Lymphoma Updates From ASH 2018

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February 27, 2019

UNC LINEBERGER

Objectives

- Discuss results of the ASH 2018 Lymphoma abstracts
- Role of brentuximab vedotin in patients with CD30+ Peripheral T Cell Lymphoma
- Recognize that a short course of RCHOP chemotherapy alone may be effective in treatment of young patients with low risk DLBCL.
- Recognize that the optimal treatment for ABC/non-GCB type DLBCL is still R-CHOP, but the addition of ibrutinib to RCHOP may benefit some younger patients
- Recognize the increasing role of check point inhibitors in Hodgkin lymphoma

Three interesting RCT

- Echelon 2 Trial
  - Phase III of Brentuximab vedotin + CHP versus Placebo + CHOP in CD30+ PTCL
- Flyer Trial
  - 6 vs. 4 Cycles RCHOP-21 in Young Patients with Low Risk DLBCL
- Ibrutinib + R-CHOP vs. Placebo + R-CHOP in non-GCB DLBCL

One phase I/II Trial

- Ipilimumab, nivolumab and brentuximab vedotin in rel/ref HL

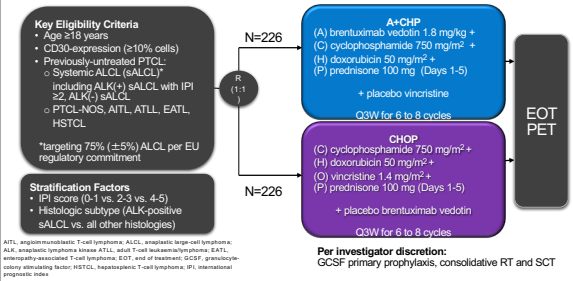
Echelon 2 Trial
Brentuximab Vedotin + CHP in CD30+ PTCL

- Peripheral T-cell lymphoma (PTCL) is a rare heterogeneous group of lymphoid malignancies
- Frontline standard of care is CHOP/CHOP-like regimen with curative intent
  - Poor or inadequate outcomes for PTCL patients[1-3]
  - ALK+ systemic ALCL (sALCL) is exception, with more favorable outcomes dependent upon age and IPI[1]
  - High unmet need for new therapies; high risk for disease relapse or progression
- Across subtypes, approximately 50% of patients express CD30
  - sALCL universally express CD30
  - Variable CD30 expression among other PTCL subtypes[4,5]
- Brentuximab vedotin, antibody-drug conjugate targeting CD30, FDA approved for
  - HL – relapsed refractory
  - CD30+ CTCL
  - relapsed/refractory sALCL
  - **Previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone**

1. Savage KJ, et al., Ann Oncol 15(10): 1467-75; 2004
2. Savage KJ, et al., Blood 111(12):5496-504; 2008
3. Simon A, et al., Br J Haematol 151(2): 159-66;
4. Bossard et al., Blood 124(19):2983-6; 2014
5. Sabattini et al., Haematologica 98(8): e81-82; 2013

Modified Slide courtesy of Steven Horwitz

ECHELON-2 Study Design (NCT01777152)



AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase ATLL, adult T-cell leukaemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; GCSF, granulocyte-colony stimulating factor; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index

Per investigator discretion:
GCSF primary prophylaxis, consolidative RT and SCT

Blood 2018 132:997.
Slide courtesy of Steven Horwitz

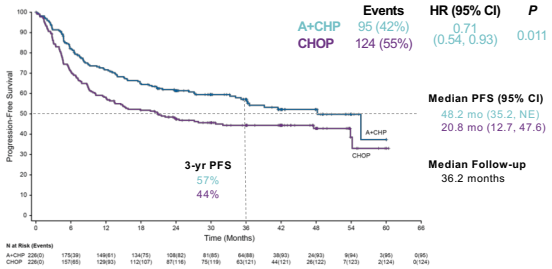
Baseline Characteristics

	A+CHP (N=226)	CHOP (N=226)
Male, n (%)	133 (59)	151 (67)
Age in years, median (range)	58 (18-85)	58 (18-83)
IPI score, n (%)		
0-1	53 (23)	48 (21)
2-3	140 (62)	144 (64)
4-5	33 (15)	34 (15)
Stage III/IV, n (%)	184 (81)	180 (80)

	A+CHP (N=226)	CHOP (N=226)
Disease diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

Blood 2018 132:997.
Slide courtesy of Steven Horwitz

Echelon-2 Progression-free Survival



	Events	HR (95% CI)	*P*
A+CHP	95 (42%)	0.71 (0.54, 0.93)	0.011
CHOP	124 (55%)		

