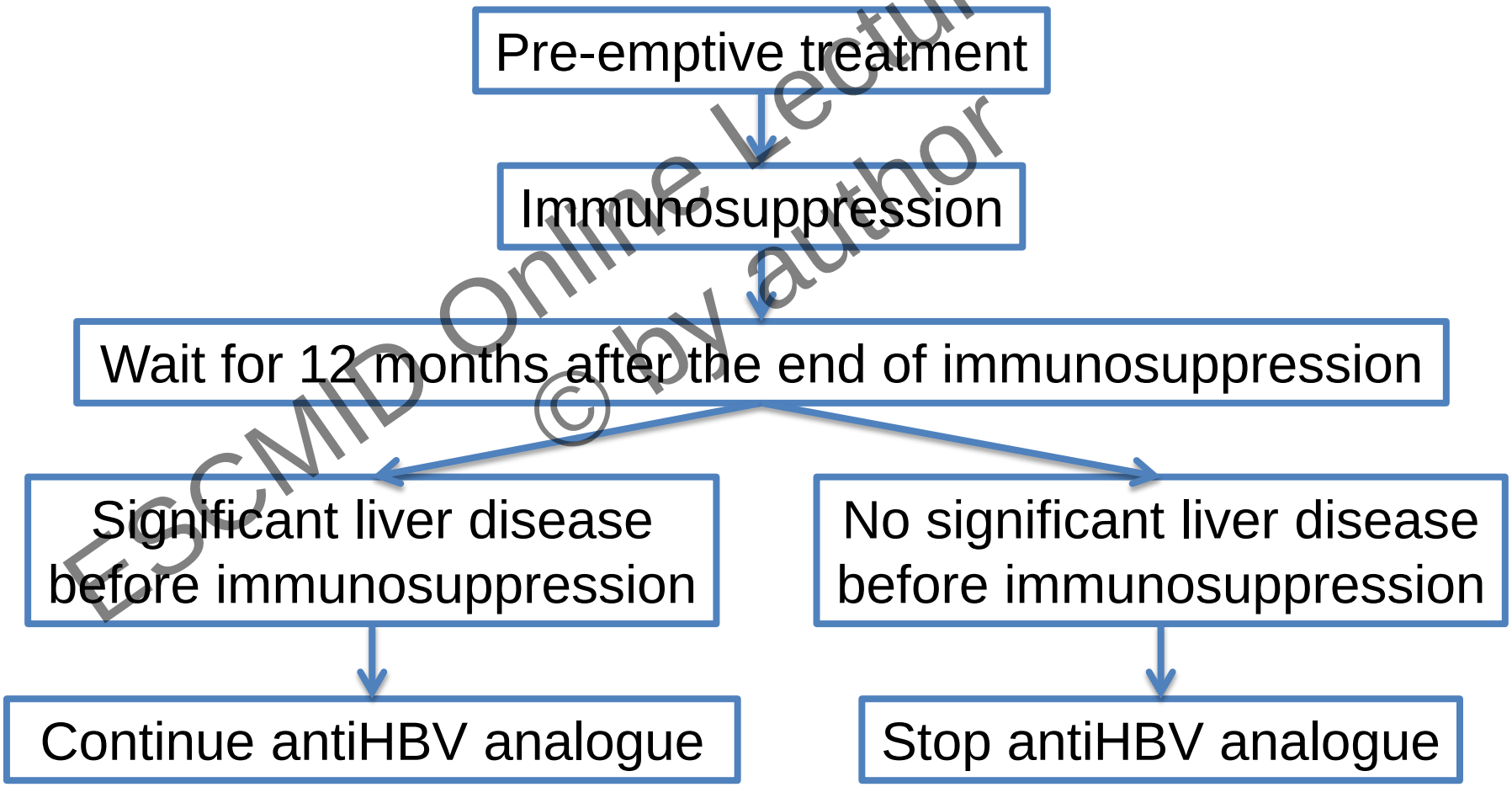
"HBsAg-positive candidates for chemotherapy and immunosuppressive therapy should … receive pre-emptive NA administration during therapy (regardless of HBV DNA levels) and **for 12 months** after cessation of therapy (A1)."

