



HPV+ Oropharynx Cancer: Are We Ready to De-Intensify Treatment?

Jonathan J Beitler, MD, MBA, FACR

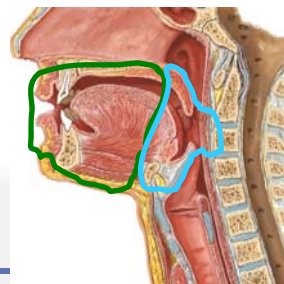
Depts of Radiation Oncology, Otolaryngology, Hematology & Medical Oncology

Winship Cancer Center of Emory University



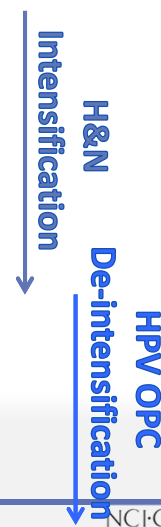
What is Oropharyngeal cancer

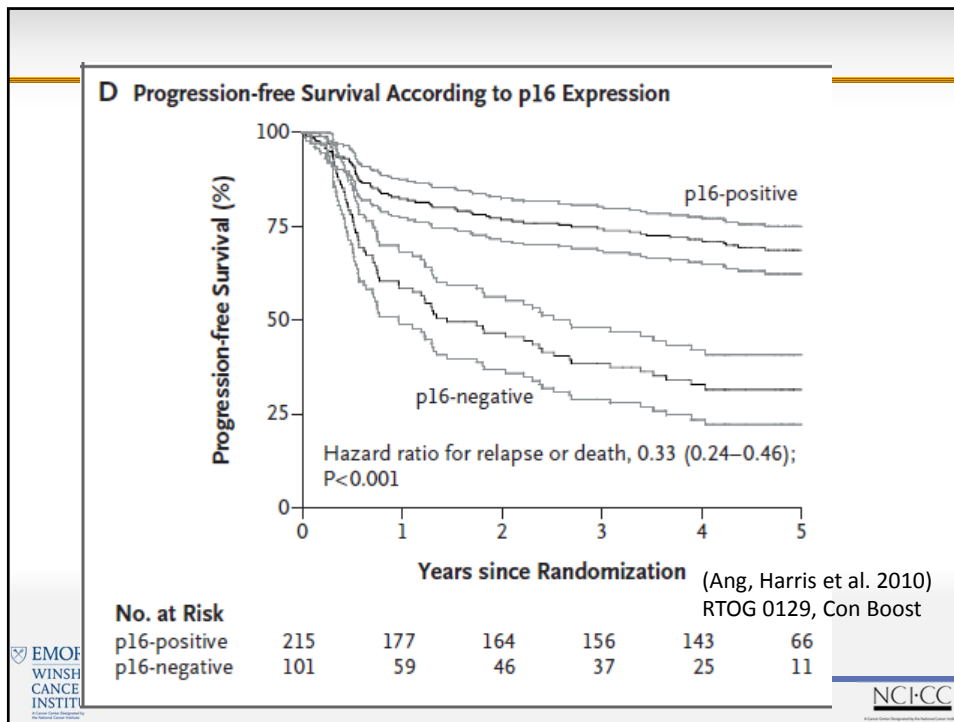
- Anatomically distinct from oral cavity cancers
- Classically treated with radiation-based approaches
- Classically associated with smoking/alcohol risk factors
- 5-year survival rates 43-58%



Paradigm shift: De-intensification

- Intergroup: 70Gy vs 70Gy+cisplatin vs splitcourse-chemoRT
- RTOG 0129: 70Gy+cisplatin vs Accel70Gy+cisplatin
- RTOG 0522: Accel70 Gy+cisplatin vs Accel70Gy+cisplatin+cetuximab
- RTOG 1016: Accel70 Gy+cisplatin vs Accel70Gy+cetuximab – closing 2014
- NRG HN002: In development, based on principles of de-intensification