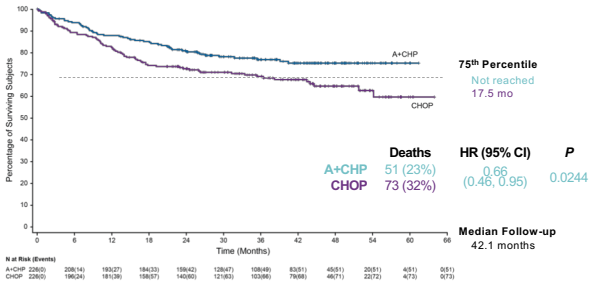
Median PFS (95% CI)
48.2 mo (35.2, NE)
20.8 mo (12.7, 47.6)

3-yr PFS
57%
44%

Median Follow-up
36.2 months

Blood 2018 132:997.
Slide courtesy of Steven Horwitz

Echelon-2 Overall Survival



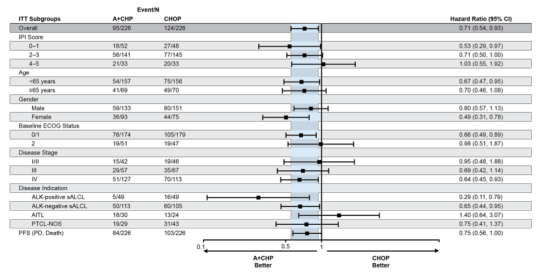
75th Percentile
Not reached
17.5 mo

	Deaths	HR (95% CI)	*P*
A+CHP	51 (23%)	0.66 (0.46, 0.95)	0.0244
CHOP	73 (32%)		

Median Follow-up
42.1 months

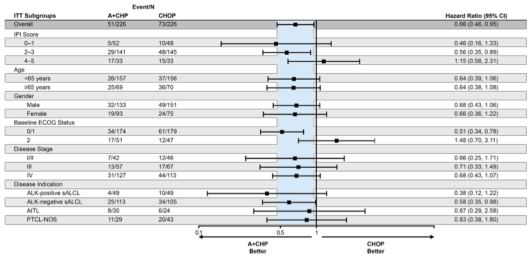
Blood 2018 132:997.
Slide courtesy of Steven Horwitz

Prespecified Subset Analyses: PFS



Blood 2018 132:997.
Slide courtesy of Steven Horwitz

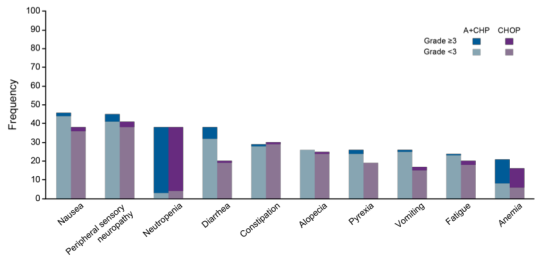
Prespecified Subset Analyses: OS



Blood 2018 132:997.

Slide courtesy of Steven Horwitz

Adverse Events in ≥20% of Subjects

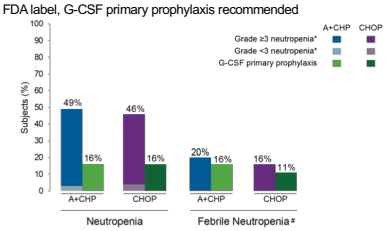


Blood 2018 132:997.

Slide courtesy of Steven Horwitz

Neutropenia

- G-CSF primary prophylaxis was permitted at investigator discretion
- Per FDA label, G-CSF primary prophylaxis recommended



*Includes preferred terms of neutropenia and neutrophil count decreased, #febrile neutropenia of any grade

Blood 2018 132:997.

Slide courtesy of Steven Horwitz

Summary and Conclusions

- ECHELON-2 first prospective trial in PTCL to show OS benefit over CHOP
- A+CHP provided clinically meaningful improvement in PFS and OS versus CHOP
  - 29% reduction in the risk of a progression event
    - 3-yr PFS: A+CHP 57% versus CHOP 44%
  - 34% reduction in the risk of death
- A+CHP has a comparable safety profile to CHOP
- FDA approved brentuximab vedotin in combination with CHP for adults with previously-untreated sALCL or other CD30-expressing PTCL, including AITL and PTCL-NOS

Blood 2018 132:997.