American Association for the Study of Liver Diseases (AASLD)

"Prophylactic antiviral therapy should be administered to hepatitis B carriers (regardless of baseline serum HBV DNA level) at the onset of cancer chemotherapy or a finite course of immunosuppressive therapy, and maintained **for 6 months** afterwards.
… HBsAg-positive persons with serum HBV DNA levels > 2,000 IU/mL prior to undergoing cytotoxic chemotherapy should continue antiviral therapy until they reach therapeutic endpoints for chronic hepatitis B."

EASL – Clinical Practice Guidelines. J Hepatol 2012
Lok & McMahon. AASLD Practice Guidelines. Hepatology 2009

In practice
When you can stop antiHBV analogue?



QUESTION 5

Recommendations

European Association for the Study of Liver Diseases (EASL)

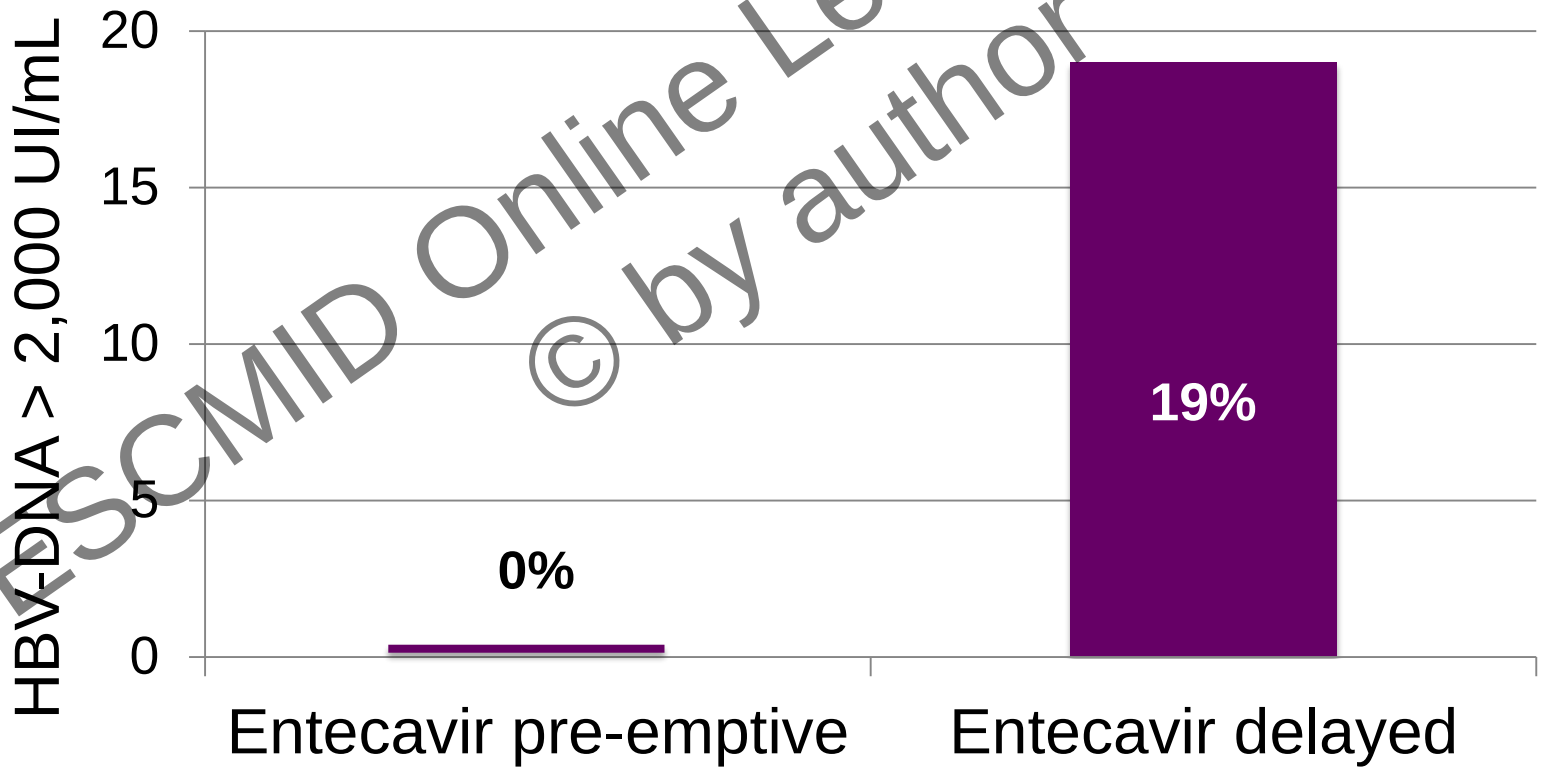
"HBsAg-negative patients with positive anti-HBc antibodies should be tested for HBV DNA. HBsAg-negative, anti-HBc positive patients with detectable serum HBV DNA should be treated similarly to HBsAg positive patients (C1).
HBsAg-negative, anti-HBc positive patients with undetectable serum HBV DNA and regardless of anti-HBs status who receive chemotherapy and/or immunosuppression should be followed carefully by means of ALT and HBV DNA testing and treated with NA therapy upon confirmation of HBV reactivation before ALT elevation (C1)"