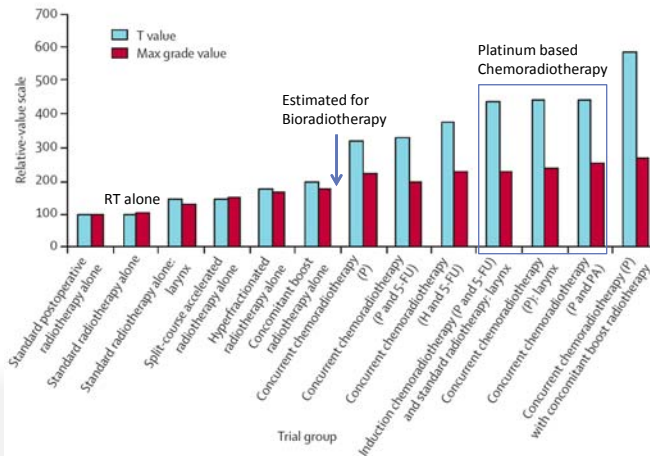




What is P16

- Cyclin-dependent kinase (CDK) inhibitor
- Inactivates CDKs that phosphorylate retinoblastoma (Rb)
- HPV oncoprotein E7 binds and inactivates Rb, causing upregulation of p16
- Immunohistochemical stain
- Cheap and readily optimized for clinical labs
- Has become the surrogate marker for HPV – and a selection criterion in RTOG clinical trials

Acute Toxicity Burden of current chemoradiation approach



Long-term morbidity of full-dose chemoradiation

- Swallowing dysfunction
- Pharyngeal strictures
- Xerostomia and dental effects
- Chronic pain
- Osteoradionecrosis/chondroradionecrosis
- Particularly germane because HPV+ OPC patients are 15 years younger than other HN cancer patients

What Can We DO?

- 1) Decrease chemotherapy
 - a) Less toxic chemotherapy
 - b) Radiation Alone
 - c) Surgery alone and Surgery + prn XRT/chemo
- 2) Decrease the XRT
 - Induction Chemo and Chemo Selection-E1308
- 3) New Trials
 - TORS
 - HN01

RTOG 1016

a) Less Toxic Chemotherapy

Phase III Trial of Radiotherapy Plus Cetuximab versus Chemoradiotherapy
in HPV-Associated Oropharynx Cancer

SCHEMA (6/25/13)

		T Stage	
		1. T1-2	
R	S	2. T3-4	R Arm 1 (Control):
E	T	N Stage	A Accelerated IMRT, 70 Gy for 6 weeks
G	Mandatory p16	R 1. N0-2a	N + high dose DDP (100 mg/m ²) Days 1 and 22
I	analysis	A 2. N2b-3	D (Total: 200 mg/m ²)
S	T	Zubrod	O
T	I	Performance	M Arm 2: Accelerated IMRT, 70 Gy for 6 weeks
E	F	Status	I + cetuximab (400 mg/m ²)
R	Y	1. 0	Z loading dose pre-IMRT, then
		2. 1	E 250 mg/m ² weekly during IMRT,
		Smoking History	and for 1 week after IMRT for a total
		1. ≤ 10 pack-years	of 8 doses of cetuximab
		2. > 10 pack-years	

Patients must be positive for p16, determined by the Innovation Center CLIA lab at The Ohio State University (OSU) prior to Step 2 registration (randomization); see 10.2 for

RTOG 1016

a) Less Toxic Chemotherapy

- Primary Objective-5 Year Survival
- Opened June 2011
 - After a hiatus the study was enlarged to 1,000 patients to allow for 834 eligible patients
- Waiting for 45 events....
 - The study is doing well...



b) Radiation Alone

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JOURNAL OF CLINICAL ONCOLOGY