Slide courtesy of Steven Horwitz

Flyer Trial

Less Chemotherapy in Young Patients with Low Risk DLBCL

Patients:
- 18-60yo patients
- aaIPI=0
  - Normal LDH, Good PS, Stage I/II disease
- No bulky disease (<7.5cm)

6 x R-CHOP
n=295

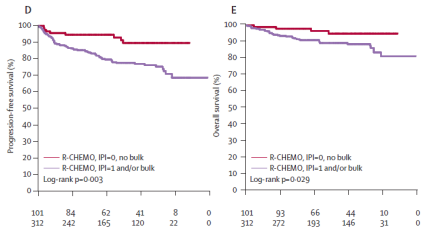
4 x R-CHOP + 2 x rituximab
n=293

- 21 day cycles
- No preplanned consolidative radiation
- Primary Endpoint PFS
- Non-inferiority study

Peoschel et al. Blood 2018 132:781

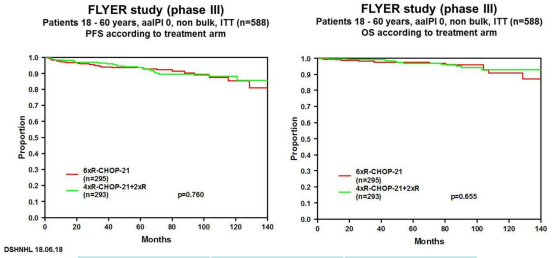
Flyer Trial Background

- MinT Trial: 6 cycles CHOP +/- rituximab
  - 18-60yo patients
  - Bulky stage I and Stage II-IV



Pfreundschuh et al. Lancet Oncol 2011;12:1013-22.

4 RCHOP + 2 R non-inferior to 6 R-CHOP



	6 cycles	4 cycles + 2 R
3 yr PFS	94%	96%
3 yr OS	98%	99%

Peoschel et al. Blood 2018 132:781

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Conclusion of Flyer

- In young patients with non-bulky limited stage disease, normal LDH and good performance status:
  - 4 cycles RCHOP + 2 cycles R have excellent long term survival and low chance of relapse
  - It does not address the question of radiation or not
  - Late relapses are occurring in both arms

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Current NCCN Recommendations for Stage I/II DLBCL

- R-CHOP-14 x 4-6 cycles +/- ISRT
- R-CHOP-21 x 6 cycles +/- ISRT
- R-CHOP x 3 + ISRT
  - This is a category one recommendation

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Ibrutinib + R-CHOP in non-GCB type

Patient population (n=838):
- Non-GCB DLBCL
- Previously untreated

Primary Endpoint: EFS

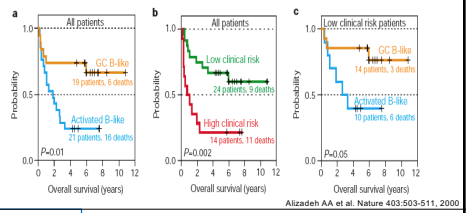
→ 6-8 x R-CHOP + placebo

→ 6-8 x R-CHOP + ibrutinib 560mg/day

Subtype determined centrally:
- Non-GCB determined by immunohistochemistry
- ABC determined by gene expression profiling

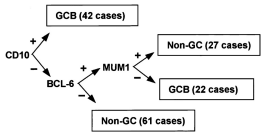
Younes et al. Blood 2018 132:784

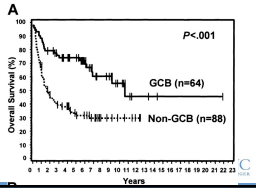
Gene Expression Profiling



Alizadeh AA et al. Nature 403:503-511, 2000

Immunohistochemistry





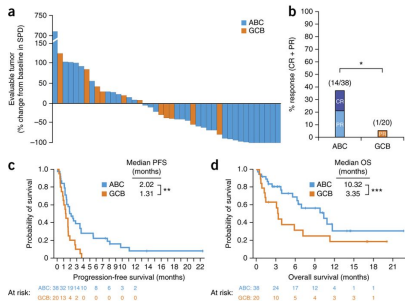
Hans et al. Blood 103:275-282, 2004.

Ibrutinib in ABC/non-GCB

- ABC DLBCL has mutations that lead to chronic active B cell receptor (BCR) signaling
  - Bruton's tyrosine kinase links BCR activity to NF-KB activity
  - Ibrutinib is a BTK inhibitor

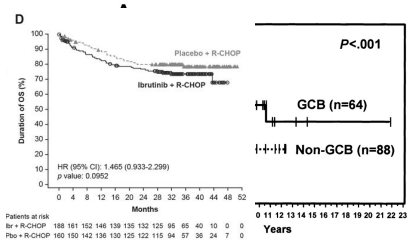
Wilson et al. Nat Med 21:922-6, 2015.