EASL – Clinical Practice Guidelines. J Hepatol 2012

Rituximab in HBsAg - /antiHBc + patients

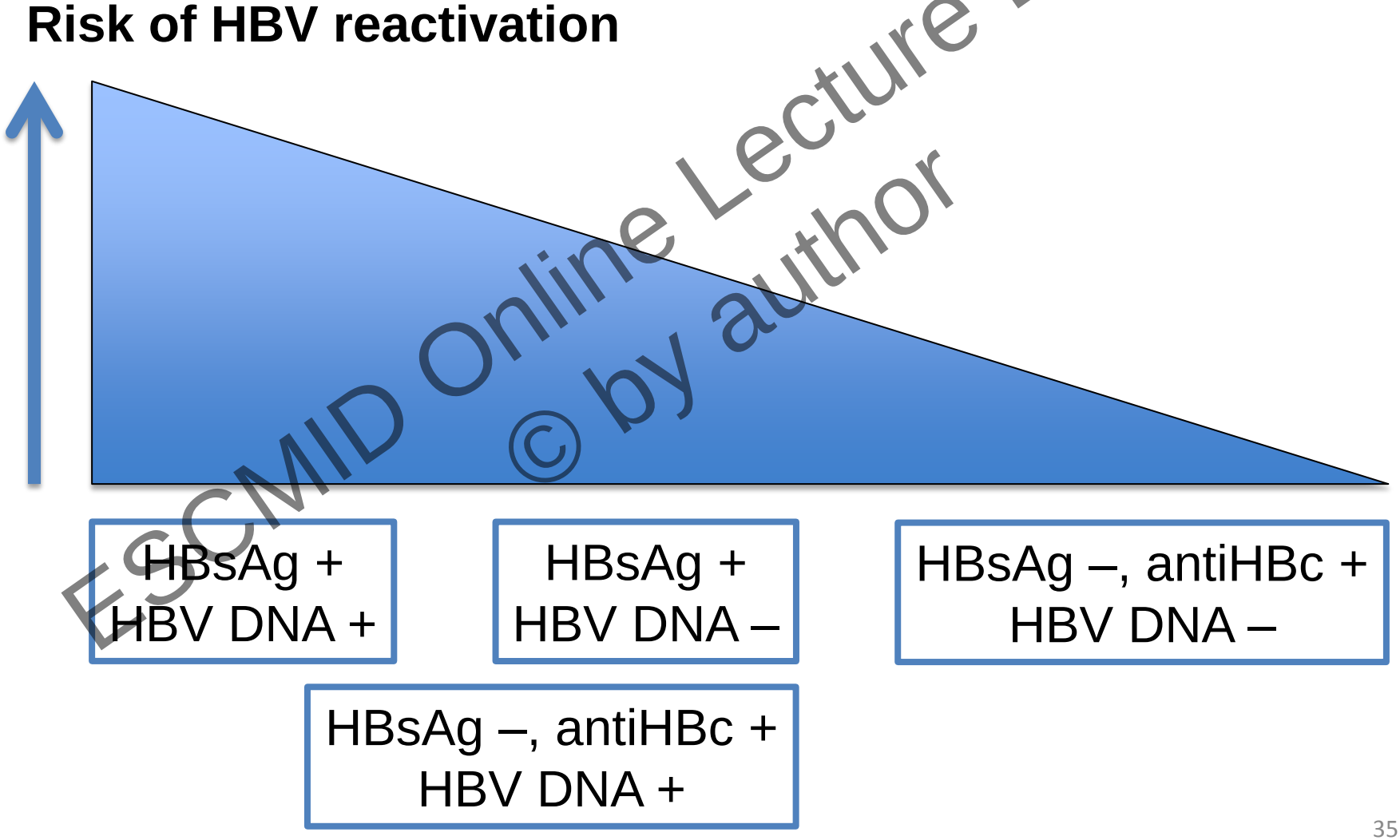
Risk of reactivation / pre-emptive vs. delayed