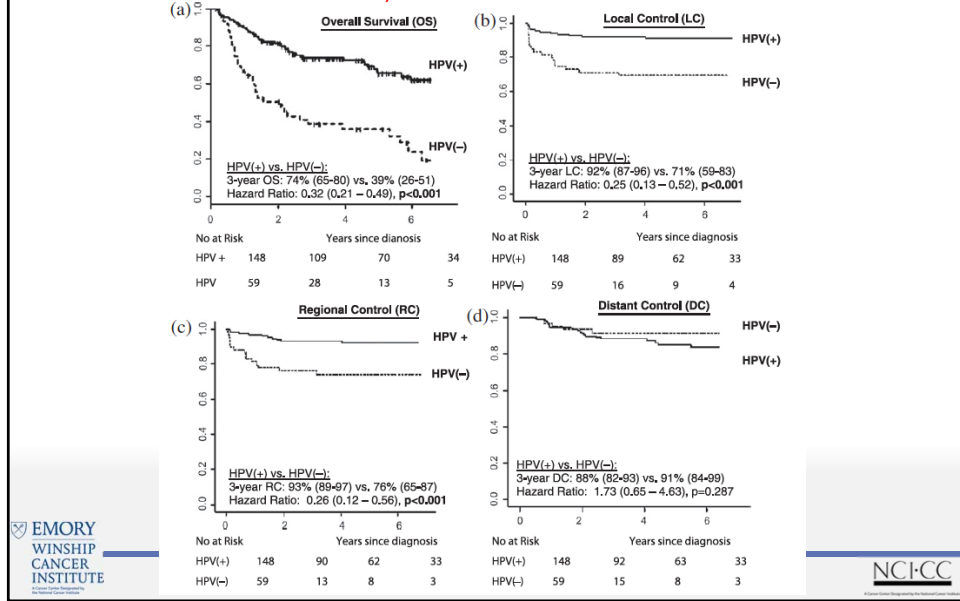
ORIGINAL REPORT

Deintensification Candidate Subgroups in Human Papillomavirus–Related Oropharyngeal Cancer According to Minimal Risk of Distant Metastasis

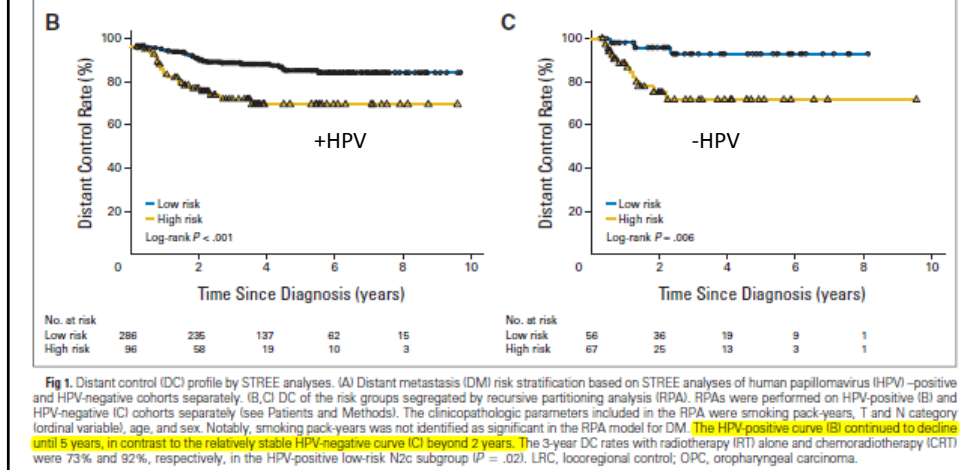
Brian O'Sullivan, Shao Hui Huang, Lillian L. Siu, John Waldron, Helen Zhao, Bayardo Perez-Ordonez, Ilan Weinreb, John Kim, Jolie Ringash, Andrew Bayley, Laura A. Dawson, Andrew Hope, John Cho, Jonathan Irish, Ralph Gilbert, Patrick Gullane, Angela Hui, Fei-Fei Liu, Eric Chen, and Wei Xu

PMH XRT Alone

b) Radiation Alone



Natural History of HPV Disease



b) Radiation Alone

- The Distant Control rates for +HPV low risk patients (T1-T3, N0-N2a, or less than 10 pack year N2b) was... similar between RT and CRT alone
- MD Anderson-Similar
- Would keep T3 out of LR group



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Deintensification Candidate Subgroups in Human Papillomavirus-Related Oropharyngeal Cancer According to Minimal Risk of Distant Metastasis

Brian O'Sullivan, Shao Hui Huang, Lillian L. Siu, John Waldron, Helen Zhao, Ricardo Perez-Ordonez, Ilan Winerch, John Kim, Julie Kingsook, Andrew Barley, Laura A. Dawson, Andrew Hodge, John Cho, Jonathan Irlin, Ralph Gilbert, Patrick Gallone, Angela Hui, Fan-Fai Liu, Eric Chen, and Wei Ye