Ibrutinib in rel/ref ABC DLBCL



Wilson et al. Nat Med 21:922-6, 2015.

Ibrutinib+R-CHOP: Did not improve EFS



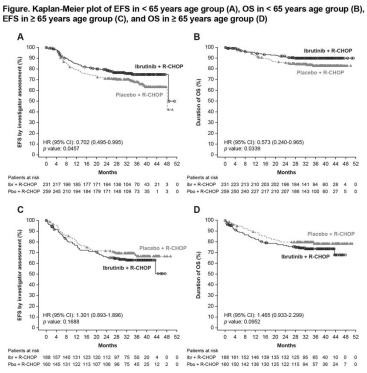
Hans et al. Blood 103;275-282, 2004.
Younes et al. Blood 2018 132:784

Ibrutinib Increases Toxicity

	Ibr-RCHOP	Pbo-RCHOP
Received ≥6 cycles • ≥ 65yo received ≥6 cycles • <65yo received ≥6 cycles	80.8% • 69% • 90%	90.7% • 90% • 91%
Discontinued due to AEs (mostly febrile neutropenia and pneumonia)	12.2%	5.3%
Grade≥3 AEs	89.9%	87.1%
Serious AEs • ≥65yo • <65yo	53.1% • 67.4% • 41.5%	34% • 40.6% • 29.8%

Younes et al. Blood 2018 132:784

Ibrutinib+R-CHOP in Younger Patients



Younes et al. Blood 2018 132:764

Conclusions Ibrutinib + R-CHOP

- In patients with non-GCB DLBCL, 1st line ibrutinib + R-CHOP did not prolong EFS in the ITT population
  - May improve outcomes in patients <65 with ABC/non-GCB type DLBCL but a prospective trial is needed
  - Even the older pts, on either arm, did much better than historical expectations

Triple drug therapy for rel/ref HL

- Phase I/2 trial ipilimumab, nivolumab and brentuximab vedotin

Nivo 3mg/kg every 21 days x 32 cycle
+
BV (1.2mg/kg or 1.8mg/kg) every 21 days x 16 cycle
+
Ipi 1mg/kg every 12 weeks

3+3 design for the two BV dose levels (7 and 6 patients)
9 patient dose expansion at the 1.8mg/kg dose

Diefenbach et al., Blood 2018;132:679.

Patients

- n=22
- Rel/ref HL
- Median of 2 prior therapies (range, 1-5)
- 9 with prior SCT
- 1 with prior BV

Diefenbach et al. Blood 2018;132:679.

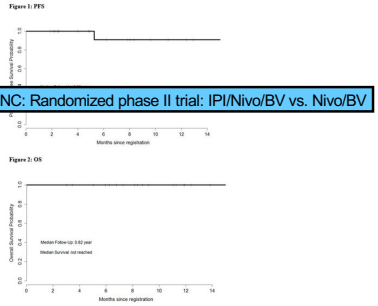
Toxicity

- 3 DLTs:
  - Grade 3 diabetic ketoacidosis
  - Grade 3 AST elevation
  - Grade 4 Steven Johnson syndrome with rash and GVHD in a post Allo-SCT patient
- Significant Grade 3 AEs: rash, colitis, gastritis, pancreatitis, arthritis

Diefenbach et al. Blood 2018;132:679.

Ipi + Nivo + BV Response

- ORR 82% and CR 68%



Opening soon at UNC: Randomized phase II trial: IPI/Nivo/BV vs. Nivo/BV

Diefenbach et al. Blood 2018;132:679.

ANY QUESTIONS?

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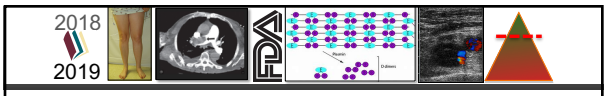


2019 Update

VTE, Anticoagulation, Thrombophilia

Stephan Moll, MD
UNC Chapel Hill, NC

UNC Telehealth
Feb 27th, 2019

Content

1. Cancer and DVT/PE
2. VTE: How Long to Treat?
3. Direct Oral Anticoagulants: Update

Key 2018/2019 publications

Take-home points

1 2 3 4

Cancer and VTE

Cancer and VTE Treatment

Guidelines

1. ASCO 2015:
   - LMHW recommended. DOACs not currently recommended"

[Lyman GH, et al. *J Clin Oncol*. 2015;33(6):654-656]