Patients treated for lymphoma with CHOP-Rituximab
Patients HBsAg – and antiHBc + (+/- antiHBs +)
Randomization Entecavir pre-emptive vs. Entecavir delayed



Huang et al. EASL 2012

HBV reactivation: HBV-related risk factor



HBV reactivation: Chemotherapy-related risk factor

- 244 consecutive patients treated for lymphoma
- and HBsAg – (Jan 2000 – May 2005)

➢ HBV-related hepatitis: 3.3%

Multivariate analysis of risks for HBV reactivation in patients with HBsAg –

Regimen	aRR	CI 95%	p
Rituximab + Steroids-containing	13.8	2.8 – 68.3	.001
Rituximab-containing	1.3	0.1 – 20.4	.263
Steroids-containing	5.0	0.6 – 40.9	.105

Hui et al. Gastroenterology 2006

Rituximab in HBsAg - /antiHBc + patients

Risk of reactivation / control chemotherapy

Study of subgroup	RR
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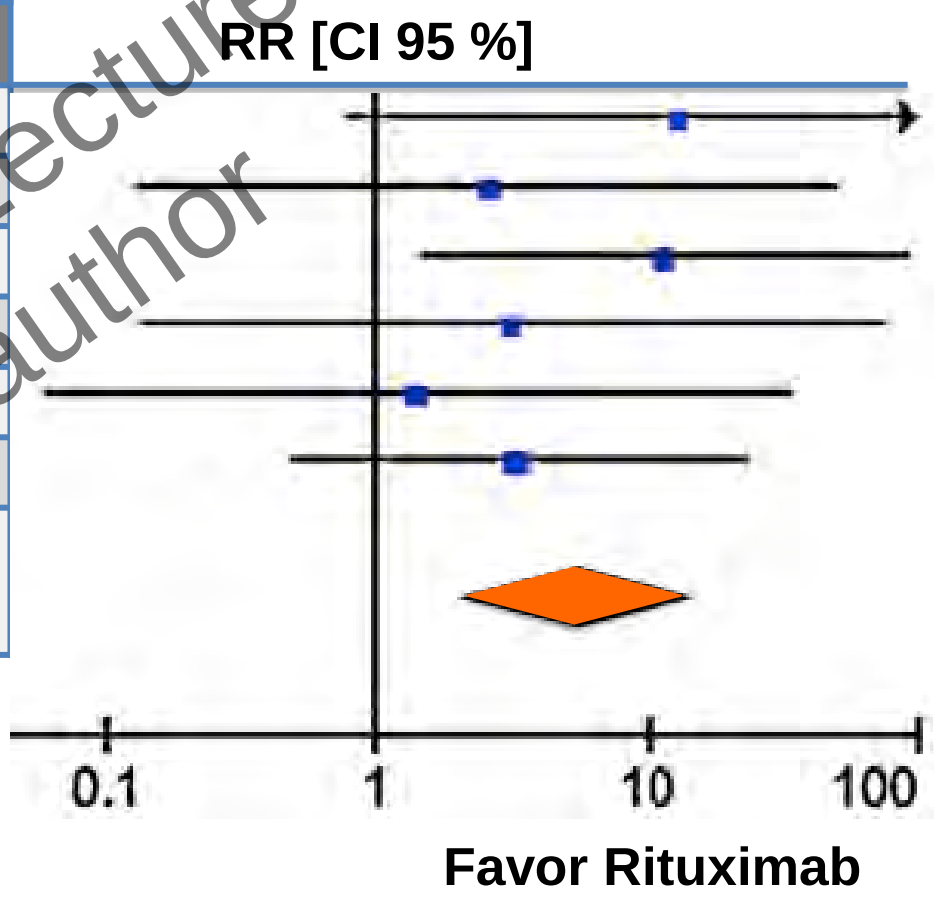