EMORY WINSHIP CANCER INSTITUTE

NCI-CC

c) Surgery alone

Transoral Robotic Surgery Alone for Oropharyngeal Cancer

An Analysis of Local Control

Gregory S. Weinstein, MD; Harry Quon, MD; H. Jason Newman, MD; J. Ara Chalian, MD; Kelly Malloy, MD; Alexander Lin, MD; Arati Desai, MD; Virginia A. Livolsi, MD; Kathleen T. Montone, MD; K. Roger Cohen, MD; Bert W. O'Malley Jr, MD

Under the treatment regimen of primary TORS and staged neck dissection without postoperative radiation, this cohort achieved local, regional, and distant disease control in 29 of 30 (97%), 27 of 30 (90%), and 30 of 30 (100%) cases, respectively, at a minimum follow-up of 18 months. Overall survival for this cohort at the time of last follow-up was 30 of 30 (100%), also at a minimum follow-up of 18 months.

Table 2. Clinical TNM Staging

T Stage	N Stage*					Total
	0	1	2a	2b	2c	
1	5	2	1	1	0	9
2	9	5	0	2	0	16
3	1	2	0	1	0	4
4	0	1	0	0	0	1
Total	15	10	1	4	0	30

NCI-CC

Surgery + prn XRT/Chemo

Transoral Robotic Surgery for Advanced Oropharyngeal Carcinoma

Gregory S. Weinstein, MD; Bert W. O'Malley Jr, MD; Marc A. Cohen, MD; Harry Quon, MD

Table 2. TNM Staging of the 47 Study Patients^a

T Stage	N Stage				Total
	0	1	2a	2b	
1	0	8	1	4	13
2	0	13	0	9	23
3	1	2	0	5	9
4	0	1	0	1	2
Total	1	24	1	19	47

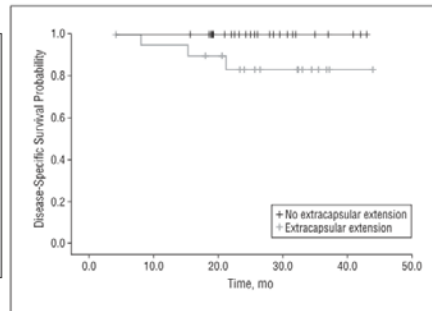


Figure 2. Disease-specific survival related to extracapsular extension.

38% avoided chemotherapy and 11% avoided XRT



Arch Otolaryngol Head Neck Surg. 2010;136(11):1079-1085



Lots of Enthusiasm(2012)

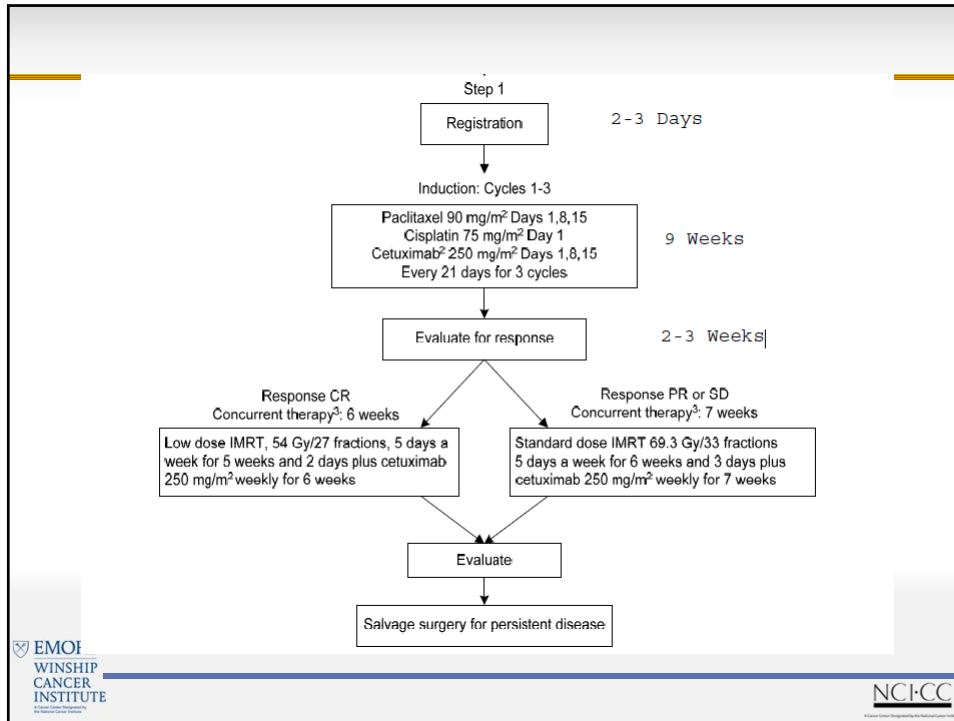
Journal of Clinical Oncology, 2012 ASCO Annual Meeting Abstracts.
Vol 30, No 15_suppl (May 20 Supplement), 2012: 5566
© 2012 American Society of Clinical Oncology