2. ACCP 2016:
   - Suggest LMWH over DOAC or warfarin"

[Kearon C, et al. *Chest*.149(2):315-352]

3. ACF 2016:
   - "Suggest LMWH"

[Khorana A, et al. *J Thromb Thrombolysis*. 2016;41(1):81-91]

ACCP, American College of Clinical Pharmacy; ACF, Anticoagulation Forum; ASCO, American Society of Clinical Oncology

Cancer and VTE

Completed prospective randomized trials

	New Drug	Comparator	n		
HOKUSAI	Edoxaban	Dalteparin	1046	[Rascob GE, et al. *N Engl J Med*. 2017;378(7):615-624]	2017
SELECT-D	Rivaroxaban	Dalteparin	406	[Young AM, et al. *J Clin Oncol*. 2018;36(20):2017-2023]	2018
ADAM	Apixaban	Dalteparin	287	[McBane RD, et al. *Blood*. 2018;132: Abstract 421]	2018

Ongoing prospective randomized trials

	New Drug	Comparator	n		
CARAVAGGIO	Apixaban	Dalteparin	1161 (949*)	[ClinicalTrials.gov NCT03045406. https://clinicaltrials.gov/ct2/show/NCT03045406. Accessed Feb 7th, 2019]	2019

* Last updated 2/7/2019

Cancer and VTE

1 Edoxaban

Table 2. Clinical Outcomes during the Overall Trial Period.*

Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	77 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for superiority
Secondary outcomes				
Recurrent venous thromboembolism — no. (%)	41 (7.9)	58 (11.1)	0.71 (0.48–1.06)	0.09
Recurrent deep-vein thrombosis — no. (%)	19 (3.6)	33 (6.7)	0.56 (0.32–0.97)	
Recurrent pulmonary embolism — no. (%)†	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)	
Major bleeding — no. (%)	34 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04
Severity of major bleeding among those with major bleeding — no./total no. (%)‡				
Category 1	0	0		
Category 2	24/36 (66.7)	8/21 (38.1)		
Category 3	12/36 (33.3)	12/21 (57.1)		
Category 4	0	1/21 (4.8)		
Clinically relevant nonmajor bleeding — no. (%)§	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)	
Major or clinically relevant nonmajor bleeding — no. (%)§¶	97 (18.6)	73 (13.9)	1.40 (1.03–1.89)	
Death from any cause — no. (%)	206 (39.5)	192 (36.6)	1.12 (0.92–1.37)	
Event-free survival — no. (%)‖	287 (55.0)	296 (56.5)	0.93 (0.77–1.11)	

[Raskob GE, et al. *N Engl J Med*. 2018;378(7):615-624]

Cancer and VTE

2018

2 Rivaroxaban

SELECT-D trial
- *Rivaroxaban* vs dalteparin
- n = 406

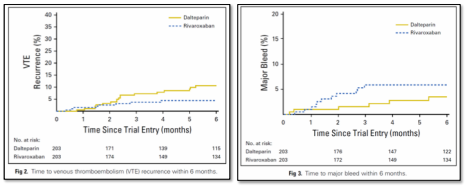


Fig 2. Time to venous thromboembolism (VTE) recurrence within 6 months.

Fig 3. Time to major bleed within 6 months.

[Young AM, et al. *J Clin Oncol*. 2018;36(20):2017-2023]

Cancer and VTE

2018

3 Apixaban

ADAM-trial
- *Apixaban* vs dalteparin
- n = 287
- publication pending)

Clinical Outcomes During Treatment Period

	Apixaban (N=145)	Dalteparin (N=142)	Hazard Ratio (95% CI)	p value
Primary Safety Endpoint				
Major Bleed	0 (0.0)	3 (2.1)	0.0 (0.0 –)	0.9956
Secondary Safety Endpoint				
Major plus CRNM Bleeding n (%)	9 (6.2)	9 (6.3)	0.9 (0.41 – 1.94)	0.8816
Major Bleed	0 (0.0)	3 (2.1)		
Clinically Relevant Non-Major Bleed	9 (6.2)	6 (4.2)		
Secondary Efficacy Endpoint				
Thromboembolism n (%)	5 (3.4%)	20 (14.1%)	0.21 (0.09 – 0.47)	0.0182
Pulmonary Embolism	4 (80.0)	4 (20.0)		
Lower Extremity DVT	0 (0.0)	8 (40.0)		
Upper Extremity DVT	0 (0.0)	5 (25.0)		
Splanchnic VT	0 (0.0)	3 (15.0)		
Cerebral VT	1 (20.0)	1 (5.0)		

CRNM, clinically relevant non-major; DVT, deep vein thrombosis; VT, venous thrombosis

[McBane RD, et al. *Blood*. 2018;132: Abstract 421]

Cancer and VTE

1 3 DOACs

Take-home points

- Reasonable to use edoxaban (evidence-based).
- Looks like it's ok to use apixaban or rivaroxaban.