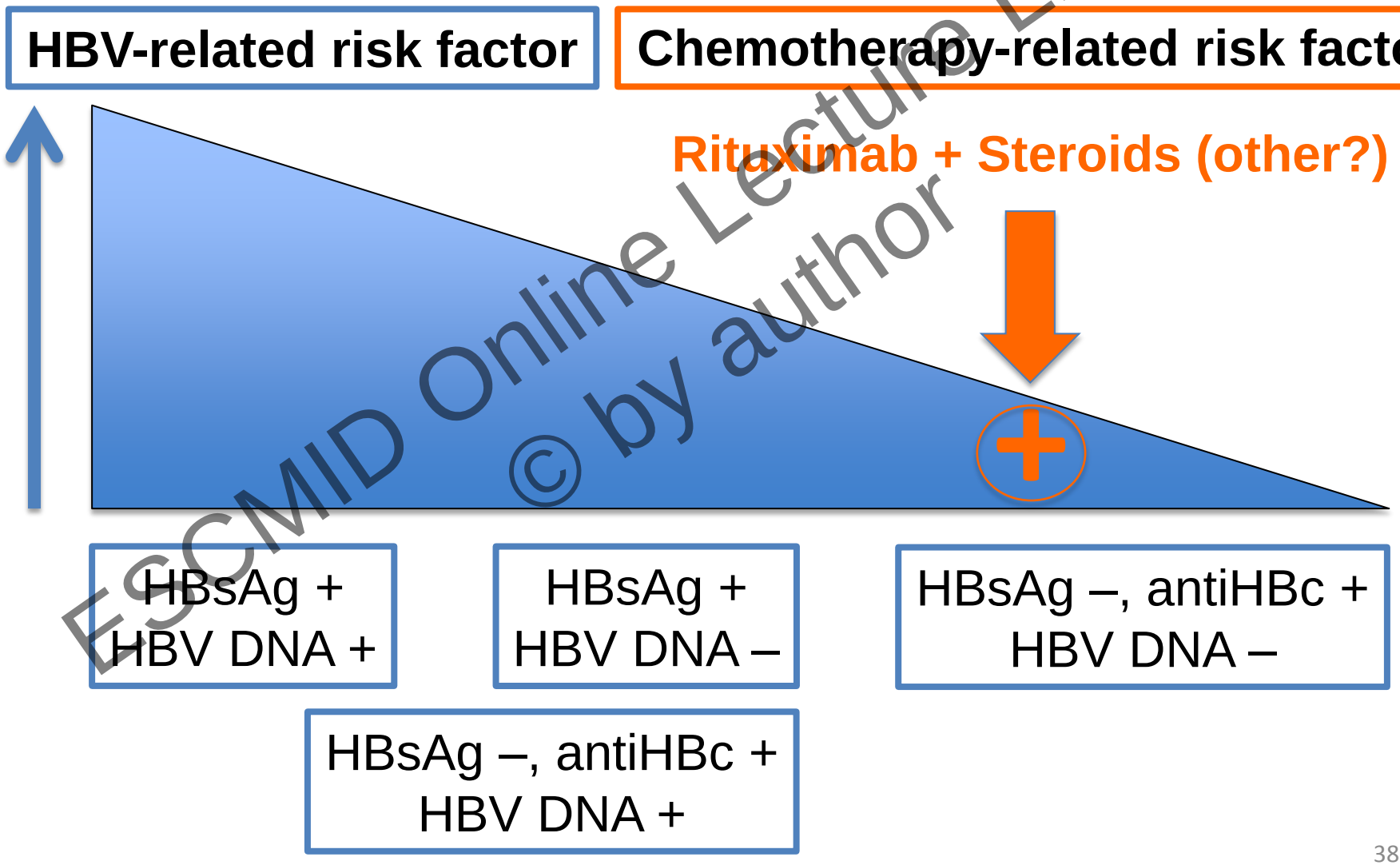
Total	**5.52 [2.05 – 14.85]**



Dong et al. J Clin Virol 2013

HBV reactivation: risk factor



In conclusion

1. HBV screening has to be performed systematically before chemotherapy or immunosuppressive therapy
2. In HBsAg + patients, a pre-emptive treatment has to be initiated before immunosuppression
3. The choice of the analogue depends on HBV DNA level, the duration of immunosuppression and the presence or not of a significant liver disease
4. The pre-emptive treatment has to be continue until (6 to) 12 months after cessation of therapy
5. HBsAg – & antiHBc + patients has to be tested for HBV-DNA. In case of HBV-DNA +, pre-emptive treatment has to be initiated. In case of HBV-DNA –, follow-up with HBV-DNA and ALT every 3 months have to be performed