ECOG 1308: A phase II trial of induction chemotherapy followed by cetuximab with low dose versus standard dose IMRT in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx (OP).

Shanthi Marur, Ju-Whei Lee, Anthony Cmelak, Weiqiang Zhao, William H. Westra, Christine H. Chung, Maura L. Gillison, Jill Gilbert, Julie E. Bauman, Lynne I. Wagner, Robert L. Ferris, David R. Trevarthen, A. Dimitrios Colevas, Balkrishna N. Jahagirdar, Barbara Burtneiss and Eastern Cooperative Oncology Group

Conclusions: Enrollment has just completed with no data analysis available.





2013

Journal of Clinical Oncology, 2013 ASCO Annual Meeting Abstracts.
Vol 31, No 15_suppl (May 20 Supplement), 2013: 6005
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E 1308: A phase II trial of induction chemotherapy (IC) followed by cetuximab with low dose versus standard dose IMRT in patients with human papilloma virus (HPV)-associated resectable squamous cell carcinoma of the oropharynx (OPSCC).

Shanthi Marur, Shuli Li, Anthony Cmelak, Maura L. Gillison, Robert L. Ferris, Julie E. Bauman, Weiqiang Zhao, William H. Westra, Christine H. Chung, Lynne I. Wagner, David R. Trevarthen, Balkrishna N. Jahagirdar, A. Dimitrios Colevas, Barbara Burtneess and Eastern Cooperative Oncology Group

Data on PFS are premature.

A 2 year PFS of 85% or better will be considered worthy of further study

2014

Journal of Clinical Oncology, 2014 ASCO Annual Meeting Abstracts.
Vol 32, No 18_suppl (June 20 Supplement), 2014: LBA6008
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E1308: Reduced-dose IMRT in human papilloma virus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC).

Anthony Cmelak, Shuli Li, Shanthi Marur, Weiqiang Zhao, William H. Westra, Christine H. Chung, Maura L. Gillison, Jill Gilbert, Julie E. Bauman, Lynne I. Wagner, Robert L. Ferris, David R. Trevarthen, A. Dimitrios Colevas, Balkrishna N. Jahagirdar and Barbara Burtness