VTE Prevention in Ambulatory Patients With Cancer

a AVERT trial

b CASSINI trial

AVERT Trial - Apixaban

Khorana score: 2 or more

1. Type of cancer
   - 2: Pancreas, gastric, brain
   - 1: Lung, lymphoma, gyn, bladder, testicular
   - 0: others
2. Hbg < 10 g/dL
3. WBC > 11 x 10^9/L
4. Plts > 350 x 10^9/L
5. BMI > 35 kg/m^2

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Apixaban (N = 291)	Placebo (N = 283)
Age — yr	61.2±12.4	61.7±11.3
Male sex — no. (%)	121 (41.6)	119 (42.0)
Weight — kg	80.0±22.3	82.6±21.4
Creatinine clearance >50 ml/min — no. (%)	275 (94.5)	265 (93.6)
Tumor type — no. (%)		
Brain	14 (4.8)	10 (3.5)
Bladder	1 (0.3)	4 (1.4)
Lung	31 (10.7)	28 (9.9)
Testicular	2 (0.7)	1 (0.4)
Stomach	25 (8.6)	19 (6.7)
Pancreatic	37 (12.7)	41 (14.5)
Lymphoma	76 (26.1)	69 (24.4)
Myeloma	7 (2.4)	8 (2.8)
Gynecologic	74 (25.4)	74 (26.1)
Colon	3 (1.0)	8 (2.8)
Prostate	0	1 (0.4)
Other	21 (7.2)	20 (7.1)

25 % high VTE-risk cancers

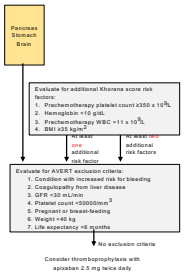
[Carrier M, et al. *N Engl J Med*. 2018 Dec 4 Epub ahead of print]

AVERT Trial - Apixaban

Outcome		Apixaban (N=288)	Placebo (N=275)	Hazard Ratio (95% CI)*	P Value
Venous thromboembolism — no. (%)	NNT: 17	12 (4.2)	28 (10.2)	0.41 (0.26–0.65)	<0.001
Deep-vein thrombosis — no. (%)		7 (2.4)	12 (4.4)		
Pulmonary embolism — no. (%)†		5 (1.7)	16 (5.8)‡		
Incidental pulmonary embolism — no./total no.		3/5	6/16		
Major bleeding episode					
Any episode — no. (%)	NNH: 59	10 (3.5)	5 (1.8)	2.00 (1.01–3.95)	0.046
Severity of episode — no./total no. (%)§					
Category 1		1/10 (10)	0		
Category 2		8/10 (80)	3/5 (60)		
Category 3		1/10 (10)	2/5 (40)		
Category 4		0	0		
Clinically relevant nonmajor bleeding — no. (%)¶		21 (7.3)	15 (5.5)	1.28 (0.89–1.84)	
Outcome occurred during the treatment period — no. (%)					
Venous thromboembolism		3 (1.0)	20 (7.3)	0.14 (0.05–0.42)	
Major bleeding episode		6 (2.1)	3 (1.1)	1.89 (0.39–9.24)	
Death from any cause — no. (%)		35 (12.2)	27 (9.8)	1.29 (0.98–1.71)	

[Carrier M, et al. *N Engl J Med*. 2018 Dec 4.Epub ahead of print]

VTE Prevention in Ambulatory Cancer Patients

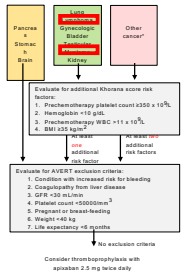


BMI, body mass index; GFR, glomerular filtration rate; WBC, white blood cell count

[May J, et al. *The Hematologist*. 2019 In press]

[Carrier M, et al. *N Engl J Med*. 2018 Dec 4.Epub ahead of print]

VTE Prevention in Ambulatory Cancer Patients



Take-home points

Higher-risk outpatient patients with cancer:
Reasonable to offer Apixaban 2.5 mg bid

BMI, body mass index; GFR, glomerular filtration rate; WBC, white blood cell count

[May J, et al. *The Hematologist*. 2019 In press]

[Carrier M, et al. *N Engl J Med*. 2018 Dec 4.Epub ahead of print]

CASSINI Trial - Rivaroxaban

Methods

- Outpatients with cancer
- Khorana score 2 or more
- Placebo vs rivaroxaban 10 mg qd
- Double blind, randomized
- Pre-randomization ve

Endpoints

- Composite of
  - Symptomatic distal or proximal leg DVT
  - Asymptomatic proximal leg DVT
  - Symptomatic or asymptomatic upper extremity DVT
  - PE
  - VTE-related death
- During 6 months of follow-up (intention to treat)

[Khorana A, et al. *Blood*. 2018;132: Abstract LBA-1]

CASSINI Trial

Secondary Analyses

- Primary endpoint in the on-treatment group
- Primary endpoint PLUS splanchnic and arterial thrombosis
- Primary endpoint PLUS asymptomatic distal DVT

Safety Analyses

- Primary: Major bleeding
- Secondary: Clinically relevant non-major bleeding

[Khorana A, et al. *Blood*. 2018;132: Abstract LBA-1]

CASSINI Trial

Results

a) 4.53 % had DVT on baseline screening
b) Study drug discontinuation was high (47%)
c) Primary efficacy endpoint: 5.95 % (riva) vs 8.79 (placebo); *P* = .101
d) Primary endpoint ON treatment: 2.62 (riva) vs 6.41 (placebo); *P* = .007
e) Major bleeding: 1.98 (riva) vs 0.99 (placebo); *P* = .265
f) Clinically relevant non-major bleeding: 2.72 (riva) vs 1.98 (placebo); *P* = .532

Conclusions

- Riva did NOT decrease primary endpoint (intention to treat)
- Riva did decrease primary endpoint while on treatment
- High study discontinuation rate
- Riva did not significantly increase major bleeding rate

[Khorana A, et al. *Blood*. 2018;132: Abstract LBA-1]

2 CASSINI Trial

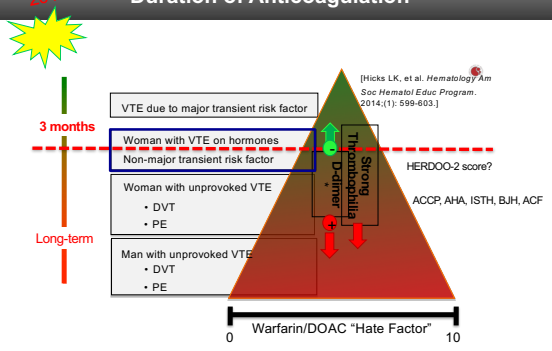
Take-home points

- High rate of leg DVT (5 %) upon screening
- Outpatients with cancer treated with rivaroxaban 10 mg qd: Beneficial (and safe) while being taken
- Wait for full publication

1 2 3

VTE – How Long to Treat?

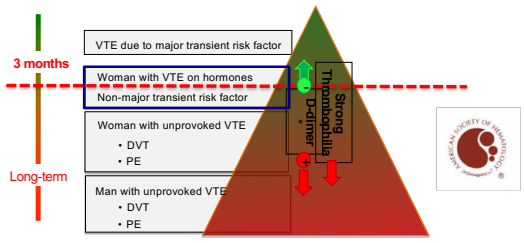
2019 Duration of Anticoagulation



[Hicks LK, et al. *Hematology Am Soc Hematol Educ Program.* 2014;(1): 599-603.]

* [Verhovsek M, et al. *Ann Intern Med.* 2008;149(7):481-490.]

2019 Duration of Anticoagulation



* [Verhovsek M, et al. *Ann Intern Med.* 2008;149(7):481-490]

How Long to Anticoagulate?

Take-home points

- Try the "Recurrence Triangle"
- D-Dimer predicts recurrence
- Repeated positive APLA predict recurrence

1 2 **3**

DOAC Update

DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Atrial fibrillation	FDA approved	FDA approved	FDA approved	FDA approved	No FDA activity
VTE treatment	FDA approved	FDA approved	FDA approved	FDA approved	No FDA activity
VTE prevention	Ortho FDA approved	Ortho FDA approved	Ortho FDA approved	No FDA activity	Medical FDA approved
Reversal agent	Idarucizumab	Andexanet 2018			

[las

[last updated: Feb 7th, 2019]

DOACs in Special Populations

Apixaban and Renal Failure

2017

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1)]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

[Apixaban package insert 2/2017: https://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed January 24, 2019]

Dosing in HD (package insert):

- 5 mg q 12 hrs
- 2.5 mg q 12 hrs if ≥ 80 yrs or ≤ 60 kg

Rivaroxaban and Renal Failure

2017

Patients with End-Stage Renal Disease on Dialysis
Clinical efficacy and safety studies with rivaroxaban did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of rivaroxaban 15 mg once daily will result in concentrations of rivaroxaban and pharmacodynamics activity similar to those observed in the ROCKET AF study *[see Clinical Pharmacology (12.2, 12.3)]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ROCKET AF.