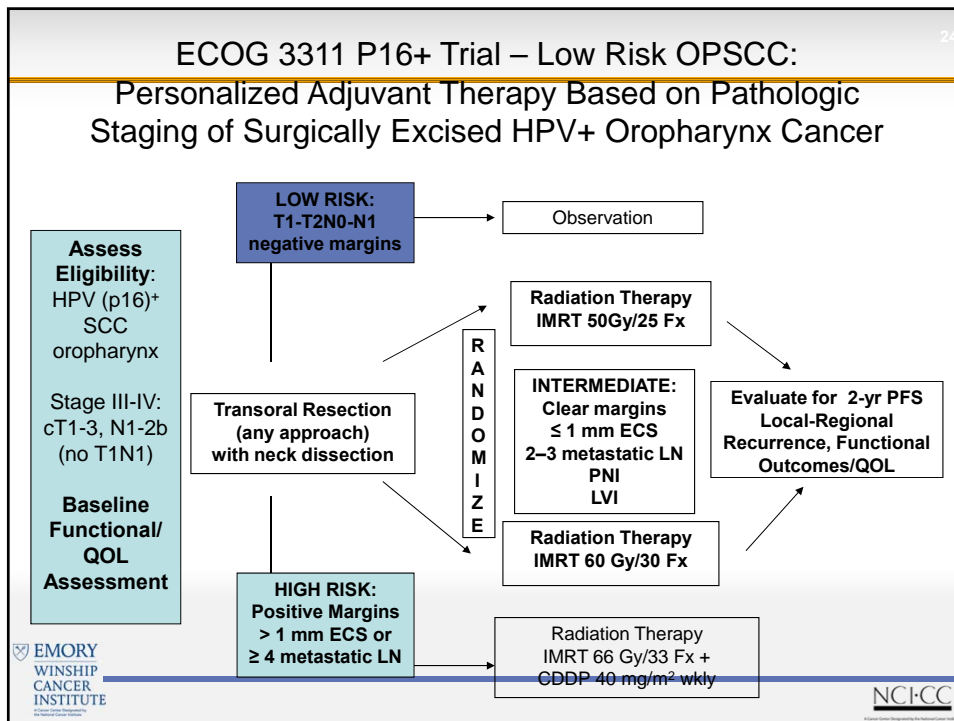
Median Follow up was 23.4 months. This is from time of registration and Includes three 21-day cycles of induction chemo and 2-3 weeks for assesment Of response....Possible lead time bias? **3 Months**

At 23 months, ECOG 1308 just MISSED it's target

30mo. **Conclusions:** IC + reduced-dose Cetux-IMRT produced high tumor control rates. Late toxicities were minimal. **Low dose pts achieved 84% PFS at 23mo** and 95% 2-yr survival. Pts with <10yrs smoking, T1-3 and N0-2b disease achieved 96% PFS. Further studies of reduced-dose IMRT in chemoresponsive HPV+ pts are warranted. Clinical trial information: NCT01084083.

A 2 year PFS of 85% or better will be considered
worthy of further study

Variable (n)	23mo PFS (90% CI)	24mo OS (90% CI)
All reduced-dose pts (62)	0.84 (0.74, 0.90)	0.95 (0.87, 0.98)
T4A (7)	0.69 (0.29,0.89)	0.86 (0.45, 0.97)
T1-T3(55)	0.86 (0.75, 0.92)	0.96 (0.88, 0.99)
N2C (19)	0.77 (0.56, 0.89)	0.95 (0.76, 0.99)
N0-N2b(43)	0.87 (0.75, 0.94)	0.95 (0.85, 0.98)
Smoker > 10 pkyr (21)	0.71 (0.48, 0.85)	0.90 (0.71, 0.97)
Smoker <= 10 pkyr (40)	0.92 (0.81, 0.97)	0.97 (0.87, 0.995)
Smoker<=10 pkyr, <T4, <N2c (n=27)	0.96 (0.82, 0.99)	0.96 (0.82, 0.99)
All standard-dose pts (15)	0.64 (0.39, 0.81)	0.87 (0.63, 0.96)



NRG HN002: A Randomized Phase II Trial for Patients with P16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

Eligibility

- OP SCCA
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

REGISTRATION

Central review
p16+
IHC

STRATIFY

Declare Intent
Unilat vs Bilat
Neck XRT

RANDOMIZE

60 Gy XRT (2Gy/fx)
in 6 weeks +
cisplatin 40 mg/m²
weekly x 6 cycles

60 Gy XRT (2 Gy/fx)
at 6 fractions/week
for 5 weeks

44% of RTOG 1016
population eligible



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Weather: 04-Jul-2014 06:20PM

N904AT
BEITLER JONATHAN
[\(registration\)](#)

Connellsville [\(KVVV - info\)](#)
Connellsville, PA

05:24PM EDT

Scheduled: 05:15PM EDT
[Other flights betw](#)

Duration: 2 hr
Friday, Ju

Status	Landed 6 days ago. (
Aircraft	Beechcraft Bonanza (3 photos)
Speed	Filed: 145 kts (graph)
Altitude	Filed: 7,000 feet (graph)
Distance	Direct: 338 sm Planne
Route	BLINK LAAYK T216 IGN C.

[Get notifi](#)

Waiting Until Hurricane Arthur Had Passed

Sometimes time clears the air....