(Rivaroxaban [package insert 10/2017]: www.xarelltohcp.com/shared/product/xarelto/prescribing-information.pdf. Accessed January 24, 2019]

Dosing in HD (package insert):

15 mg once daily

Severe Obesity and DOACs

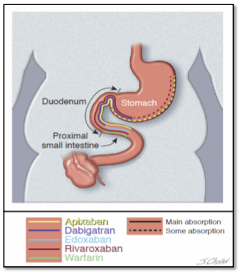
1. Ok to use DOAC up to BMI 40 kg/m^2 or 120 kg
2. Suggest NOT to use DOAC if BMI >40 kg/m^2 or >120 kg
3. If DOAC is used in a patient with BMI >40 kg/m^2 or >120 kg, then obtain peak and trough level. If level below expected range: switch to warfarin

[Martin K, et al. *J Thromb Haemost.* 2016;14(6):1308-1313]

[Moll S, et al. *Direct oral anticoagulants in extremely obese patients: OK to use?* Res Pract Thromb Haemost. 2019;1–4]

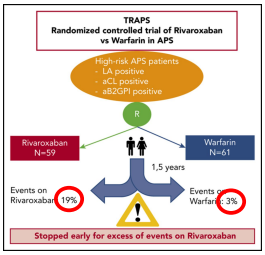
Bariatric Surgery and DOACs

2017



[Martin KA, et al. *Am J Med.* 2017;130(5):517-524]

APS and DOACs



Primary endpoint:

Composite of:

- Thromboembolic events
- Major bleeding
- Vascular death

APS, antiphospholipid syndrome; LA, lupus anticoagulant

[Pengo V, et al. *Blood*. 2018;132(13):1365-1371]

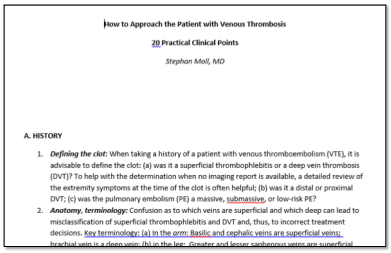
DOACs and Special Populations

Take-home points

- **Renal impairment/ hemodialysis:** May be apixaban, may be rivaroxaban; but: Be careful! Dosing?
- **Severe obesity** (BMI >40 kg/m^2): Suggest warfarin; or DOAC with trough level testing.
- **Bariatric surgery**: Suggest warfarin; or DOAC with (repeated) level testing.
- **Antiphospholipid Syndrome:** Triple positive—cave DOACs
- **Cancer** and VTE: Edoxaban good choice. Others: probably, too.

[Martin K, et al. *J Thromb Haemost*. 2016;14(6):1308-1313]
[Moll S, et al. *Direct oral anticoagulants in extremely obese patients: OK to use?* Res Pract Thromb Haemost. 2019;1–4]
[Martin KA, et al. *Am J Med*. 2017;130(5):517-524]

The 20 VTE Teaching Points



How to Approach the Patient with Venous Thrombosis

20 Practical Clinical Points

Stephan Moll, MD

A. HISTORY

1. ***Defining the clot:*** When taking a history of a patient with venous thromboembolism (VTE), it is advisable to define the clot: (a) was it a superficial thrombophlebitis or a deep vein thrombosis (DVT)? To help with the determination when no imaging report is available, a detailed review of the extremity symptoms at the time of the clot is often helpful; (b) was it a distal or proximal DVT; (c) was the pulmonary embolism (PE) a massive, submassive, or low-risk PE?
2. ***Anatomy, terminology:*** Confusion as to which veins are superficial and which deep can lead to misclassification of superficial thrombophlebitis and DVT and, thus, to incorrect treatment decisions. Key terminology: (a) In the *arm*: Basilic and cephalic veins are superficial veins; brachial vein is a deep vein; (b) in the *leg*: Greater and lesser saphenous veins are superficial

Comments?

Questions?

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